VOLUME 37 NUMBER 1 JANUARY - FEBRUARY 2022

Academic Journal of Health Sciences

MEDICINA BALEAR

PUBLICATION OF THE ROYAL ACADEMY OF MEDECINE OF THE BALEARIC ISLANDS

www.medicinabalear.org

ACADEMIC JOURNAL OF HEALTH SCIENCES

www.medicinabalear.org

Academic Journal of Health Sciences Medicina Balear is the organ of the ***Royal Academy of Medicine of the Balearic Island***,It was created in 1986 with the aim of following up the scientific concerns and promoting the research spirit of health professionals in the Balearic Islands and with the additional objective of projecting health issues of interest to society.

Currently ***Academic Journal of Health Sciences Medicina Balear*** publishes in English, Spanish or Catalan original papers, review articles, letters to the editor and other writings of interest related to health sciences. The journal submits the originals to the anonymous review of at least two external experts (peer review).

Medicina Balear is included in the Digital Library of the Balearic Islands, of the University of the Balearic Islands, and is included in the following databases: Emerging Sources Citation Index (ESCI), Sherpa Romeo, Dulcinea, Latindex (catàleg), Dialnet, Índice Médico Español, DOAJ, Imbiomed, REDIB, Google Scholar and Journal Citation Indicator (JCI).

EDIT
Royal Academy of Medicine of the Balearic Islands

www.ramib.org

Campaner, 4, 07003 Palma de Mallorca Tel. 971 72 12 30 Email: info@ramib.org
Pàgina web: http://www.ramib.org

Dipòsit Legal: PM 486 - 95

eISSN: 2255 - 0569

Design and layout
Intelagencia Publicitat - www.intelagencia.es - intelagencia@intelagencia.es

Academic Journal of Health Sciences

Three-monthly journal of the Royal Academic of Medicine of the Balearic Island

Balears cardioprotegida

SOPORTE VITAL BÁSICO
Y
DESFIBRILACIÓN EXTERNA AUTOMÁTICA

Cursos iniciales y de reciclaje en SVB y DEA

Información: Fundació Patronat Científic del Col·legi Oficial de Metges de les Illes Balears
Passeig Mallorca, 42 - Palma
Telf.: 971 722 200 (ext. 1153)
patronatcientific@comib.com

AVALAN:

GOIB / CONSELLERIA SALUT I CONSUM
DIRECCIÓ GENERAL RECERCA SALUT, FORMACIÓ I ACREDITACIÓ

Declarado de interés sanitario

RCP
PLAN NACIONAL DE RCP

SEMICYUC
LOS PROFESIONALES DEL ENFERMO CRÍTICO

CONTENTS

VOLUME 37 NUM. 1
JANUARY - FEBRUARY 2022

EDITORIAL

ORIGINALS ARTICLES

SPECIAL ARTICLES

CASE REPORT

¿Qué profesional puede tener 45 años de edad y 90 de experiencia?

La respuesta es Banca March

La experiencia de un profesional no está únicamente en su edad, sino también en la edad de la firma para la que trabaja.

Y 90 años de experiencia es lo que ofrecen los profesionales de Banca March.

90 años gestionando patrimonios y demostrando entre otras cosas, que la prudencia no está reñida con la rentabilidad.

BancaMarch

90 ANIVERSARIO

www.bancamarch.es

SUMARIO

VOLUMEN 37 NUM. 1
ENERO - FEBRERO 2022

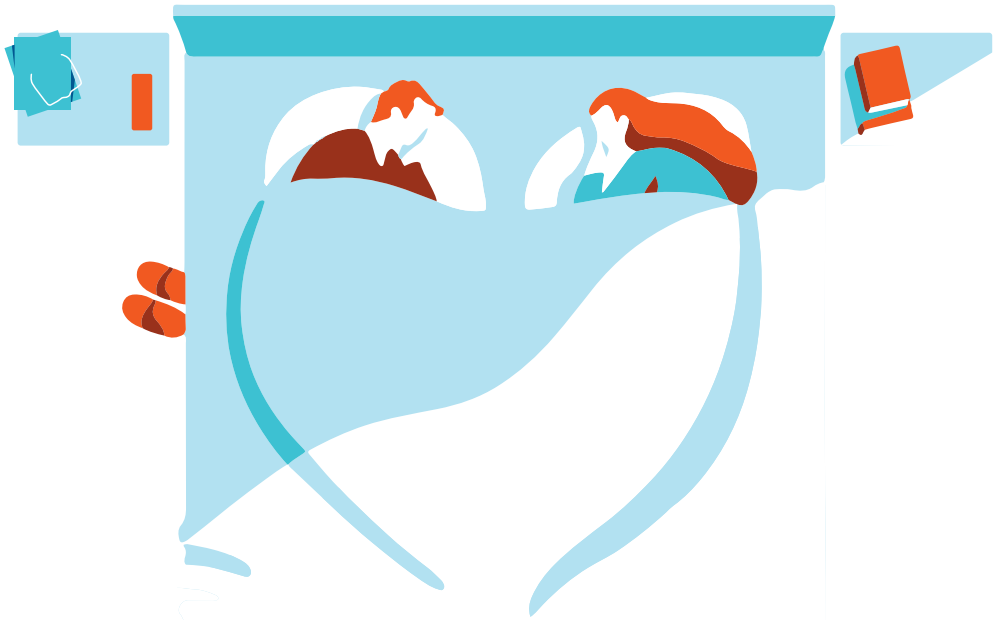
EDITORIAL

ORIGINALES

ARTÍCULOS ESPECIALES

ESTUDIO DE CASOS

Haz algo grande por tu salud



#Duerme1HoraMás

En Asisa somos expertos en salud y sabemos que el sueño es vital para el buen funcionamiento de tu corazón, tu cerebro y todo tu organismo.
Los especialistas determinan que **una persona adulta necesita entre 7 y 9 horas diarias de sueño** para estar bien.
Sin embargo, se estima que el 80% de los españoles duermen menos de este tiempo, exponiéndose a **sufrir hipertensión, taquicardia, depresión, pérdida de memoria, sobrepeso y diabetes**, entre otros problemas. Y como sabes, **en Asisa solo nos preocupa tu salud. Por eso invertimos todos nuestros recursos en cuidarte**, incluido este anuncio en el que te aconsejamos que duermas una hora más todos los días.

Empresa Colaboradora:

R 200 AÑOS

Asisa Palma de Mallorca.
C/ Pere Dezcallar i Net, 10
asisa.es **901 10 10 10**

Nada más que tu salud
Nada menos que tu salud

asisa

eISSN 2255-0569

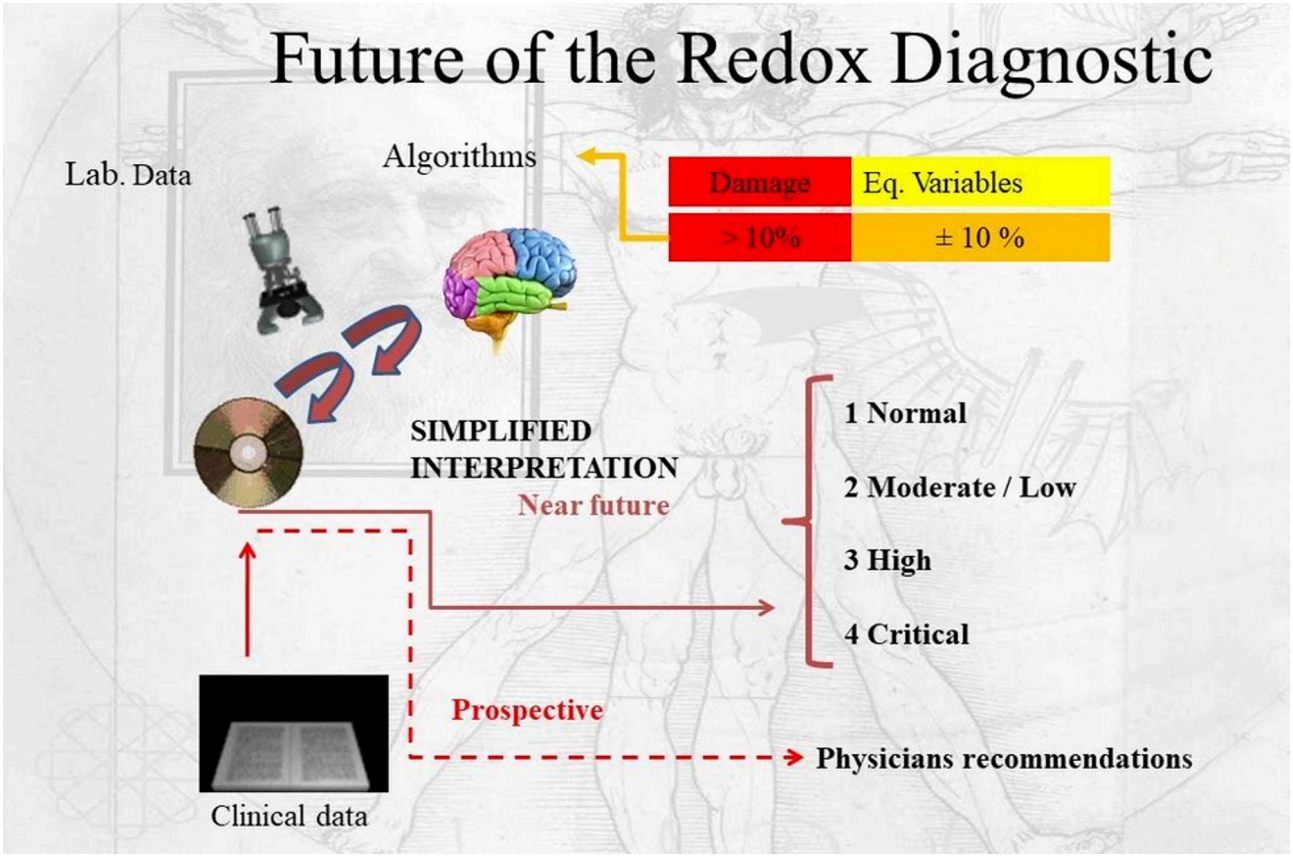
EDITORIAL

Biomarkers of oxidative stress, challenges

Biomarcadores de estrés oxidativo, desafíos

Gregorio Martínez-Sánchez

Dr. Pharmaceutical Sciences, Ph.D., Senior Researcher, Freelance. Ancona. Italy.
President of the International Scientific Committee of Ozone Therapy (ISCO3).



The overproduction of reactive oxygen species (ROS) has been implicated in the development of various chronic and degenerative diseases such as cancer, respiratory, neurodegenerative, and digestive diseases. However, the methodology to detect the oxidative stress status at a clinical level is difficult to find in the literature. There are some useful methods to investigate the oxidative profile, but they are not applicable to the clinical diagnosis. Despite the high morbidity of diseases in which oxidative stress is involved (cancer, diabetes, neurological, cardiovascular, etc.)[1], a comprehensive diagnostic system has not been developed. The education and training of professional staff (doctors, biochemists, nutritionists and health-related personnel) is also insufficient to deal with the analysis of the data that form part of the antioxidant / pro-oxidant diagnosis and its impact on the modification of life styles and another measure aimed at correcting the imbalance of the redox environment[2].

Only one variable of the antioxidant / pro-oxidant system (as indices of total antioxidant activity) is not advisable as unique maker of oxidative stress. Markers of damage to bio-molecules (such as malondialdehyde, advanced products of protein oxidation, etc.), activities of enzymes (e.g., catalase, superoxide dismutase, glutathione peroxidase), antioxidants (e.g., glutathione) and indicators of total antioxidant activity; are recommended[3].

The indicators chosen for the diagnosis must be adjusted to the concept of biomarker. The single measurement of variables of total antioxidant activity such as: TAS, FRAS, DPPH, ORAC, among others, will be useful only in the context of the measurement of other system variables indicative of damage to biomolecules or the functioning of the enzymes involved. Otherwise, errors in the interpretation of the system are incurred, or variables with a high dispersion are determined that although relatively easy to measure from the analytical point of view, do not reflect the real situation of the system[3].

The adequate methodology would be one that includes markers of damage to biomolecules, antioxidant enzymes, the concentration of low molecular weight antioxidants (including thiol balance) and indicators of total antioxidant activity. The ideal analytical method should be low cost, high precision, rapid analysis and should allow the comprehensive evaluation of the redox system. The study of a wide range of oxidative stress indices allows the examination of the role of oxidative stress in different diseases as: in diabetic patients with macro-angiopathic complications[4], HIV[5], dengue[6], infertility, neurological diseases[7],among others and nutritional follow-up[8] or correction of lifestyles and in other cases intervene with supplements, ozone therapy[9] or drugs[10].

Under physiological conditions, the concentrations of ROS are subtlety regulated by antioxidants, which can be either generated endogenously or externally supplemented. However, some results indicate that antioxidants exert no favourable effects on disease control. Thus, more studies are warranted to investigate the complicated interactions between ROS and different types of antioxidants for restoration of the redox balance under pathologic conditions. In this context, is strictly necessary to count with a valid battery of biomarkers to be applied at clinical level.

References

1. Liu Z, Ren Z, Zhang J, et al. Role of ROS and Nutritional Antioxidants in Human Diseases. *Front Physiol*. 2018;9:477.

2. Núñez Sellés A, Garrido Garrido G, Delgado Hernández R, et al. *El Reto de La Terapia Antioxidante*. La Habana, Cuba: Editorial Científico Técnica; 2008.

3. Martínez-Sánchez G, Candelario-Jalil E, García García I, León Fernández O, Bilbao Reboredo T, Ledesma Rivero L. Ambiente Antioxidante/Pro-oxidante. Su impacto medico. In: Aracne, ed. Roma 2012:680.

4. Martínez-Sánchez G, Popov I, Al-Dalaen SM, Horwat-Delaporte R, Giuliani A, León-Fernández OS. Contribution to characterization of oxidative stress in Diabetic patients. *Acta Farmacéutica Bonaerense*. 2005;24(2):197-203.

5. Gil L, Martinez G, Gonzalez I, et al. Contribution to characterization of oxidative stress in HIV/AIDS patients. *Pharmacol Res*. Mar 2003;47(3):217-224.

6. Gil L, Martinez G, Tapanes R, et al. Oxidative stress in adult dengue patients. *Am J Trop Med Hyg*. Nov 2004;71(5):652-657.

7. Penton-Rol G, Cervantes-Llanos M, Martinez-Sanchez G, et al. TNF-alpha and IL-10 downregulation and marked oxidative stress in Neuromyelitis Optica. *J Inflamm (Lond)*. Jun 2 2009;6(1):18.

8. Gil L, Lewis L, Martinez G, et al. Effect of increase of dietary micronutrient intake on oxidative stress indicators in HIV/AIDS patients. *Int J Vitam Nutr Res*. Jan 2005;75(1):19-27.

9. Martínez-Sánchez G, Al-Dalain SM, Menendez S, et al. Therapeutic efficacy of ozone in patients with diabetic foot. *Eur J Pharmacol*. Oct 31 2005;523(1-3):151-161.

10. Martínez-Sánchez G, Re L. Clinical diagnostic of redox balance an up-date Paper presented at: European Meeting of the Society for Free Radical Research 2008; Berlin, Germany

eISSN 2255-0569

ORIGINAL

The relationship between internet addition with social isolation and psychological well-being: a case study of female junior high school students of Rafsanjan, Iran

La relación entre la adición a Internet con el aislamiento social y el bienestar psicológico: un estudio de casos de las estudiantes de secundaria de Rafsanjan, Irán

Nahid Rezaei Hematabadb

MSc in Clinical Psychology, Islamic Azad University, Anar Branch, Ahar, Iran.

Corresponding author
Nahid Rezaei Hematabadb
MSc in Clinical Psychology, Islamic Azad University,
Anar Branch, Ahar, Iran.
E-mail: Nahidrezaei3167@gmail.com

Received: 6 - IX - 2021
Accepted: 2 - XI - 2021

doi: 10.3306/AJHS.2022.37.01.11

Abstract

Introduction: Internet use is developing, and it is considered an important part of people's lives; the internet has dominated all aspects of human's lives. Excessive use of the internet deprives people of beliefs and social communications; by eliminating social interactions and dominating people's lives, it can cause feelings of loneliness and social isolation and threaten the mental health and psychological well-being of individuals.
Methods: The present study is descriptive-correlational one, and it is an applied study in terms of purpose. The statistical population of this study was 5537 female students in the junior high schools of Rafsanjan. In order to select the sample, Morgan's sampling table was used. According to this table, a sample size of 360 people was selected. To select the samples, a two-stage cluster sampling method was used; in the first stage, four junior high schools were selected, and 3 classes were randomly selected in each high school. were chosen. The data collection tools in this study are the standard questionnaires including: 1. Young's Internet Addiction Test (1996) 2. Modaresi Yazdi's Social Isolation Questionnaire (2014) and 3. Ryff's Scales of Psychological Well-being (1989). The reliability and validity of all of these questionnaires have been reported to be good. Descriptive and inferential statistical methods were used to analyze the collected data. In order to organize and summarize the information, descriptive statistical methods such as mean, standard deviation, graph, skewness and kurtosis indices and normality test have been used. To test the hypothesis, statistical methods such as correlation coefficient and path analysis have been used.
Results: The results indicate that the relationship between internet addiction and social isolation ($P < 0.01$, $r = 0.344$) is both positive and significant. However, the relationship between internet addition and psychological well-being ($P < 0.01$, $r = -0.374$) is both negative and significant. The relationship between social isolation and psychological well-being ($P < 0.01$, $r = -0.708$) is negative and significant.
Conclusion: Internet addiction affects students' social isolation in various ways and leads them to mental illnesses such as depression and threatens people's mental well-being.

Keywords: Internet addiction, Social isolation, Psychological well-being, Female students.

Resumen

Introducción: El uso de Internet se está desarrollando y se considera una parte importante de la vida de las personas; Internet ha dominado todos los aspectos de la vida de los seres humanos. El uso excesivo de Internet priva a las personas de creencias y comunicaciones sociales; al eliminar las interacciones sociales y dominar la vida de las personas, puede causar sentimientos de soledad y aislamiento social y amenazar la salud mental y el bienestar psicológico de los individuos.
Métodos: El presente estudio es descriptivo-correlacional, y es un estudio aplicado en cuanto a su finalidad. La población estadística de este estudio fue de 5537 alumnas de las escuelas secundarias de Rafsanjan. Para seleccionar la muestra se utilizó la tabla de muestreo de Morgan. Según esta tabla, se seleccionó una muestra de 360 personas. Para seleccionar las muestras, se utilizó un método de muestreo por conglomerados en dos etapas; en la primera etapa, se seleccionaron cuatro escuelas secundarias y se eligieron 3 clases al azar en cada escuela secundaria. Los instrumentos de recogida de datos en este estudio son los cuestionarios estándar, que incluyen 1. El test de adicción a Internet de Young (1996) 2. Cuestionario de aislamiento social de Modaresi Yazdi (2014) y 3. Las escalas de bienestar psicológico de Ryff (1989). La fiabilidad y la validez de todos estos cuestionarios han sido reportadas como buenas. Se utilizaron métodos estadísticos descriptivos e inferenciales para analizar los datos recogidos. Para organizar y resumir la información, se han utilizado métodos estadísticos descriptivos como la media, la desviación estándar, el gráfico, los índices de asimetría y curtosis y la prueba de normalidad. Para comprobar la hipótesis, se han utilizado métodos estadísticos como el coeficiente de correlación y el análisis de trayectorias.
Resultados: Los resultados indican que la relación entre la adicción a Internet y el aislamiento social ($P < 0{,}01$, $r = 0{,}344$) es positiva y significativa. Sin embargo, la relación entre la adicción a Internet y el bienestar psicológico ($P < 0{,}01$, $r = -0{,}374$) es negativa y significativa. La relación entre el aislamiento social y el bienestar psicológico ($P < 0{,}01$, $r = -0{,}708$) es negativa y significativa.
Conclusiones: La adicción a Internet afecta al aislamiento social de los estudiantes de diversas maneras y les lleva a padecer enfermedades mentales como la depresión y amenaza el bienestar mental de las personas.

Palabras clave: Adicción a Internet, Aislamiento social, Bienestar psicológico, Mujeres estudiantes.

Introduction

The use of the Internet has grown increasingly in recent decades[1]. The present age is at the height of the digital industrial revolution. Each revolution will undoubtedly bring about different changes, either good or bad. The tensions resulting from these changes are not always harmful, but the way of dealing with these changes can determine whether they are harmful or beneficial[2].

The unique features of the internet, such as being easily accessible, the possibility of 24-hour internet communication, low cost, anonymity of users, and ease of use have all led to its widespread use worldwide[3]. The widespread use of the internet in science and technology and its absorbing applications have led to the emergence of the phenomenon of Internet addiction in recent years[4]. Internet addiction is a behavioral dependence that is associated with indicators such as increasing costs for Internet users, suffering from unpleasant emotions, such as anxiety, depression, etc. when a person is not connected to the Internet, increasing users' tolerance and dependence against the bad effects of using the internet, and denying problematic behaviors by the users. The consequences of internet addiction include changing one's lifestyle in order to spend more time on the internet, ignoring one's health, avoiding important life activities, reducing social relationships, ignoring family and friends, suffering from financial problems due to the internet usage costs, and educational problems. People with this disorder suffer from a variety of psychological, social, and occupational problems[5].

Unfortunately, this addiction is not for a specific group or category; it affects everyone. But this addiction is more commonly observed in teenagers and young people compared to other groups. As we know, adolescence is one of the most important periods of human life and the lack of adaptation to the changes and stresses of this period of life can cause many physical and mental harms. One of the components of mental health is psychological well-being. According to Ryff, psychological well-being is what a person needs for well-being and includes feeling good about one and one's life[6]. Ryff expresses her views in the theoretical dimensions of autonomy, environmental mastery, personal growth, positive relations with others, purpose in life, and self-acceptance[7].

In the scientific researches of Brener (1997)[8] and Caplan (2002)[9], concluded that students with Internet addiction have lower psychological and social well-being than students without Internet addiction. Uncontrolled use of the Internet endangers the physical, social, and mental development of users. The results of numerous studies on high school and college students indicate that the incidence and prevalence rates of the internet addiction are increasing among these people. Internet addiction in students leads to problems such as reduced interpersonal communication, damage to various components of mental health, and difficulties in social interactions[10]. On the other hand, people differ, biologically and individually, in the degree of vulnerability to mental illness. However, the extent of these differences is influenced by social factors, and a large proportion of different forms of mental illness are strongly associated with social models. Social isolation is one of the social factors affecting health. Social isolation has two dimensions: mental and objective that are close, in terms of concept, to social involvement, social cohesion and social capital, of alienation, loneliness and withdrawal. The internet, as a new communication technology, accelerates and facilitates the possibility of communication and interaction between people, but it can reduce these interactions and increase the social isolation of people[11]. Social isolation refers to either lack or weakness of an individual in establishing connections with others, groups, and society. Undoubtedly, social isolation deprives individuals of informal and formal participation in society, reduces social exchange and social attachment, prevents the constant exchange of thoughts and feelings from an individual to the whole and from the whole to the individual, weakens or disrupts warm relations and exchanges as well as verbal relations, and deprives individuals of the opportunity to live together, work together, experience events together, and be together. Ultimately, social isolation makes the creation of lasting, deep relationships impossible. The abovementioned problems are likely to lead to various consequences such as loneliness, helplessness, social despair and decreased social tolerance[12].

Given the unfortunate increase in the rate of internet addiction and the risk of young people being involved and roaming in cyberspace, the poor performance of measures taken in the field of cyberspace control by governments, the lack increasing public awareness on the correct use of the internet, as well as risk including social isolation, feeling of loneliness, reduced interpersonal relationships and lowered level of health and well-being of individuals, and ultimately the destruction of social capital of the country, especially girls owing to mental sensitivities and their future role as mothers, managers, and life managers, it is required to conduct studies to determine factors influencing this emerging phenomenon. It is also essential to consider these factors in designing preventive and intervention programs[13].

According to the high importance of issue, the present study was performed to assess the relationship between internet addition with social isolation and psychological well-being (a case study: female junior high school students of Rafsanjan, Iran).

Materials and methods

The present study is descriptive-correlational one. In terms of purpose, it is an applied one. The statistical

population of this study was 5537 female students studying in junior high schools of Rafsanjan, Iran. In order to select the sample, Morgan sampling table was used; according to this table, a sample size of 360 people was selected. To select the sample, two-stage cluster sampling method was used; in the first stage, 4 junior high schools were selected, and 3 classes were randomly chosen in each high school. The data collection tools in this research are standard questionnaires. They include Young's Internet Addiction Test (1996). This scale consists of 20 questions. The validity of the questionnaire has been evaluated and confirmed as "good" by using the opinions of supervisor and the reader. The reliability of this questionnaire was measured to be %78 using Cronbach's alpha test. The reliability of the questionnaire was measured to be %95 in this study by applying Cronbach's alpha. The next questionnaire is Modaresi Yazdi's Social Isolation Questionnaire (2014). This questionnaire includes 18 questions and its components (loneliness (1 to 6), helplessness (7 to 9), social despair (10 to 14), reduced social tolerance (15 to 18)). In order to measure the reliability of each of the dimensions of this questionnaire, Cronbach's alpha method was used; according to the results of each component of the questionnaire, an acceptable reliability has been reported. Cronbach's alpha coefficient has been reported to be 79% for loneliness, 85% for hopelessness, 73% for social despair, and 78% for reduced social tolerance. The reliability of the questionnaire in this study was measured to be 82% with Cronbach's alpha. Also, the validity of the questionnaire was conducted by using face validity. The next questionnaire is Ryff's Scale of Psychological Well-being (1989). Ryff's Scale of Psychological well-being (short form) has 18 questions that aim to evaluate and investigate psychological well-being has 6 dimensions (Autonomy: questions 12-9-18; environmental mastery: questions 1- 4-6, personal growth: questions 17-15-7, positive relations with others: questions 3-13-11; purpose in life: questions 16-14-5; and self-acceptance questions 10-8-2). The reliability of the questionnaire in this study was measured to be 72% with Cronbach's alpha. Descriptive and inferential statistical methods were used to analyze the collected data. In order to organize and summarize the information, descriptive statistical methods such as mean, standard deviation, graph, skewness and kurtosis indices and normality test have been used. To test the hypothesis, statistical methods such as correlation coefficient and path analysis have been used.

Results

Descriptive indicators of research variables

Table I shows the descriptive indicators of mean, standard deviation, minimum and maximum scores of the present study's participants in terms of research variables. The results reported the mean and standard deviation of internet addiction (SD = 1.21, M = 69.20), social isolation (SD = 0.62, M = 59.20), and psychological well-being (SD = 0.5, M = 33.40).

The distribution of the research variables

Table II shows how the studied variables are distributed in terms of normality. The results showed that the variables of internet addiction (ku = -0.8, sk = 0.5, p <0.05, KS (357) = 0.111), social isolation (ku = -0.05, 0.35 sk =, p< 0.05, KS (357) = 0.054) and psychological well-being (ku = -0.06, sk = 0.39, p< 0.05, KS (357) = 0.067) are not normal in terms of Kolmogorov-Smirnov index. However, since this index is significant in large samples, the condition of being normal is accepted if the two indices of skewness and kurtosis are between ±2. In this study, for all of the investigated variables, the skewness and kurtosis were between ±2.

Testing the research hypotheses

The correlation matrix between the research variables

The main Hypothesis: There is a significant relationship between internet addiction with social isolation and psychological well-being.

Table I: Descriptive indicators of the participants' scores in terms of the research variables.

Variable	Number	Mean	Standard deviation	Minimum score	Maximum score
Internet addition	357	69.2	1.21	1	6.5
Social isolation	357	59.2	0.62	17.1	72.4
Psychological well-being	357	33.4	0.5	78.2	56.5

Table II: The indictors of the distribution status of the research variables.

Component	Skewness	Kurtosis	Kolmogorov-Smirnov index	Degree of freedom	Significance level
Internet addiction	0.5	-0.8	0.111	357	0.000
Social isolation	0.35	-0.05	0.054	357	0.013
Psychological well-being	-0.39	-0.06	0.067	357	0.001

Table III: The relationship between the research variables.

Component	Internet addiction	Social isolation	Psychological well-being
Internet addiction	1		
Social isolation	0.344**	1	
Psychological well-being	-374**	-0.708**	1

Table III shows the results of the correlation between the research variables. The results indicated that the relationship between internet addiction and social isolation (P <0.01, r = 0.344) was positive and significant, but the relationship between internet addiction and psychological well-being (P <0.01, r = -0.374) was negative and significant. Finally, the relationship between social isolation and psychological well-being (P <0.01, r = -0.708) is negative and significant.

Testing the model

The results of **table IV** show the fit indices of the analyzed model. The results indicated that the values of SRMR = 0.047, RSMEA = 0.08, p = 0.000, df = 29, X^2 = 95.45 indicates the optimal fit of the model in the population. Moreover, to determine the suitability of the fit of the model with data, fitness indicators were used. The results showed that the normed fit index is (NFI) = 0.909, and the comparative fit index is = 0.941 (CFI); this indicates the acceptable fit of the model with the data, especially the CFI value which according to Muller (1999) should be above 0.9 and from the point of view of Weston & Gore Jr (2006), it should be above 0.95 in order to have a good fit model with the data, since it is not affected by the sample size. Also, if the root mean square error of approximation (RMSEA ≤ 0.05) is very good i.e. between 0.05 and 0.08, the fit is acceptable, and if it is higher than 0.08, the fit is poor, and the standardized root mean square residual (SRMR ≤ 0.08) indicates optimal and undesirable fit. In this study, RMSEA was between 0.05 and 0.08 and SRMR was below 0.08; this indicates acceptable fit.

Testing the secondary hypotheses of the research

Table V shows the results of the study of the direct effects of the investigated variables on each other in the general model.

First sub-hypothesis: The direct effect of internet addiction on the psychological well-being of high school students is significant.

The results showed that the direct effect of internet addiction on the psychological well-being of high school students is not significant (p > 0.05, t = -1.76, β = -0.079). As a result, the null hypothesis is accepted and hypothesis 1 is rejected.

Second sub-hypothesis: The direct effect of internet addiction on social isolation of high school students is significant.

The results showed that the direct effect of internet addiction on social isolation of high school students is positive and significant (p < 0.01, t = 5.28, β = 0.191). As a result, null hypothesis is rejected and hypothesis one is accepted.

Third sub-hypothesis: The direct effect of social isolation on the psychological well-being of high school students is significant.

The results indicated that the direct effect of social isolation on the psychological well-being of high school students is negative and significant (p < 0.01, t = -3.17, β = -0.205). Therefore, the null hypothesis is rejected and hypothesis one is accepted.

Discussion

The rapid internet expansion and proliferation have provided better communication, information, and social interaction opportunities. However, the excessive undisciplined use by some individuals has led to the emergence of the concept of internet addiction. Younger internet users (i.e., between 18 and 24 years old) were more at risk of becoming internet addicts than older users. Psychological and environmental factors in the lives of college students may leave them disproportionately vulnerable to internet addiction. Possible reasons for this are (a) students have huge blocks of unstructured time, (b) schools and universities provide free and unlimited access to the internet, (c) students from the ages of 18-22 years are for the first time away from parental control without anyone monitoring or censoring what they say or do online, (d) young students experience new problems of adapting to university life and finding new friends, and often end up seeking a companionship using different applications of the internet, (e) students receive full

Table IV: The fit indicators of the model.

Fit indicators	X2	df	df/x2	Sig	RMSEA	SRMR	NFI	CFI
The indicator value	95.45	29	3.29	0.000	0.08	0.047	0.909	0.941

Table V: Direct effects of the investigated variables on each other in the general model.

Endogenous and exogenous variables	Direct effects				
	Non-standardized coefficient	Standardized coefficient	Standard error	t value	R^2
On psychological well-being From internet addiction From social isolation	-0.008 -0.039	-0.079 -0.205	0.045 0.065	-1.76 - 3.17**	0.759
On social isolation From internet addiction	0.099	0.191	0.036	5.28**	0.558

encouragement from faculty and administrators in using the different internet applications, (f) adolescents are more trained to use the different applications of technological inventions and especially the internet, (g) students desire to escape university sources of stress resulting from their obligations to pass examinations, compose essays, and complete their degrees in the prescribed time with reasonable marks, and finally (h) students feel that university life is alienated from social activities, and when they finish their studies, the job market with all its uncertainties is a field where they must participate and succeed in finding employment[14].

The present survey was performed to assess the relationship between internet addition with social isolation and psychological well-being (a case study: female junior high school students of Rafsanjan, Iran). Findings showed that relationship between internet addiction and social isolation ($P < 0.01$, $r = 0.344$) was positive and significant. the direct effect of internet addiction on the psychological well-being of high school students is not significant. The direct effect of internet addiction on the social isolation of high school students is significant. Additionally, the direct effect of internet addiction on the social isolation of high school students is positive and significant. The direct effect of social isolation on the psychological well-being of high school students is negative and significant. Similar reports have been recorded in this field. Kraut et al. (1998)[15] found that excessive internet usage presents a negative effect on face-to-face interactions by reducing time spent with friends and family members, which leads to increased loneliness and depression, thus decreasing psychological well-being (PWB). Liu reported that internet use increased the degree of loneliness in college students[16]. The previous studies observed the negative effect of internet on their daily lives and a break in the PWB of young adults. These studies defined well-being in the concept of mental illness and distress such as loneliness and depression[17], behavioral difficulties[18], impulsivity, sensation and novelty-seeking, and social isolation[19].

Various studies conducted by Ko et al (2008) (20) and Rashidiyan et al. (2017)[21] have indicated that the rate of depression is higher among the users addicted to the internet in comparison to the normal users of the internet. Çardak (2013)[22] reported that students with higher levels of Internet addiction are more likely to be low in psychological well-being. The results indicated that psychological well-being was affected by Internet addiction negatively; and provided a better understanding on the relationship between psychological well-being and Internet addiction. A Chinese survey showed the relationships between social support, loneliness, and internet addiction in postsecondary students[23].

Similar to our findings, the results of Alqahtani et al. (2020)[24] showed that most of the participants were nonaddicted to internet, had a moderate level of feeling of loneliness that were highly satisfied about their life. Based on this result it was conclude that there is no relationship between internet addiction, loneliness and life satisfaction ($p>0.01$). It is recommended to broad the population for increasing the generalizability of the results to all Saudi population. Previous survey in Iran[25] showed that there was a significant positive correlation between Internet addiction and test anxiety. There is also an inverse correlation between social adjustment and test anxiety. The results of step-by-step regression analysis showed that among the variables under study, the Internet addiction variable predicts 0.32 and along with the social adjustment variable 0.37 variance of test anxiety.

Conclusion

In explaining the results of the present study, it can be stated that in general, overusing the internet results in physical laziness, increased inactivity, reduced relationship with the others in the real world, and mental problems. In addition, being too much involved with the virtual not only harms the individual's physical health (due to inactivity) but also involves one's mind with issues in an unreal world and causes tiredness and depression as well. Therefore, the excessive use of the internet can be a major problem for one's psychological well-being. In the present study, the lack of a relationship between internet addiction and psychological well-being can be explained as such that owing to adolescence and high energy, teenagers are likely to be unaware of the physical and especially mental damages caused by excessive use of the internet; they are less likely to give due attention to the complications and harms caused by the internet addiction.

In explaining the direct and positive effect of internet addiction and social isolation, it can be stated that a when a person is socially isolated or generally does not have the ability to establish relationships with others in the real world, or his interpersonal relationships have been damaged for various reasons such as negative expectations and predictions, he or she turns to the internet and cyberspace communications where communication with others is much easier than that of the real world, so that he/she will compensate the abovementioned problems. Many people also turn to the internet to manage and avoid the unwanted emotions such as stress, loneliness, depression, anxiety and worry. The Internet is the easiest way to get out of these feelings when a person has been through an ordeal and is looking for a solution to escape their problems or immediate relief. Over time, being involved with the internet isolates the individual and makes him/her a lonely one. The present study has confirmed these findings.

In explaining this part of the research, it can be stated that social isolation deprives people of formal and informal participation in society, reduces exchange and social

attachment, and weakens or disrupts warm exchanges and discourse relations. Thus, the individual will be isolated, and his/her health will be at risk. The results of this study and the negative relationship between social isolation and psychological well-being indicate this issue. In general, the reasons behind people's psychological well-being can be found when their mental needs and high-level needs to achieve self-fulfillment are met. The isolated person suffers from some kind of mental damage, and his/her needs are at very low levels; this can confirm the negative relationship between psychological well-being and isolation.

Based on the results of the present study, the following practices are recommended to be conducted:

- Doing group work and advising families to hold party and family meetings to strengthen social support and more hope among their children;
- Teaching the correct ways of using new technology by holding training courses and workshops at schools;
- Holding courses to make parents familiar with the internet addiction, social isolation and its dangers and complications, and the risks posed to the psychological health of their children and ways to prevent them.

Other researchers are also recommended to study the effects of gender differences on the relationship between variables. One of the limitations of the present study is the lack of control over nuisance variables such as level of culture, economic status, and social status of female students.

Interests conflict

The researchers declare that they have no conflict of interest.

References

1. Apăvăloaie El. The impact of the internet on the business environment. Procedia Economics and finance. 2014 Jan 1;15:951-8.

2. Bessière K, Pressman S, Kiesler S, Kraut R. Effects of internet use on health and depression: a longitudinal study. Journal of Medical Internet Research. 2010 Mar 12;12(1):e1149.

3. Aggarwal B, Xiong Q, Schroeder-Butterfill E. Impact of the use of the internet on quality of life in older adults: review of literature. Primary Health Care Research & Development. 2020;21.

4. Mihajlov M, Vejmelka L. Internet addiction: A review of the first twenty years. Psychiatria Danubina. 2017 Sep 26;29(3):260-72.

5. Pontes HM, Kuss DJ, Griffiths MD. Clinical psychology of Internet addiction: a review of its conceptualization, prevalence, neuronal processes, and implications for treatment. Neuroscience and Neuroeconomics. 2015 May 28;4:11-23.

6. Ryff CD, Singer BH. Best news yet on the six-factor model of well-being. Social science research. 2006 Dec 1;35(4):1103-19.

7. Brenner V. Psychology of computer use: XLVII. Parameters of Internet use, abuse and addiction: the first 90 days of the Internet Usage Survey. Psychological reports. 1997 Jun;80(3):879-82.

8. Caplan SE. Problematic Internet use and psychosocial well-being: development of a theory-based cognitive–behavioral measurement instrument. Computers in human behavior. 2002 Sep 1;18(5):553-75.

9. Hadi S, Noury R, Mohammadkhani S, Monshei GH. A comparison of cognitive wellbeing, social acceptance and adaptation among Internet non-addicted and addicted high school girls. Iranian Journal of Rehabilitation Research. 2015 Feb 10;1(2):52-62.

10. Siomos KE, Dafouli ED, Braimiotis DA, Mouzas OD, Angelopoulos NV. Internet addiction among Greek adolescent students. CyberPsychology & Behavior. 2008 Dec 1;11(6):653-7.

11. Evans IE, Martyr A, Collins R, Brayne C, Clare L. Social isolation and cognitive function in later life: A systematic review and meta-analysis. Journal of Alzheimer's disease. 2019 Jan 1;70(s1):S119-44.

12. Hazrati Someeh Z. Social Factors Affecting Students' Social Isolation (Case Study: Islamic Azad University Central Tehran Branch). Quarterly Journal of Social Development (Previously Human Development). 2018 Feb 20;12(2):109-42.

13. Rashidiyan S, Rashidi N, Ghanbari N. Prediction of Internet Addiction in Students based on Social Support and Academic Expectations Stress. Quarterly Journal of Child Mental Health. 2017 Dec 10;4(3):176-86.

14. Sharma A, Sharma R. Internet addiction and psychological well-being among college students: A cross-sectional study from Central India. Journal of family medicine and primary care. 2018 Jan;7(1):147.

15. Kraut R, Patterson M, Lundmark V, Kiesler S, Mukophadhyay T, Scherlis W. Internet paradox: A social technology that reduces social involvement and psychological well-being?. American psychologist. 1998 Sep;53(9):1017.

16. Liu J. The relationship between college student's internet use and loneliness. Chinese Journal of Clinical Psychology. 2001 Jan 1(03).

17. Whang L, Lee H, Chang G. Internet Over-Users' Psychological Profiles: A Behavior Sampling Analysis on Internet Addiction. 2016. [Last accessed on 2016 Apr 23]. Available from: http://www.encognitive.com/files/Internet%20Over.Users'%20Psychologica.

18. Mannell RC, Zuzanek J, Aronson R. Internet/Computer Use and Adolescent Leisure Behavior, Flow Experiences and Psychological Well-Being: The Displacement Hypothesis. 2013. [Last accessed on 2016 Apr 23]. Available from: http://www.lin.ca/sites/default/files/attachments/CCLR11.89.pdf.

19. Young KS, Rogers RC. Internet Addiction: Personality Traits Associated with Its Development. 1998. Available from: http://www.netaddiction.com/articles/personality_correlates.pdf.

20. Ko CH, Yen JY, Chen CS, Chen CC, Yen CF. Psychiatric comorbidity of internet addiction in college students: an interview study. CNS spectrums. 2008 Feb;13(2):147-53.

21. Rashidiyan S, Rashidi N, Ghanbari N. Prediction of Internet Addiction in Students based on Social Support and Academic Expectations Stress. Quarterly Journal of Child Mental Health. 2017 Dec 10;4(3):176-86.

22. Cardak M. Psychological well-being and Internet addiction among university students. Turkish Online Journal of Educational Technology-TOJET. 2013 Jul;12(3):134-41.

23. Zhang S, Tian Y, Sui Y, Zhang D, Shi J, Wang P, Meng W, Si Y. Relationships between social support, loneliness, and internet addiction in Chinese postsecondary students: A longitudinal cross-lagged analysis. Frontiers in psychology. 2018 Sep 11;9:1707.

24. Alqahtani AF, Alqarni MH, Alotaibi SB, Fattah S, Alhalawany RM. Relationship between Level of Internet Addiction, Loneliness and Life Satisfaction among College of Health and Rehabilitation Sciences Students' at Princess NourahBint Abdulrahman University. Menoufia Nursing Journal. 2020 Nov 1;5(2):55-74.

25. Naeim M, Rezaeisharif A, Zandian H. The Relationship Between Internet Addiction and Social Adjustment, and Test Anxiety of the Students of Ardabil University of Medical Sciences. Shiraz E-Medical Journal. 2020 Nov 30;21(11).

eISSN 2255-0569

ORIGINAL

The evaluation of diagnostic value of serum Lactate dehydrogenase/pleural Adenosine deaminase ratio compared with pathology in diagnose of malignancy in exudative pleural effusion

Evaluación del valor diagnóstico de la relación entre la lactato deshidrogenasa sérica y la adenosina desaminasa pleural en comparación con la patología para el diagnóstico de malignidad en el derrame pleural exudativo

Abolhasan Halvani[1], Mahtab Torabi[2], Mohammad Shafiee[2], Zahra Shojaei[3]

1. Department of internal medicine, Yazd medical science, branch Islamic Azad University, Yazd, Iran
2. General Practitioner, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
3. Medical student, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

Corresponding author
Zahra Shojaei
Shahid Sadoughi University of Medical Sciences, Yazd, Iran.
E-mail: zahrashojaaei@gmail.com

Received: 8 - IX - 2021
Accepted: 5 - XI - 2021

doi: 10.3306/AJHS.2022.37.01.17

Abstract

Background: In recent studies, it has been somewhat determined that the Lactate dehydrogenase(LDH) ratio of serum to Adenosine deaminase(ADA)of pleural fluid has a diagnostic value in malignant pleural effusions. We decided to study the diagnostic value of these enzymes by conducting a wider study and a higher statistical society.
Methods: This is a descriptive-analytic study that was conducted in a cross-sectional method. Sampling method was census and 39 patients with exudative pleural effusion were enrolled. Age, sex, biopsy report, serum LDH and ADA of pleural fluid were recorded in a preformed form. The LDH ratio of serum to ADA of pleural fluid was calculated. The collected data were entered into SPSS18, using statistical tests were analyzed.
Results: Of the 39 patients,61.5% had cancer and 38.5% had infections. There was a significant relationship between mean pleural ADA and mean ratio of serum LDH to pleural ADA in terms of type of disease. The sensitivity, specificity, positive predictive value and negative predictive value of ratio of serum LDH level to pleural ADA level were 95.8%, 80%, 88.5% and 92.3%, respectively.
Conclusions: Can be concluded that serum LDH /pleural ADA ratio are very consistent with pathological finding and can be used to diagnose of malignancy in exudative pleural effusion.

Keywords: Lactate dehydrogenase, Adenosine deaminase, pleural effusion, malignancy.

Resumen

Antecedentes: En estudios recientes, se ha determinado en cierta medida que la relación entre la lactato deshidrogenasa (LDH) del suero y la adenosina desaminasa (ADA) del líquido pleural tiene un valor diagnóstico en los derrames pleurales malignos. Decidimos estudiar el valor diagnóstico de estas enzimas realizando un estudio más amplio y una mayor relación estadística.
Métodos: Se trata de un estudio descriptivo-analítico que se realizó con un método transversal. El método de muestreo fue censal y se inscribieron 39 pacientes con derrame pleural exudativo. La edad, el sexo, el informe de la biopsia, la LDH sérica y la ADA del líquido pleural se registraron en un formulario elaborado al efecto previamente. Se calculó la relación entre la LDH sérica y la ADA del líquido pleural. Los datos recogidos se introdujeron en el SPSS18 y se analizaron mediante pruebas estadísticas.
Resultados: De los 39 pacientes, el 61,5% tenía cáncer y el 38,5% tenía infecciones. Hubo una relación significativa entre la media de ADA pleural y la media de la relación entre la LDH sérica y la ADA pleural en función del tipo de enfermedad. La sensibilidad, la especificidad, el valor predictivo positivo y el valor predictivo negativo de la relación entre el nivel de LDH sérica y el nivel de ADA pleural fueron del 95,8%, el 80%, el 88,5% y el 92,3%, respectivamente.
Conclusiones: Se puede concluir que la relación LDH sérica / ADA pleural son muy consistentes con el hallazgo patológico y pueden ser utilizados para diagnosticar de malignidad en el derrame pleural exudativo.

Palabras clave: Lactato deshidrogenasa, Adenosina desaminasa, derrame pleural, malignidad.

Introduction

Lactate dehydrogenase (LDH) is an enzyme that is almost present in all living cells. This enzyme plays a significant role in the conversion of lactate to pyruvate and vice versa. It occurs abundantly in blood cells and cardiac muscles. Since the amount of LDH increases with tissue injuries, it is known as an important factor used to assess trauma such as myocardial infarction (MI)[1,2]. Previous studies have shown that LDH can serve as a marker in cancer prognosis. Also, regarding stomach cancer, the incidence of LDH and Vascular endothelial growth factor (VEGF) in the tumor and stroma is rendered as an important factor in cancer prognosis. On the other hand, the LDH rate increases in cellular turnover leading to the use of this enzyme in follow-up of cancer patients[3,4]. Moreover, LDH is used in exploring the rate of pleural fluid absorption and its comparison with serum level to determine whether the fluid accumulated in the pleural space is exudate or transudate[5-7]. Adenosine deaminase (ADA) is an enzyme that plays a role in purine metabolism. The main function of this enzyme in humans is development and maintenance of the immune system, though other physiological roles of the enzyme are not known yet[8,9]. The low rate of ADA may indicate pulmonary inflammation, death of thymus cells, and also reduced T-cells[10,11]. ADA is additionally used in investigating the pleural fluid and ascites fluid in various differential diagnoses[12]. The most common causes of exudative pleural effusions are bacterial infections, cancers (like lung cancer, breast cancer, and lymphoma), viral infections, and pulmonary embolism[13]. The studies conducted so far have relatively demonstrated the role and diagnostic value of LDH alone in exudative pleural effusions indicating its low sensitivity[14]. Nevertheless, recent studies have relatively revealed that the serum LDH to pleural fluid ADA ratio possesses some diagnostic value[15]. Hence, this study investigated the diagnostic value of the proportion of serum LDH to pleural fluid ADA compared to pathology tests in diagnosing cancer in exudative pleural effusions.

Materials and methods

In this descriptive-analytic cross-sectional study, a sample volume of 30 was considered to investigate the patients presenting to Internal Pulmonary Ward and Oncology Ward of Yazd hospitals. A total of 39 patients who qualified for entering the study on the basis of the inclusion criteria, i.e., affliction with exudative pleural effusions, participated in the study. First, the patients were investigated for pleural effusion and the patients with exudative pleural effusion were selected. Then, the patients underwent pleural aspiration to study protein, LDH, albumin, cell counts, ADA, Bacille de Koch (BK), and pathology. If diagnosis could not be established on the basis of these tests, pleural biopsy was done. Along with these tests and on the basis of predetermined goals, serum LDH was also requested. After determining LDH and ADA, the ratio of these two enzymes was estimated. The patients were subsequently divided into cancer and non-cancer patients. The cancer group was, in turn, subdivided into three subgroups of tuberculosis group (diagnosed on the basis of BK), parapneumonic group (on the basis of response to treatment and the appearance of pleura), and miscellaneous causes group (on the basis of exclusion of other causes). The cancer group was subdivided into pulmonary origin subgroup and metastatic subgroup diagnosed on the basis of pleural cytology or biopsy. Next, on the basis of results, the estimated ratio was compared to pathology reports from pleural biopsy which is the standard diagnostic method for differentiating the malignant exudative cases form benign exudative cases. The culled data were analyzed with SPSS20 using Mean±SD, frequencies, Kappa test, and T-test. The best cut-off point was determined by ROC curve (P<0.05).

Results

Our findings showed that of 39 patients with pleural effusion, 24 (61.5%) were affected with cancer and 15 (38.5%) had no cancer. The findings demonstrated that the mean age of the patients under study was 59.94±16.63 years with an age range of 18-86 years, mean serum LDH was 676.74±634.42 IU/L with a range of 131-3345, and the mean ADA level was 29.28±28.06 IU/L with a range of 1-96.8. The results of mean serum LDH level in the samples under study in terms of disease type suggested that the mean serum LDH was 826.75±761.45 in the cancer group and 436.73±199.09 in the non-cancer group (P=0.061) indicating no significant difference in serum LDH level between the two groups. The results of mean pleural ADA level in the samples under study in terms of disease type, cancer type, and non-cancerous diseases are presented in **table I**. The analysis of results using T-test indicated a significant difference in the mean pleural ADA in the samples under study in terms of disease type (cancerous and non-cancerous) and type of cancer (pulmonary and metastatic) (P<0.05).

Table I: Mean pleural ADA in the samples under study in terms of disease type, cancer type, and non-cancerous disease type.

Variables		Frequency	Mean±SD	P-value
Non-cancerous Disease type	Tuberculosis	6	55.33±26.05	0.602
	Miscellaneous causes	5	68.36±23.83	
	Parapneumonic	4	54.75±18.19	
Disease Type	Cancerous	24	114.96±155.17	0.000
	Non-cancerous	15	8.13±4.27	
Cancer Type	Pulmonary	4	6.47±4.54	0.037
	Metastatic	20	11.17±3.73	

The results of the study concerning the mean ratio of serum LDH to pleural ADA (cancer ratio) in the samples under study in terms of disease type, cancer type, and non-cancerous diseases are displayed in **table II**. T-test

Table II: Mean serum LDH to pleural ADA ratio in the samples under study in terms of disease type, cancer type, and non-cancerous disease type.

Variables		Frequency	Mean±SD	P-value
Non-cancerous Disease type	Tuberculosis	6	7.30±2.88	0.635
	Miscellaneous causes	5	7.66±4.41	
	Parapneumonic	4	9.96±6.25	
Disease Type	Cancerous	24	10.38±4.17	0.012
	Non-cancerous	15	59.52±22.74	
Cancer Type	Pulmonary	4	297.74±304.85	0.007
	Metastatic	20	78.41±77.68	

analysis (P<0.05) indicated a significant difference in mean serum LDH to pleural ADA ratio in the samples under study in terms of disease type (cancerous and non-cancerous), and cancer type (pulmonary and metastatic).

Moreover, T-test analysis of results suggested no significant difference in mean serum LDH level in the samples under study in terms of disease type (cancerous and non-cancerous) and non-cancerous disease type, and cancer type (pulmonary and metastatic) (P>0.05). The correspondence between serum LDH to pleural ADA ratio and pathology findings was examined by Kappa test and gave Kappa=0.778 indicating a high correspondence. ROC curve was used to determine the best cut-off point for serum LDH to pleural ADA ratio in diagnosing cancer resulting in AUC=0.981 that is a good value. This value was tested to the power of 0.5 that was significant at P=0.000. This means that the use of serum LDH to pleural ADA index is helpful in cancer diagnosis. Given the sensitivity and specificity values given by the computer, the best cut-off point lied between 13.6 and 14.08; so, we selected 13.5 as the cut-off point in this study. Using the cut-off point obtained in this study, the following diagnostic values of serum LDH to pleural ADA ratio were acquired:

- Sensitivity=95.8%
- Specificity=80%
- Positive predictive value=88.5%
- Negative predictive value=92.3%
- Accuracy=89%

Discussion

There are countless challenges facing various sciences, especially medicine, health and experimental sciences[16-22]. The results of the study by Lee conducted on the serum LDH level in patients with pulmonary cancer showed that the serum LDH level in these patients is directly correlated with the rate of tumor spread in the patients' whole body[23]. These results are not consistent with our findings that there was no significant correlation between mean serum LDH levels in terms of disease type (cancerous and non-cancerous). The difference may be attributed to the difference in the type of tumors under study as our study examined all types of exudative pleural effusions regardless of their type while Lee's study investigated only exudative pleural effusions induced by non-small cell carcinoma. Also, the findings of the study by Hermes carried out on the role of serum LDH level in the remainders of patients with pulmonary cancer of small cell type demonstrated that the serum LDH level serves as an independent and reliable parameter in exploring the patients' survival rate[24]. Another study in 2016 revealed that the LDH to ADA ratio has great diagnostic value in diagnosing exudative effusions[15]. The results of the study above are consistent with the findings by Zhang[14] and Lumachi[25] wherein the serum LDH to pleural ADA ratio showed high correspondence with pathological findings. Besides, the results of the study by Verma (2016), performed on diagnostic value of serum LDH to pleural ADA ratio in differentiating malignant exudatives from tuberculosis, demonstrated that the LDH to ADA ratio is of great diagnostic value in differentiating malignant exudatives from TB[26]. This is consistent with our finding that indicated a significant correlation between mean serum LDH to pleural ADA ratio in terms of disease type (cancerous and non-cancerous). Furthermore, the results of this study showed that the serum LDH level was significantly higher in the malignant cancer group compared to the TB group. Although the LDH level was higher in the malignant cancer group than the infection group, the difference was not statistically significant (P=0.061). The difference may be due to disparities in the groups under study since our study examined all factors of non-cancerous exudative pleural effusions (TB, parapneumonic, and miscellaneous causes) while Verma's study explored merely TB. The study above found a significant correlation between pleural ADA and serum LDH to pleural ADA ratio between the two groups under study which was not consistent with our results. In addition, in the mentioned study, the rates of sensitivity and specificity of serum LDH to pleural ADA ratio were 98% and 94%, respectively, that were greater than those in our study, i.e., 95.8% and 80%, respectively. The difference can be attributed to the differences in sample volumes in the two studies as we investigated 39 patients with exudative pleural effusions whereas Verma explored 987 patients leading to the wide differences in the specificity of the intended index in the two studies. Finally, the study above considered a cut-off point smaller than 20 which was higher than our cut-off point that was 13.5. Moreover, in that study the mean ADA level was significantly higher in the cancer group with pulmonary origin compared to the metastatic cancer group which is not consistent with our study wherein the mean ADA level was higher in the metastatic cancer group. This inconsistency of results may be due to differences in sample volumes in the two studies since the number of samples with cancer of pulmonary origin was less than cancer of metastatic origin.

Conclusion

On the basis of our findings, it may be concluded that the use of serum LDH to pleural ADA index is beneficial

in cancer diagnosis so that it can be used in diagnosing cancers in exudative pleural effusions. The presence of high specificity (95.8%) in the correspondence between serum LDH to pleural ADA ratio and pathological results indicates that the negativity of the index can greatly reject the malignant exudative pleural effusion though, of course, a relatively low specificity (80%) suggests that the positivity of this index is not of much help in diagnosing malignant exudative pleural effusion and shows more false positive results. Ultimately, considering the significant difference in mean serum LDH to pleural ADA ratio in the samples under study in terms of disease type, it may be concluded that this index can be used in differentiating malignant exudative pleural effusion from other miscellaneous non-malignant exudative pleural effusions like infections.

Acknowledgement

The authors give their special thanks to all hospital managers at Yazd who helped them in data collection for this paper.

Interests conflict

The researchers declare that they have no conflict of interest.

References

1. Holmes RS, Goldberg E. Computational analyses of mammalian lactate dehydrogenases: human, mouse, opossum and platypus LDHs. Computational biology and chemistry. 2009;33(5):379-85.

2. Eventoff W, Rossmann MG, Taylor SS, Torff HJ, Meyer H, Keil W, et al. Structural adaptations of lactate dehydrogenase isozymes. Proceedings of the National Academy of Sciences of the United States of America. 1977;74(7):2677-81.

3. Xu HN, Kadlececk S, Profka H, Glickson JD, Rizi R, Li LZ. Is higher lactate an indicator of tumor metastatic risk? A pilot MRS study using hyperpolarized (13) C-pyruvate. Academic radiology. 2014;21(2):223-31.

4. Kim HS, Lee HE, Yang HK, Kim WH. High lactate dehydrogenase 5 expression correlates with high tumoral and stromal vascular endothelial growth factor expression in gastric cancer. Pathobiology : journal of immunopathology, molecular and cellular biology. 2014;81(2):78-85.

5. Heffner JE, Brown LK, Barbieri CA. Diagnostic value of tests that discriminate between exudative and transudative pleural effusions. Primary Study Investigators. Chest. 1997;111(4):970-80.

6. Light RW, Macgregor MI, Luchsinger PC, Ball WC, Jr. Pleural effusions: the diagnostic separation of transudates and exudates. Annals of internal medicine. 1972;77(4):507-13.

7. Joseph J, Badrinath P, Basran GS, Sahn SA. Is the pleural fluid transudate or exudate? A revisit of the diagnostic criteria. Thorax. 2001;56(11):867-70.

8. Wilson DK, Rudolph FB, Quiocho FA. Atomic structure of adenosine deaminase complexed with a transition-state analog: understanding catalysis and immunodeficiency mutations. Science. 1991;252(501):1278-84.

9. Cristalli G, Costanzi S, Lambertucci C, Lupidi G, Vittori S, Volpini R, et al. Adenosine deaminase: functional implications and different classes of inhibitors. Medicinal research reviews. 2001;21(2):105-28.

10. Blackburn MR, Kellems RE. Adenosine deaminase deficiency: metabolic basis of immune deficiency and pulmonary inflammation. Advances in immunology. 2005;86:1-41.

11. Apasov SG, Blackburn MR, Kellems RE, Smith PT, Sitkovsky MV. Adenosine deaminase deficiency increases thymic apoptosis and causes defective T cell receptor signaling. The Journal of clinical investigation. 2001;108(1):131-41.

12. Jimenez Castro D, Diaz Nuevo G, Perez-Rodriguez E, Light RW. Diagnostic value of adenosine deaminase in nontuberculous lymphocytic pleural effusions. The European respiratory journal. 2003;21(2):220-4.

13. Porcel JM, Light RW. Pleural effusions due to pulmonary embolism. Current opinion in pulmonary medicine2008;14(4):337-42.

14. Zhang F, Hu L, Wang J, Chen J, Chen J, Wang Y. Clinical value of jointly detection serum lactate dehydrogenase/pleural fluid adenosine deaminase and pleural fluid carcinoembryonic antigen in the identification of malignant pleural effusion. Journal of clinical laboratory analysis. 2017;31(5).

15. Verma A, Abisheganaden J, Light RW. Identifying Malignant Pleural Effusion by A Cancer Ratio (Serum LDH: Pleural Fluid ADA Ratio). Lung. 2016;194(1):147-53.

16. Rahimi E, Yazdanpour S, Dehkordi FS. Detection of Toxoplasma gondii antibodies in various poultry meat samples using enzyme linked immuno sorbent assay and its confirmation by polymerase chain reaction. J Pure Appl Microbiol. 2014;8(1):421-7.

17. Halaji M, Farahani A, Ranjbar R, Heiat M, Dehkordi FS. Emerging coronaviruses: first SARS, second MERS and third SARS-CoV-2: epidemiological updates of COVID-19. Infez Med. 2020;28(suppl):6-17.

18. Dehkordi FS, Saberian S, Momtaz H. Detection and segregation of Brucella abortus and Brucella melitensis in Aborted Bovine, Ovine, Caprine, Buffaloes and Camelid Fetuses by application of conventional and real-time polymerase chain reaction. The Thai Journal of Veterinary Medicine. 2012;42(1):13.

19. Sheikhshahrokh A, Ranjbar R, Saeidi E, Dehkordi FS, Heiat M, Ghasemi-Dehkordi P, Goodarzi H. Frontier therapeutics and vaccine strategies for sars-cov-2 (COVID-19): A review. Iranian Journal of Public Health. 2020;49(Suppl 1):18.

20. Ranjbar R, Seif A, Dehkordi FS. Prevalence of antibiotic resistance and distribution of virulence factors in the shiga toxigenic Escherichia coli recovered from hospital food. Jundishapur Journal of Microbiology. 2019;12(5):8.

21. Nejat S, Momtaz H, Yadegari M, Nejat S, Safarpour Dehkordi F, Khamesipour F. Seasonal, geographical, age and breed distributions of equine viral arteritis in Iran. Kafkas Univ Vet Fak Derg. 2015;21(1):111-6.

22. Rahi A, Kazemeini H, Jafariaskari S, Seif A, Hosseini S, Dehkordi FS. Genotypic and phenotypic-based assessment of antibiotic resistance and profile of staphylococcal cassette chromosome mec in the methicillin-resistant Staphylococcus aureus recovered from raw milk. Infection Drug Res. 2020;13:273.

23. Lee DS, Park KR, Kim SJ, Chung MJ, Lee YH, Chang JH, et al. Serum lactate dehydrogenase levels at presentation in stage IV non-small cell lung cancer: predictive value of metastases and relation to survival outcomes. Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine. 2016;37(1):619-25.

24. Hermes A, Gatzemeier U, Waschki B, Reck M. Lactate dehydrogenase as prognostic factor in limited and extensive disease stage small cell lung cancer - a retrospective single institution analysis. Respiratory medicine. 2010;104(12):1937-42.

25. Lumachi F, Tozzoli R, Mazza F, Chiara GB, Basso S. 50P Accuracy of serum/pleural fluid lactate dehydrogenase ratio measurement in patients with malignant pleural effusion. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2016;11(4 Suppl):S75-6.

26. Verma A, Dagaonkar RS, Marshall D, Abisheganaden J, Light RW. Differentiating Malignant from Tubercular Pleural Effusion by Cancer Ratio Plus (Cancer Ratio: Pleural Lymphocyte Count). Canadian respiratory journal. 2016;2016:7348239.

eISSN 2255-0569

ORIGINAL

Influence of physical activity and mediterranean diet on the values of different scales of overweight and obesity

Influencia de la actividad física y la dieta mediterránea en los valores de diferentes escalas de sobrepeso y obesidad

Pere Riutord Sbert[1], Bartomeu Riutord Fe[1], Neus Riutord Fe[1], Sebastiana Arroyo Bote[1], Ángel Arturo López González[1], José Ignacio Ramírez Manent[2]

1. ADEMA University School . Palma. Balearic Island. Spain. 2. Balearic Islands Health Service. Balearic Islands. Spain

Corresponding authors
Pere Riutord Sbert
ADEMA University School
Gremi Passamaners, 11 - 2º 07009 - Palma Balearic Islands. Spain
E-mail: pereriutord@gmail.com

Received: 10 - IX - 2021
Accepted: 2 - XI - 2021

doi: 10.3306/AJHS.2022.37.01.21

Abstract

Introduction: Obesity is the most common metabolic disorder in developed society and has a multifactorial origin. In this paper, we assess that affects how the Mediterranean diet and regular physical exercise in the prevalence of obesity in the population studied.
Materials and methods: A descriptive, cross-sectional study was carried out in 1457 workers in the Spanish Mediterranean area to determine the influence of adherence to the Mediterranean diet, assessed with the PREDIMED questionnaire, and physical activity, quantified with the IPAQ questionnaire, on the values of different scales of overweight and obesity.
Results: Most of the overweight and obesity scales and body fat estimation scales analyzed show an improvement in values as the level of physical activity increases, both in men and women. A similar situation is observed with adherence to the Mediterranean diet.
Conclusions: Physical activity and heart-healthy eating improve overweight and obesity-related scales

Keywords: Physical activity, healthy food, mediterranean food, obesity, body fat.

Resumen

Introducción: La obesidad es el trastorno metabólico más frecuente en la sociedad desarrollada y tiene un origen multifactorial. En este trabajo, se evalúa cómo afecta la dieta mediterránea y el ejercicio físico regular en la prevalencia de la obesidad en la población estudiada.
Material y métodos: Se realizó un estudio descriptivo y transversal en 1457 trabajadores del área mediterránea española para determinar la influencia de la adherencia a la dieta mediterránea, evaluada con el cuestionario PREDIMED, y de la actividad física, cuantificada con el cuestionario IPAQ, en los valores de diferentes escalas de sobrepeso y obesidad.
Resultados: La mayoría de las escalas de sobrepeso y obesidad y de estimación de la grasa corporal analizadas muestran una mejora de los valores a medida que aumenta el nivel de actividad física, tanto en hombres como en mujeres. Una situación similar se observa con la adherencia a la dieta mediterránea.
Conclusiones: La actividad física y la alimentación cardiosaludable mejoran las escalas relacionadas con el sobrepeso y la obesidad.

Palabras clave: Actividad física, Alimentación saludable, Alimentación mediterránea, Obesidad, Grasa corporal.

Introduction

It is currently accepted that the main cause of obesity is an energy imbalance between calories ingested and calories expended with exercise and daily activities, resulting in a significant storage of calories in the form of fat[1].

The etiology of obesity is complex and involves multiple factors. It is known that excess weight is not simply due to an increase in food intake, different epidemiological studies have found that there are factors related to obesity. Among them, we can highlight age[2], noting that as we get older, hormonal changes and a less active life will favor it. Also the female sex[3], especially related to pregnancy[4] and menopause[5]. It is common to observe a higher prevalence of obesity in women with polycystic ovary syndrome[6], which prevents correct ovulation. Race[7] also influences the occurrence of obesity, with a higher incidence observed in African-American and Hispanic ethnic groups. Sociocultural factors also play a role in obesity, with people with lower levels of education or income[8] having a higher prevalence, probably related to lower availability to consume healthy foods. Another factor associated with obesity is certain addictive behaviors, especially excessive alcohol consumption[9]. Some studies have assessed the influence of genetics on obesity, concluding that there may be a genetic predisposition that affects the amount of body fat and its distribution[10]. Certain medications[11] such as antidepressants, anticonvulsants, steroids, antipsychotics, oral antidiabetics and beta-blockers can increase weight.

The two factors that have most influenced the increase in obesity have been unhealthy eating and sedentary lifestyles. In the last five decades we have witnessed an increase in fast food and the consumption of foods rich in fats, salt and sugars with the consequent increase in calories. Our society follows a sedentary lifestyle due to the automation of work activities, modern means of transport and increased urban life, which leads to a decrease in the practice of physical exercise.

In view of the above, a study is proposed to assess the influence of healthy eating, represented by the Mediterranean diet, and physical activity on obesity.

Materials and methods

A retrospective and cross-sectional study is carried out in 1584 workers in the Balearic Islands and Valencian Community in companies of different productive sectors during the period between January 2017 and December 2017. Of these 127 are excluded (69 for not accepting to participate and 58 for being under 20 years old) leaving 1457 workers who are the ones finally included in the study, of them 718 are women (mean age 43.30 years) and 739 are men (mean age 46.02 years). The workers were selected from among those who attended periodic occupational medical check-ups.

Inclusion criteria

- Age between 18 and 69 years.
- To be an active worker.
- Belonging to one of the companies collaborating in the study.
- Accepting to participate in the study.

The anthropometric measurements of height and weight, both clinical and analytical, are performed by the health personnel of the different occupational health units participating in the study, after homogenizing the measurement techniques.

To measure weight, which is expressed in kilograms, and height, which is expressed in cm, a scale with measuring rod is used: model SECA 700 with a capacity of 200 kg and 50-gram divisions, which has a SECA 220 telescopic measuring rod with millimetric division and a 60-200 cm interval.

The abdominal waist circumference is measured in cm with a measuring tape: SECA model 20, with an interval of 1-200 cm and millimetric division. The person is placed in a standing position, feet together and trunk erect, abdomen relaxed and upper limbs hanging on both sides of the body. The tape measure is placed parallel to the floor at the level of the last floating rib. Hip circumference: it is measured with a SECA model 200 tape with a measuring interval of 12-200 cm and millimeter division. The same position is adopted as for the waist circumference and the measuring tape is passed horizontally at hip level. The waist/height and waist/hip indices are obtained by dividing the waist circumference by the height and hip circumference respectively. The cut-off point for the former is 0.50 and for the latter 0.85 for women and 0.95 for men.

Blood pressure was measured in the supine position with a calibrated OMRON M3 automatic sphygmomanometer and after 10 minutes of rest. Three measurements are taken at one-minute intervals and the mean of the three is obtained. Blood tests are obtained by peripheral venipuncture after a 12-hour fast. Samples are sent to reference laboratories and processed within 48-72 hours. Automated enzymatic methods are used for blood glucose, total cholesterol and triglycerides. Values are expressed in mg/dl. HDL is determined by precipitation with dextran sulfate Cl2Mg, and values are expressed in mg/dl. LDL is calculated using the Friedewald formula (provided that triglycerides are less than 400 mg/dl). Values are expressed in mg/dl.

Friedewald's formula: LDL= total cholesterol -HDL-triglycerides/5

BMI is calculated by dividing weight by height in meters squared. Obesity is considered to be over 30.

We have used 4 formulas to estimate the percentage of body fat:

- CUN BAE(12) (Clínica Universidad de Navarra Body Adiposity Estimator) The formula is:

-44.988 + (0.503 x age) + (10.689 x gender) + (3.172 x BMI) - (0.026 x BMI2) + (0.181 x BMI x gender) - (0.02 x BMI x age) - (0.005 x BMI2x gender) + (0.00021 x BMI2 x age).

Where male sex equals 0 and female sex equals 1.

The CUN BAE cut-off points for obesity are from 25% in men and 35% in women.

- ECORE-BF1[13] (Equation Córdoba for Estimation of Body Fat) It is calculated by the formula: -97.102 + 0.123 (age) + 11.9 (gender) + 35.959 (LnIMC).

Being male is valued as 0 and female as 1. The same cut-off points as CUN BAE are proposed.

-Palafolls formula[14]. It is calculated as

Men = ([BMI/PA]*10) + BMI. Women = ([BMI/PA]*10) + BMI + 10.

The authors propose the same cut-off points as CUN BAE.

- Deuremberg fat mass index[15].

Fat mass %= 1.2 x (BMI) + 0.23 x (Age in years) - 10.8 x (gender) - 5.4

Women are given a value of 0 and men a value of 1. Obesity is considered to be 25% or more in men and 32% or more in women.

- The normalized weight-adjusted index[16] (NWAI) is calculated by the formula :

(weight/10) - (10 x height) + 10] weight is expressed in kg and height in meters.

- The body adiposity index (BAI)[17] is determined by the formula:

BAI = ((waist circumference)/((height)1.5)-18)

- The abdominal volume index (AVI)[18] is calculated:
AVI=[2 cm (waist)2+0.7 cm (waist-hip)2]/1000

-Visceral adiposity index (VAI)[19]

Females:

$$VAI = \left(\frac{WC}{36{,}58 + (1{,}89 \times BMI)}\right) \times \left(\frac{TG}{0{,}81}\right) \times \left(\frac{1{,}52}{HDL}\right)$$

Males:

$$VAI = \left(\frac{WC}{39{,}68 + (1{,}88 \times BMI)}\right) \times \left(\frac{TG}{1{,}03}\right) \times \left(\frac{1{,}31}{HDL}\right)$$

- Body roundness index (BRI)[20]
BRI = 364.2-365.5x√1-[(WC/(2π)2)/(0.5 x Height)2]

-Body Surface Index (BSI)[21] and Body Surface Area (BSA). w is weight and h is height

$$BSA = w^{0{,}425} * h^{0{,}725} * 0{,}007184$$

$$BSI = \frac{WEIGHT}{\sqrt{BSA}}$$

Body fat was determined by bioelectrical impedance measurement using a Tanita BC-420MA monitor. The Gallagher[22] criteria were used to classify this percentage.

A smoker was considered to be a person who had regularly consumed at least 1 cigarette/day (or the equivalent in other types of consumption) in the last month, or had stopped smoking less than a year ago.

Social class was determined from the 2011 National Classification of Occupations (CNO-11) and based on the proposal made by the social determinants group of the Spanish Society of Epidemiology[23]. We opted for a classification into 3 categories: Class I. Directors/managers, university professionals, athletes and artists. Class II. Intermediate occupations and self-employed workers without employees. Class III. Unskilled workers.

Diet is assessed by means of the "Mediterranean diet adherence questionnaire"[24] which is based on the PREDIMED test and consists of 14 questions rated with 0 or 1 point each. Scores below 9 are considered low adherence and above 9 good adherence.

Physical activity is determined by means of the International Physical Activity Questionnaire (IPAQ)[25]. This is a 7-question self-administered questionnaire that assesses the type of physical activity performed in daily life during the last 7 days.

Statistical analysis

A descriptive analysis of the categorical variables was performed, calculating the frequency and distribution of responses for each of them. For quantitative variables,

the mean and standard deviation were calculated, and for qualitative variables, the percentage was calculated. The bivariate association analysis was performed using the 2 test (with correction of Fisher's exact statistic when conditions required it) and Student's t test for independent samples. For the multivariate analysis, binary logistic regression was used with the Wald method, with calculation of the Odds ratio and the Hosmer-Lemeshow goodness-of-fit test. Statistical analysis was performed with the SPSS 27.0 program, with an accepted statistical significance level of 0.05.

Ethical considerations and aspects

The study was approved by the Clinical Research Ethics Committee of the Illes Balears health area no. IB 4383/20. All procedures were performed in accordance with the ethical standards of the institutional research committee and with the 2013 Declaration of Helsinki. All patients signed written informed consent documents before participating in the study.

Results

The values are generally more unfavorable in males. The characteristics of the sample are presented in **table I**.

Most of the overweight and obesity scales analyzed show an improvement in the mean values as the level of physical activity increases; this situation is observed in both men and women. The complete data are presented in **table II**.

Something similar to that observed with physical activity occurs with the Mediterranean diet, such that those persons, both men and women, with high adherence to

Table I: Characteristics of the population.

	Women (n=718) mean (SD)	Men (n=739) mean (SD)	Total (n=1457) mean (SD)	p-value
Age (years)	43.30 (8.44)	46.02 (8.50)	44.68 (8.57)	<0.0001
Height (kg)	66.29 (12.29)	82.24 (13.81)	74.38 (15.32)	<0.0001
weight (m)	1.62 (0.06)	1.73 (0.07)	1.68 (0.09)	<0.0001
BMI (kg/m²)	25.36 (4.61)	27.40 (4.13)	26.39 (4.49)	<0.0001
Waist (cm)	89.44 (16.36)	97.00 (10.65)	93.27 (14.27)	<0.0001
Hip (cm)	105.78 (13.22)	108.77 (10.27)	107.29 (11.91)	<0.0001
Systolic Blood Pressure (mm Hg)	121.31 (17.05)	133.76 (18.11)	127.62 (18.66)	<0.0001
Diastolic Blood Pressure (mm Hg)	75.03 (10.58)	80.63 (11.43)	77.87 (11.36)	<0.0001
Cholesterol (mg/dl)	186.02 (31.14)	183.37 (31.72)	184.67 (31.46)	0.108
HDL (mg/dl)	60.18 (13.55)	49.83 (12.16)	54.93 (13.86)	<0.0001
LDL (mg/dl)	107.88 (28.16)	108.94 (29.15)	108.42 (28.66)	0.483
Triglycerides (mg/dl)	86.57 (43.59)	119.55 (87.42)	103.30 (71.28)	<0.0001
Glycaemia (mg/dl)	92.16 (16.31)	98.68 (19.54)	95.47 (18.30)	<0.0001
	Percentage	Percentage	Percentage	p-value
<35 years	16.71	10.42	13.52	<0.0001
35-49 years	57.80	51.01	54.36	
≥ 50 years	25.49	38.57	32.12	
Social class I	18.94	8.80	13.80	<0.0001
Social class II	63.65	82.67	73.30	
Social class III	17.41	8.53	12.90	
No tobacco	71.87	72.94	72.41	<0.0001
Yes tobacco	28.13	27.06	27.59	
MET low	23.68	19.08	21.35	<0.0001
MET moderate	48.05	36.4	42.14	
MET high	28.27	44.52	36.51	
Predimed low	36.49	48.17	42.42	<0.0001
Predimed high	63.51	51.83	57.58	

Table II: Mean values of the different overweight-obesity scales according to physical activity by gender.

	Women				Men			
	MET low n=170	MET moderate n=345	MET high n=203		MET low n=141	MET moderate n=269	MET high n=329	
	mean (SD)	mean (SD)	mean (SD)	p-value	mean (SD)	mean (SD)	mean (SD)	p-value
Waist to height ratio	0.56 (0.09)	0.55 (0.11)	0.55 (0.10)	0.157	0.58 (0.06)	0.56 (0.07)	0.55 (0.06)	<0.0001
Waist to hip ratio	0.85 (0.07)	0.83 (0.08)	0.85 (0.09)	ns	0.90 (0.05)	0.89 (0.06)	0.89 (0.06)	ns
Normalized weight adjusted index	0.73 (1.12)	0.45 (1.27)	0.24 (1.16)	<0.0001	1.34 (1.39)	0.91 (1.26)	0.71 (1.11)	<0.0001
Body adiposity index	21.28 (7.17)	20.71 (7.19)	20.93 (6.23)	ns	18.29 (5.74)	18.83 (5.64)	17.40 (6.47)	<0.0001
Abdominal volume index	16.76 (4.98)	16.76 (6.39)	16.76 (6.39)	ns	20.37 (4.55)	19.28 (4.29)	18.56 (3.90)	<0.0001
Visceral adiposity index	1.69 (1.43)	1.31 (0.88)	1.22 (0.86)	<0.0001	2.08 (1.72)	1.65 (1.35)	1.32 (1.09)	<0.0001
Body surface index	39.08 (2.98)	38.19 (3.47)	37.71 (3.21)	<0.0001	42.31 (3.38)	41.19 (3.14)	40.74 (2.81)	<0.0001
Body mass index	26.38 (4.20)	25.34 (4.88)	24.55 (4.31)	<0.0001	28.85 (4.58)	27.42 (4.19)	26.75 (3.70)	<0.0001
Deuremberg formula	36.70 (5.76)	34.90 (6.63)	33.71 (5.75)	<0.0001	29.30 (6.01)	27.54 (5.77)	26.16 (5.36)	<0.0001
Palafolls formula	39.37 (4.39)	38.20 (4.96)	37.31 (4.40)	<0.0001	31.73 (4.76)	30.23 (4.35)	29.56 (3.84)	<0.0001
CUN BAE	37.68 (5.65)	35.77 (6.45)	34.67 (5.89)	<0.0001	29.28 (5.82)	27.39 (5.77)	26.23 (5.33)	<0.0001
ECORE-BF	37.64 (5.91)	35.72 (6.77)	34.56 (6.03)	<0.0001	29.19 (5.68)	27.36 (5.68)	26.25 (5.18)	<0.0001
Body roundness index	5.15 (1.97)	5.12 (2.47)	5.10 (2.18)	ns	5.47 (1.39)	5.20 (1.48)	4.95 (1.29)	<0.0001
Body fat bioimpedance	35.76 (8.53)	34.33 (10.63)	33.17 (9.63)	<0.0001	32.29 (8.10)	30.41 (7.80)	28.61 (8.27)	<0.0001
Visceral fat bioimpedance	9.46 (3.17)	8.60 (3.98)	8.03 (3.41)	<0.0001	16.54 (6.47)	14.98 (5.88)	13.22 (6.06)	<0.0001

this type of diet have better values on the overweight and obesity scales. All the data are shown in **table III**.

As was the case with the mean values, the prevalence of altered values of overweight and obesity scales decreased in parallel with the increase in the level of physical activity, and this was observed in both women and men. The prevalence of high values of these scales also presents better results in those people with high adherence to the Mediterranean diet as shown in **table IV**.

In the multivariate analysis using binary logistic regression, male, age 50 years and older, smokers, social class II-III, MET low-moderate and low adherence to Mediterranean diet were established as covariates. Gender, age and social class are the only variables that show influence in all the scales analyzed. Of these, the one showing the greatest influence is social class, with odds ratios ranging from 1.98 (95% CI 1.42-2.75) for CUN BAE and 9.92 (95% CI 6.92-14.24) for Waist to height ratio high. All results are presented in **table V**.

Table III: Mean values of the different overweight-obesity scales according to healthy food by gender.

	Women			Men		
	Predimed low n=262	Predimed high n=456		Predimed low n=356	Predimed high n=383	
	mean (SD)	mean (SD)	p-value	mean (SD)	mean (SD)	p-value
Waist to height ratio	0.58 (0.10)	0.54 (0.11)	<0.0001	0.57 (0.06)	0.56 (0.07)	ns
Waist to hip ratio	0.86 (0.08)	0.83 (0.08)	<0.0001	0.90 (0.06)	0.89 (0.06)	ns
Normalized weight adjusted index	0.65 (1.17)	0.35 (1.23)	<0.0001	1.02 (1.33)	0.80 (1.15)	<0.0001
Body adiposity index	21.72 (6.60)	20.44 (7.06)	<0.0001	18.08 (6.05)	18.09 (6.10)	ns
Abdominal volume index	17.87 (5.88)	16.12 (5.89)	<0.0001	19.57 (4.31)	18.80 (4.10)	<0.0001
Visceral adiposity index	1.50 (1.14)	1.30 (0.98)	<0.0001	1,74 (1.50)	1.44 (1.19)	<0.0001
Body surface index	38.70 (3.26)	38.02 (3.33)	ns	41.51 (3.30)	40.92 (2.87)	ns
Body mass index	26.03 (4.42)	24.98 (4.68)	<0.0001	27.78 (4.40)	27.04 (3.83)	<0.0001
Deuremberg formula	35.68 (6.01)	34.60 (6.40)	<0.0001	27.64 (6.06)	26.91 (5.43)	<0.0001
Palafolls formula	38.85 (4.58)	37.86 (4.78)	<0.0001	30.60 (4.58)	29.86 (3.97)	<0.0001
CUN BAE	36.80 (6.07)	35.40 (6.22)	<0.0001	27.67 (5.97)	26.83 (5.40)	<0.0001
ECORE-BF	36.75 (6.26)	35.32 (6.52)	<0.0001	27.63 (5.82)	26.83 (5.29)	<0.0001
Body roundness index	5.59 (2.23)	4.89 (2.27)	ns	5.24 (1.36)	5.05 (1.42)	<0.0001
Body fat bioimpedance	36.35 (8.92)	33.19 (10.28)	<0.0001	31.26 (8.36)	28.77 (7.82)	<0.0001
Visceral fat bioimpedance	8.96 (3.82)	9.09 (3.65)	ns	15.01 (6.69)	13.82 (5.58)	<0.0001

Table IV: Prevalence of altered values of the different overweight-obesity scales according to physical activity and Mediterranean diet by gender.

	Women				Men			
	MET low n=170	MET moderate n=345	MET high n=203		MET low n=141	MET moderate n=269	MET high n=329	
	Percentage	Percentage	Percentage	p-value	Percentage	Percentage	Percentage	p-value
Waist to height ratio high	68.24	65.80	63.46	<0.0001	87.23	83.27	79.64	<0.0001
Waist to hip ratio high	46.47	44.96	43.74	<0.0001	14.18	13.01	12.37	<0.0001
BMI obesity	17.65	15.36	6.40	<0.0001	31.21	23.05	16.41	<0.0001
CUN BAE obesity	68.24	51.30	44.83	<0.0001	76.60	65.43	57.14	<0.0001
ECORE-BF obesity	67.06	50.43	43.35	<0.0001	76.57	65.41	57.75	<0.0001
Deuremberg formula obesity	80.00	62.61	58.13	<0.0001	78.72	66.17	54.41	<0.0001
Palafolls formula obesity	85.88	73.63	68.47	<0.0001	95.74	91.82	91.19	<0.0001
Body fat bioimpedance very high	36.47	35.94	28.57	<0.0001	56.03	51.67	41.95	<0.0001
	Women				Men			
	Predimed low n=262	Predimed high n=456			Predimed low n=356	Predimed high n=383		
	Percentage	Percentage	p-value		Percentage	Percentage	p-value	
Waist to height ratio high	78.62	60.96	<0.0001		83.71	81.20	<0.0001	
Waist to hip ratio high	45.42	44.08	<0.0001		14.32	13.48	<0.0001	
BMI obesity	17.18	11.18	<0.0001		25.56	18.02	<0.0001	
CUN BAE obesity	58.78	50.44	<0.0001		65.45	62.40	<0.0001	
ECORE-BF obesity	57.63	49.34	<0.0001		65.45	62.92	<0.0001	
Deuremberg formula obesity	69.47	63.16	<0.0001		63.48	63.19	<0.0001	
Palafolls formula obesity	79.01	72.81	<0.0001		92.70	91.91	<0.0001	
Body fat bioimpedance very high	38.93	31.14	<0.0001		56.46	40.47	<0.0001	

Table V: Logistic regression analysis.

	Male	Age ≥50 years	Smokers	MET low-moderate	Predimed low	social class II-III
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Waist to height ratio high	1.59 (1.21-2.11)	3.90 (2.71-5.59)	ns	ns	1.56 (1.17-2.07)	9.92 (6.92-14.22)
Waist to hip ratio high	0.13 (0.10-0.17)	1.36 (1.04-1.79)	1.39 (1.06-1.83)	ns	ns	8.23 (4.90-13.82)
BMI obesity	1.72 (1.28-2.30)	1.69 (1.27-2.25)	0.67 (0.48-0.93)	2.06 (1.49-2.84)	1.54 (1.16-2.04)	2.03 (1.22-3.40)
CUN BAE obesity	1.31 (1.04-1.65)	4.32 (3.29-5.67)	ns	1.54 (1.22-1.96)	1.27 (1.01-1.60)	1.98 (1.42-2.75)
ECORE-BF obesity	1.44 (1.14-1.81)	3.99 (3.05-5.20)	ns	1.57 (1.24-1.99)	ns	2.07 (1.49-2.86)
Deuremberg formula obesity	0.66 (0.52-0.85)	9.85 (6.90-14.06)	ns	1.73 (1.35-2.22)	ns	2.71 (1.94-3.79)
Palafolls formula obesity	3.66 (2.63-5.11)	1.85 (1.27-2.69)	0.66 (0.48-0.92)	1.67 (1.22-2.30)	ns	2.80 (1.93-4.04)
Body fat bioimpedance very high	1.58 (1.26-1.99)	1.91 (1.51-2.42)	0.77 (0.60-0.99)	1.57 (1.23-2.00)	1.59 (1.27-1.99)	4.40 (2.88-6.73)

Discussion

All the overweight and obesity scales and body fat estimation scales analyzed in this study showed mean values that improved as the level of physical activity increased; this improvement was also observed in persons with high adherence to the Mediterranean diet. When the prevalence of obesity was assessed with all the scales, a similar trend was observed. In the multivariate analysis, the level of physical activity increased the risk of presenting obesity more than adherence to the Mediterranean diet and it was observed that both variables did not increase the risk in all the scales.

The review of the existing scientific literature shows that most studies find a relationship between the level of physical activity and/or adherence to the Mediterranean diet with the values of the scales related to overweight and obesity. In general, better values are observed in people with high levels of physical activity or healthy eating.

We have found a study that evaluates, as we do, the impact of physical activity determined with the IPAQ questionnaire and the Mediterranean diet with a large number of obesity-related scales (BMI, waist circumference, waist/height index, tightness index, body roundness index, body shape index and equations to estimate the percentage of body fat such as CUN BAE and Deuremberg), this work performed in 6672 middle-aged subjects with low to moderate cardiovascular risk belonging to the Ilerda Vascular (ILERVAS) project[26] showed that, independent of sex, lower physical activity indices were associated with higher values of total body fat and central adiposity. This result was consistent and independent of the indices used to estimate adiposity. However, the association between adherence to the Mediterranean diet and obesity indices was much less marked and more sex-dependent than that observed for physical activity. These results are in general very similar to those obtained by us.

In the rest of the studies we have analyzed, the number of overweight and obesity scales included is much lower than those presented in our work.

To compare our results with those obtained in other studies, we will separate those studies that evaluate the impact of physical activity from those that evaluate the effect of healthy eating on overweight and obesity scales. Other studies have also obtained results similar to ours: an investigation in 528 adults between 30 and 80 years of age with type 2 diabetes related waist circumference values to physical activity determined with accelerometers, measurements were taken at baseline and at 6 months and it was observed that each hour of sedentary activity was associated with an increase of 1.89 cm in waist circumference[27]. Along the same lines are the results of a cohort from the PREDIMED Plus study with a high degree of cardiovascular disease, in which it was observed that more time spent in moderate or vigorous physical activity and less time spent in sedentary behaviors was inversely associated with the prevalence of obesity and some components of the metabolic syndrome[28]. Along the same lines, the 2003-2006 National Health and Nutrition Examination Survey of the United States found that moderate or vigorous physical activity determined with an accelerometer was strongly and negatively associated with BMI and waist circumference[29]. Other studies follow the same pattern, as in a group of 138 sedentary, postmenopausal Colombian women who participated in a program of controlled physical activity with sessions of one hour three times a week for four months, observed a decrease of 1.2 kg of weight and 2.0 kg of body fat at the end of the program[30]. More recently, other authors[31] demonstrated in 298 overweight adults that moderate to vigorous physical activity was inversely associated with the percentage of body fat and visceral adipose tissue assessed by DXA. In this study, the inverse relationship between physical activity and body fat percentage was stronger for non-Latinos than for Latinos, a fact that introduces the possibility that differences in diet and eating habits may modulate the impact of physical activity on anthropometric indices. All these studies show, like ours, the beneficial effect of physical activity on excess weight and body fat.

Some research presents somewhat different results to those seen so far, for example a study that analyzed data from North American adults from the National Health and Nutrition Survey between the years 1988 and 2010 where the relationship between BMI and waist circumference with physical activity and diet was evaluated showed that there was a decrease in the two parameters in people who performed physical activity compared to those who did not, however, found no relationship with diet[32].

Several studies showed that physical activity did not improve all parameters related to overweight and obesity: the first, conducted in a group of Chilean women over 60 years old, analyzed the impact of a 12-week physical exercise program on different anthropometric parameters and saw that there was a significant decrease in waist circumference and waist/hip ratio and that the same did not occur with BMI[33].

When we evaluated the effect of adherence to the Mediterranean diet on overweight and obesity scales, we found that some randomized clinical trials and meta-analyses support that physical activity added to dietary intervention further improves the amount of weight loss achieved[34]. Other research has found that high adherence to the Mediterranean diet has been associated with weight loss and reduced long-term weight gain if energy restriction is present[35]. However other authors have presented conflicting results between high adherence to

the Mediterranean diet and weight changes[36]. A possible explanation would be that the amount of calories from the components of the Mediterranean diet (olive oil, whole grains and nuts), prevented finding differences in obesity rates in the high adherence categories included in the ILERVAS trial, as they possibly did not reach a negative energy balance26. Perhaps the traditional nutritional pattern that characterizes high adherence to the Mediterranean diet may exert its effect through different pathophysiological mechanisms unrelated to weight loss, such as improving the lipid profile, modulating inflammation, improving its antioxidant properties, and reducing blood pressure and insulin resistance, among others[37].

As strengths of this study we find the high sample size, almost 1500 people, the significant number of scales of overweight, obesity and body fat estimation analyzed (15 scales) and that both physical activity and adherence to the Mediterranean diet have been assessed with validated scales such as IPAQ and PREDIMED.

The main limitation of this study is that it was carried out in a very specific geographical area, which prevents us from extrapolating our results to other countries.

Conclusions

The increase in physical activity levels determined with the IPAQ questionnaire and the increase in adherence to the Mediterranean diet assessed with the PREDIMED questionnaire improve all scales of overweight, obesity and body fat in spanish mediterranean population.

Interests conflict

The researchers declare that they have no conflict of interest.

References

1. World Health Organization. Obesity and overweight. Available at: https://www.who.int/es/news-room/fact-sheets/detail/obesity-and-overweight

2. Hajian-Tilaki KO, Heidari B. Prevalence of obesity, central obesity and the associated factors in urban population aged 20-70 years, in the north of Iran: a population-based study and regression approach. Obes Rev 2007;8(1):3-10.

3. Geer EB, Shen W. Gender differences in insulin resistance, body composition, and energy balance. Gend Med 2009;6 (Suppl 1):60-75.

4. Koch E, Bogado M, Araya F, Romero T, Díaz C, Manriquez L, et al. Impact of parity on anthropometric measures of obesity controlling by multiple confounders: a cross-sectional study in Chilean women. J Epidemiol Community Health 2008;62(5):461-70.

5. Yoo KY, Kim H, Shin HR, Kang D, Ha M, Park SK, et al. Female sex hormones and body mass in adolescent and postmenopausal Korean women. J Korean Med Sci 1998;13(3):241-6.

6. Naderpoor N, Shorakae S, Joham A, Boyle J, De Courten B, Teede HJ. Obesity and polycystic ovary syndrome. Minerva Endocrinol 2015;40(1):37-51.

7. Petersen R, Pan L, Blanck HM. Racial and Ethnic Disparities in Adult Obesity in the United States: CDC's Tracking to Inform State and Local Action. Prev Chronic Dis 2019;16:180579

8. Hajian-Tilaki KO, Heidari B, Association of educational level with risk of obesity and abdominal obesity in Iranian adults. Journal of Public Health 2010;32 (2):202-9

9. Xu X, Zhou M, Gao RQ, Guo Y, Tian XC, Bian Z, et al. Study on correlation between alcohol consumption and obesity in adults in China. Zhonghua Liu Xing Bing Xue Za Zhi 2019 10;40(7):759-64.

10. Golden A, Kessler C. Obesity and genetics. J Am Assoc Nurse Pract 2020;32(7):493-6.

11. Welcome A. Medications That May Increase Weight Available at: https://obesitymedicine.org/medications-that-cause-weight-gain

12. Gómez-Ambrosi J, Silva C, Catalán V, Rodríguez A, Galofré JC, Escalada J, et al. Clinical usefulness of a new equation for estimating body fat. Diabetes Care 2012;35(2):383-8.

13. Molina-Luque R, Romero-Saldaña M, Álvarez-Fernández C, Bennasar-Veny M, Álvarez-López Á, Molina-Recio G. Equation Córdoba: A Simplified Method for Estimation of Body Fat (ECORE-BF). Int J Environ Res Public Health 2019;16(22):4529.

14.Mill-Ferreyra E, Cameno-Carrillo V, Saúl-Gordo H, Camí-Lavado MC. Estimation of the percentage of body fat based on the body mass index and the abdominal circumference: Palafolls Formula. Semergen 2019;45(2):101-8.

15.Deurenberg P, Wetstrate JA, Seidell JC. Body mass index as a measure of body fatness: age- and sex- specific prediction formulas. Br J Nutr 1991; 65: 105-14.

16. Doménech-Asensi G, Gómez-Gallego C, Ros-Berruezo G, García-Alonso FJ, Canteras-Jordana M. Critical overview of current anthropometric methods in comparison with a new index to make early detection of overweight in Spanish university students: the normalized weight-adjusted index. Nutr Hosp 2018;35:359-67

17. López AA, Cespedes ML, Vicente T, Tomas M, Bennasar-Veny M, et al. Body Adiposity Index Utilization in a Spanish Mediterranean Population: Comparison with the Body Mass Index. PLoS ONE 2012; 7(4): e35281

18. Guerrero-Romero F, Rodríguez-Morán M. Abdominal volume index. An anthropometry-based index for estimation of obesity is strongly related to impaired glucose tolerance and type 2 diabetes mellitus. Arch Med Res. 2003 Sep-Oct;34(5):428-32

19. Amato M, Giordano C, Galia M, Criscimanna A, Vitabile S, BSC, Midiri M, et al. Visceral Adiposity Index A reliable indicator of visceral fat function associated with cardiometabolic risk. Diabetes Care. 2010;33(4):920-2

20. Rico-Martín S, Calderón-García JF, Sánchez-Rey P, Franco-Antonio C, Martínez Alvarez M, Sánchez Muñoz-Torrero JF. Effectiveness of body roundness index in predicting metabolic syndrome: A systematic review and meta-analysis. Obes Rev. 2020;21(7): e13023

21. Shirazu I , Sackey TH A, Tiburu EK , Mensah YB , Forson A. The use of Body Surface Index as a Better Clinical Health indicators compare to Body Mass Index and Body Surface Area for Clinical Application. Int. J. S. Res. Sci. Engg. Technol. 2018; 4(11): 131-6

22. Gallagher D, Heymsfield SB, Heo M, Jebb SA, Murgatroyd PR, Sakamoto Y. Healthy percentage body fat ranges: an approach for developing guidelines based on body mass index. Am J Clin Nutr. 2000;72(3):694-701.

23. Domingo-Salvany A, Bacigalupe A, Carrasco JM, Espelt A, Ferrando J, Borrell C. Propuesta de clase social neoweberiana y neomarxista a partir de la Clasificación Nacional de Ocupaciones 2011. Gac Sanit 2013;27(3):263-72

24. Miró Ò, Martín-Sánchez FJ, Jacob J, Andueza JA, Herrero P, Llorens P. Valoración del grado de adherencia a la dieta mediterránea en pacientes con insuficiencia cardiaca: Estudio DIME-EAHFE. Anales del Sistema Sanitario de Navarra 2016;39(2): 261-8

25. Seron P, Muñoz S, Lanas F. Nivel de actividad física medida a través del cuestionario internacional de actividad física en población Chilena. Rev Med Chile 2010;138(10):1232-9.

26. Sánchez M, Sánchez E, Hernández M, González J, Purroy F, Rius F, et al. Dissimilar Impact of a Mediterranean Diet and Physical Activity on Anthropometric Indices: A Cross-Sectional Study from the ILERVAS Project. Nutrients. 2019;11(6):1359

27. Cooper AR, Sebire S, Montgomery AA, Peters TJ, Sharp DJ, Jackson N, et al. Sedentary time, breaks in sedentary time and metabolic variables in people with newly diagnosed type 2 diabetes. Diabetologia 2012;55:589-99.

28. Rosique-Esteban N, Díaz-López A, Martínez-González MA, Corella D, Goday A, Martínez JA, et al. Leisure-time physical activity, sedentary behaviors, sleep, and cardiometabolic risk factors at baseline in the PREDIMED-PLUS intervention trial: A cross-sectional analysis. PLoS ONE. 2017;12:e0172253.

29. Wolff-Hughes DL, Fitzhugh EC, Bassett DR, Churilla JR. Total activity counts and bouted minutes of moderate-to-vigorous physical activity: Relationships with cardiometabolic biomarkers using 2003–2006 NHANES. J. Phys. Act Health. 2015;12:694-700

30. Restrepo-Calle MT, Monroy de Peña A, Pérez-Giraldo J, Velásquez Echeverri MC. Efecto de la actividad física controlada sobre la composición corporal de mujeres sedentarias posmenopáusicas. Rev Panam Salud Publica/ Pan Am J Public Health 2003; 14(4):229-34

31. Cameron N, Godino J, Nichols JF, Wing D, Hill L, Patrick K. Associations between physical activity and BMI, body fatness, and visceral adiposity in overweight or obese Latino and non-Latino adults. Int. J. Obes. 2017;41:873-7.

32. Ladabaum U, Mannalithara A, Myer PA, Singh G. Obesity, abdominal obesity, physical activity, and caloric intake in US adults: 1988 to 2010. Am. J. Med 2014; 127:717-27

33. Araya S, Padial P, Feriche B, Gálvez A, Pereira J, Mariscal-Arcas M, et al. Incidencia de un programa de actividad física sobre los parámetros antropométricos y la condición física en mujeres mayores de 60 años. Nutr. Hosp 2012;27(5):1472-9

34. Goodpaster BH, DeLany JP, Otto AD, Kuller L, Vockley J, South-Paul JE, et al. Effects of diet and physical activity interventions on weight loss and cardiometabolic risk factors in severely obese adults: A randomized trial. JAMA. 2010;304:1795-802

35. Ulian MD, Aburad L, da Silva Oliveira MS, Poppe ACM, Sabatini F, Perez I, et al. Effects of health at every size interventions on health-related outcomes of people with overweight and obesity: A systematic review. Obes. Rev. 2018;19:1659-66.

36. Anton SD, Hida A, Heekin K, Sowalsky K, Karabetian C, Mutchie H, et al. Effects of Popular Diets without Specific Calorie Targets on Weight Loss Outcomes: Systematic Review of Findings from Clinical Trials. Nutrients. 2017;9:822.

37. Salas-Salvadó J, Becerra-Tomás N, García-Gavilán JF, Bulló M, Barrubés L. Mediterranean diet and cardiovascular disease prevention: What do we know? Prog. Cardiovasc. Dis. 2018;61:62-7

eISSN 2255-0569

ORIGINAL

Antimicrobial resistance properties of *Helicobacter pylori* strains isolated from dental plaque and saliva samples

Propiedades de resistencia antimicrobiana de cepas de Helicobacter pylori aisladas de muestras de placa dental y saliva

Amirhossein Fathi[1], Ashkan Salehi[2]

1. Dental Material Research Center, Department of Prosthodontics, Isfahan University of Medical Sciences, Isfahan, Iran
2. Department of Dentistry, University of Traditional Medicine of Armenia (UTMA), Armenia

Corresponding authors
Ashkan Salehi
Department of Dentistry, University of Traditional Medicine of Armenia (UTMA), Armenia
E-mail: ashkansalehip@gmail.com

Received: 13 - IX - 2021
Accepted: 7 - XI - 2021

doi: 10.3306/AJHS.2022.37.01.29

Abstract

Background: It is likely that oral cavity, particularly dental plaque and saliva samples, may represent an important reservoir of *H. pylori* infection for gastric infections. The present research was performed to assess the distribution and antimicrobial resistance of *H. pylori* strains in dental plaque and saliva samples.
Methods: A total of 80 *H. pylori* strains were isolated from dental plaque (n= 42) and saliva (n= 38) samples of patients referred to the Dental Clinic of the Armenia for routine check-ups. *H. pylori* was isolated using culture. Antimicrobial resistance was determined using disk diffusion.
Results: Twenty-two out of 80 (27.50%) examined specimens were positive for *H. pylori*. *H. pylori*ori prevalence amongst dental plaque and saliva samples was 33.33% and 21.05%, respectively (P <0.05). H. pylori strains harbored the high prevalence of resistance against ampicillin (77.27%), amoxicillin (72.22%), erythromycin (68.18%), and tetracycline (68.18%), Resistance rate toward metronidazole was lower than other antimicrobials (40.90%).
Conclusion: The role of dental plaque and saliva samples as H. pylori reservoirs was determined. Due to the high antimicrobial resistance of isolates against ampicillin, amoxicillin, erythromycin, tetracycline, and even metronidazole, there is a big demand for substitute antimicrobials for the oral colonized *H. pylori*.

Keywords: Helicobacter pylori, dentalplaque, saliva, prevalence, antimicrobial resistance.

Resumen

Antecedentes: Es probable que la cavidad oral, en particular la placa dental y las muestras de saliva, puedan representar un importante reservorio de *H. pylori* para las infecciones gástricas. La presente investigación se realizó para evaluar la distribución y la resistencia antimicrobiana de las cepas de *H. pylori* en la placa dental y las muestras de saliva.
Métodos: Se aislaron un total de 80 cepas de *H. pylori* de muestras de placa dental (n= 42) y saliva (n= 38) de pacientes remitidos a la Clínica Dental de Armenia para revisiones rutinarias. El *H. pylori* se aisló mediante cultivo. La resistencia a los antimicrobianos se determinó mediante difusión en disco.
Resultados: Veintidós de las 80 muestras examinadas (27,50%) fueron positivas para *H. pylori*. La prevalencia de *H. pylori* en las muestras de placa dental y saliva fue del 33,33% y el 21,05%, respectivamente (P <0,05). Las cepas de *H. pylori* presentaban una alta prevalencia de resistencia a la ampicilina (77,27%), la amoxicilina (72,22%), la eritromicina (68,18%) y la tetraciclina (68,18%).
Conclusión: Se determinó el papel de las muestras de placa dental y saliva como reservorios de *H. pylori*. Debido a la elevada resistencia antimicrobiana de los aislados frente a la ampicilina, la amoxicilina, la eritromicina, la tetraciclina e incluso el metronidazol, existe una gran demanda de antimicrobianos sustitutivos para el *H. pylori* colonizado por vía oral.

Palabras clave: Helicobacter pylori, placa dental, saliva, prevalencia, resistencia antimicrobiana.

Introduction

The oral cavity is the primary way for the entrance of foods into the body. As the oral cavity is the entry port and first component of the gastrointestinal system, researchers have been interested in the presence of some kinds of bacteria in this niche[1]. Both dental plaque and saliva samples can be infected with diverse kinds of bacteria responsible for digestive infections and disorders[2]. There are a few studies in the literature claiming to have isolated the *Helicobacter pylori* (*H. pylori*) from dental plaque and saliva samples[3].

Helicobacter pylori (*H. pylori*) is a microaerophilic and coccoid, and spiral bacterium recognized as a reason of gastric adenocarcinoma, peptic ulcer disease, duodenal ulcer, type B gastritis, and B-cell lymphoma[4-7]. Even though the human stomach is considered the main *H. pylori* reservoir[8], it was routinely identified in the oral cavity, particularly dental plaques, saliva, tongue, root canals, tonsil tissue, and oral mucosa[9]. It has been suggested that the *H. pylori* fermenting carbohydrates in food produce a low pH in the oral cavity, and this microaerophilic acidic environment with an average oral temperature of 35-37°C can be ideal for its growth and survival[10,11].

Infections caused by *H. pylori* are mainly treated with antimicrobial therapies[12]. However, recent surveys have shown the high *H. pylori* resistance rate toward commonly prescribed antimicrobial agents[13]. In this regard, the highest resistance rate was observed against specific antimicrobials and choices of the oral and gastrointestinal infections, particularly ampicillin, amoxicillin, metronidazole and clarithromycin[14,15]. Changes in the antimicrobial administration and prescription caused severe changes in the *H. pylori's* resistance pattern during the time[16]. Thus, it is essential to assess the antimicrobial resistance of *H. pylori* strains to determine the exact bacterial manner and antimicrobial choices.

Rendering to the uncertain role of dental plaque and saliva samples as a reservoir of antibiotic-resistant H. pylori strains, the present survey was aimed to assess the antimicrobial resistance of *H. pylori* strains isolated from dental plaque and saliva samples of patients referred to the Armenia dental clinics for the routine check-up.

Materials and methods

Samples

From January 2020 to March 2021, a total of 80 H. pylori strains were isolated from dental plaque (n=42) and saliva (n=38) samples of patients referred to the Dental Clinic of the Armenia for routine check-ups.

H. pylori isolation and identification

The dental plaque and saliva specimens from each patient was cultured into a sterile tube containing 5% sheep blood agar, chocolate agar, and a selective medium and transported to the microbiology laboratory to be incubated microaerophically (5% oxygen, 85% nitrogen, and 10% CO_2) using the MART system (MART system, Lichtenvoorde, The Netherland) at a temperature of 37°C for seven days. Culture media were supplemented with 5% of horse serum (Sigma, St. Louis, MO, USA), nalidixic acid (30 mg/L), vancomycin (10 mg/L), cycloheximide (100 mg/L), and trimethoprim (30 mg/L) (Sigma, St. Louis, MO, USA). Suspected colonies were then identified using Gram stain, motility, colony morphology, and biochemical tests such as urease, oxidase, and catalase tests. For comparison, a reference strain of *H. pylori* (ATCC 43504) was employed[17].

Antimicrobial resistance

Mueller–Hinton agar (Merck, Germany) assessed antibiotic resistance patterns using the simple disk diffusion technique. Antibiotic resistance profile of *H. pylori* bacteria was researched toward different antibiotic against (Oxoid, UK) using the guidelines of previous research[18] and also those of Performance Standards for Antimicrobial Susceptibility Testing- Clinical and Laboratory Standards Institute - NCCLS, 2007[19]. Bacterial suspensions were adjusted to the 0.5 McFarland standard (equivalent to 1–2 × 10^8 CFU/mL) and inoculating Muller Hinton agar plates (Merck, Germany). The resistance of bacteria was examined toward metronidazole (5 µg), ampicillin (10 µg), tetracycline (30 µg), clarithromycin (2 µg), erythromycin (5 µg), and amoxicillin (10 µg) (Oxoid, UK). Antibiotic disks were placed on media contained the bacteria, and the plates were incubated under microaerophilic conditions at 35°C for 16-18 h. The zones of growth inhibition produced by each antibiotic were measured and interpreted by standard procedure.

Data analysis

Data were subjected to Microsoft Office Excel (version 15; Microsoft Corp., Redmond, WA, USA). The statistical analysis was performed employing the SPSS 21.0 software (SPSS Inc., Chicago, IL, USA). Chi-square test and Fisher's exact two-tailed test were applied to measure any significant relationship. *P*-value <0.05 was considered as a significant numerical level[20-25].

Results

H. pylori distribution

Table I shows the H. pylori distribution amongst the studied population. Twenty-two out of 80 (27.50%) examined specimens were positive for *H. pylori*. *H. pylori* distribution amongst dental plaque and saliva samples was 33.33% and 21.05%, respectively. A statistically significant difference was obtained for the *H. pylori* distribution between dental plaque and saliva specimens (P <0.05).

Table I: *H. pylori* distribution amongst the studied population.

Specimens	N. specimens collected	N. specimens positive for *H. pylori* (%)
Dental plaque	42	14 (33.33)
Saliva	38	8 (21.05)
Total	80	22 (27.50)

H. pylori antimicrobial resistance

Table II shows the antimicrobial resistance of *H. pylori* strains isolated from dental plaque and saliva specimens. *H. pylori* strains isolated from examined specimens harbored the high prevalence of resistance against ampicillin (77.27%), amoxicillin (72.22%), erythromycin (68.18%), and tetracycline (68.18%), antimicrobials. Resistance rate toward metronidazole was lower than other antimicrobials (40.90%). *H. pylori* isolates of dental plaque samples had a higher prevalence of resistance toward all examined antimicrobial agents (P <0.05).

Discussion

Notwithstanding an enormous expansions in medicine, varied complicated infectious diseases faced with the human[26-30]. In this regard, *H. pylori* have become a developed public health issue in the last century[31].

H. pylori prevalence among the dental plaque and saliva specimens was 33.33% and 21.05%, respectively. Higher H. pylori prevalence in saliva than dental plaque specimens was also reported from Japan[32], Mexico (33), Malaysia[34], Iran[35], and Peru[36]. Yang et al. (2015) (37) showed that 76% of dental plaque samples collected in China were positive for *H. pylori*. Rasmussen et al. (2010)[38] stated that the *H. pylori* prevalence amongst the saliva and dental plaque samples was 42.30% and 47.40%, respectively. However, these is no strict data about the exact source of *H. pylori* in dental plaque and saliva samples. Maybe foods have the main role in transmission of *H. pylori* into the oral cavity and then stomach.

H. pylori isolates of dental plaque and saliva samples harbored the high resistance rate toward ampicillin, tetracycline, amoxicillin, erythromycin, and clarithromycin. These antimicrobials are the major therapeutic options used for *H. pylori* eradication, particularly in the mouth, among Iranian practitioners. High and illegal antibiotic prescriptions in medical and dental clinics and excessive use of disinfectants and mouthwashes solutions may cause the high antimicrobial resistance observed in the present survey. Our findings showed the higher antimicrobial resistance of H. pylori strains isolated from dental plaque than saliva samples. This finding may be due to the biofilm formation of H. pylori strains in the dental plaque samples[39]. Hanafiah et al. (2019)[40] reported that resistance rates of *H. pylori* strain to metronidazole and clarithromycin antimicrobial agents were 59.30%, and 35.6%, respectively. Mashak et al. (2020)[41] reported that the resistance rates of *H. pylori* strains against ampicillin, clarithromycin, erythromycin, metronidazole, levofloxacin, tetracycline, amoxicillin, rifampin, trimethoprim, cefsulodin, streptomycin, furazolidone, and spiramycin antimicrobial agents were 59.61%, 61.53%, 80.76%, 51.92%, 63.46%, 82.69%, 63.46%, 40.38%, 65.38%, 38.46%, 59.61%, 25.00%, and 21.15%, respectively.

Totally, this survey is the first report of identification of antimicrobial resistance of *H. pylori* strains isolated from dental plaque and saliva samples in Armenia. Findings are limited to the low number of isolated bacteria, lack of demographical characters of the studied population and also absence of the determination of the history of gastrointestinal disorders among patients.

Conclusion

To sum it up, diverse antimicrobial resistance was found in the *H. pylori* strains isolated from dental plaque and saliva samples. Ampicillin, amoxicillin, clarithromycin, tetracycline, erythromycin and even metronidazole antimicrobials were not effective against isolates. *H. pylori* isolates of dental plaque samples harbored the higher antimicrobial resistance. This finding may show the predominant role of dental plaque samples as a reservoir of antimicrobial-resistant *H. pylori*. Additionally, findings may suggest that the oral cavity, particularly dental plaque and saliva samples, may be a *H. pylori* reservoir and potentially a source of transmission or reinfection.

Interests conflict

The researchers declare that they have no conflict of interest.

Table II: Antimicrobial resistance of *H. pylori* strains isolated from dental plaque and saliva specimens.

Specimens	N. H. pylori isolates harbored resistance against each antimicrobial agents (%)					
(N. positive)	Clr*	Ert	Amx	Amp	Tet	Met
Dental plaque (14)	10 (71.42)	10 (71.42)	11 (78.57)	12 (58.71)	10 (71.42)	7 (50.00)
Saliva (8)	4 (50.00)	5 (62.50)	5 (62.50)	5 (62.50)	5 (62.50)	2 (25.00)
Total (22)	14 (63.63)	15 (68.18)	16 (72.72)	17 (77.27)	15 (68.18)	9 (40.90)

*Clr: clarithromycin (2 µg), Ert: erythromycin (5 µg), Amx: amoxicillin (10 µg), Amp: ampicillin (10 µg), Tet: tetracycline (30 µg), Met: metronidazole (5 µg).

References

1. Czesnikiewicz-Guzik M, Bielanski W, Guzik TJ, Loster B, Konturek SJ. Helicobacter pylori in the oral cavity and its implications for gastric infection, periodontal health, immunology and dyspepsia. Journal of physiology and pharmacology. 2005 Dec 1;56:77.

2. Sarmah R, Khan RA, Devi KR. Microbes in human oral cavity: a review. Reviews in Medical Microbiology. 2021 Apr 1;32(2):75-82.

3. Bıcak DA, Akyuz S, Kıratlı B, Usta M, Urganci N, Alev B, Yarat A, Sahin F. The investigation of Helicobacter pylori in the dental biofilm and saliva samples of children with dyspeptic complaints. BMC oral health. 2017 Dec;17(1):1-2.

4. Yahaghi E, Khamesipour F, Mashayekhi F, Safarpoor Dehkordi F, Sakhaei MH, Masoudimanesh M, Khameneie MK. Helicobacter pylori in vegetables and salads: genotyping and antimicrobial resistance properties. BioMed Research International. 2014 Jan 1;2014.

5. Ranjbar R, Yadollahi Farsani F, Safarpoor Dehkordi F. Antimicrobial resistance and genotyping of vacA, cagA, and iceA alleles of the Helicobacter pylori strains isolated from traditional dairy products. Journal of Food Safety. 2019 Apr;39(2):e12594.

6. Atapoor S, Dehkordi FS, Rahimi E. Detection of Helicobacter pylori in various types of vegetables and salads. Jundishapur Journal of Microbiology. 2014 May;7(5).

7. Ranjbar R, Farsani FY, Dehkordi FS. Phenotypic analysis of antibiotic resistance and genotypic study of the vacA, cagA, iceA, oipA and babA genotypes of the Helicobacter pylori strains isolated from raw milk. Antimicrobial Resistance & Infection Control. 2018 Dec;7(1):1-4.

8. Al Sayed A, Anand PS, Kamath KP, Patil S, Preethanath RS, Anil S. Oral cavity as an extragastric reservoir of Helicobacter pylori. International Scholarly Research Notices. 2014;2014.

9. Singhal S, Dian D, Keshavarzian A, Fogg L, Fields JZ, Farhadi A. The role of oral hygiene in inflammatory bowel disease. Digestive diseases and sciences. 2011 Jan;56(1):170-5.

10. Yee JK. Helicobacter pylori colonization of the oral cavity: A milestone discovery. World Journal of Gastroenterology. 2016;22(2):641.

11. Yee JK. Are the view of Helicobacter pylori colonized in the oral cavity an illusion?. Experimental & Molecular Medicine. 2017;49(11):e397-.

12. Goderska K, Pena SA, Alarcon T. Helicobacter pylori treatment: antibiotics or probiotics. Applied microbiology and biotechnology. 2018 Jan;102(1):1-7.

13. Mousavi S, Dehkordi FS. Virulence factors and antibiotic resistance of Helicobacter pylori isolated from raw milk and unpasteurized dairy products in Iran. Journal of Venomous Animals and Toxins including Tropical Diseases. 2015 Jan 20;20:1-7.

14. Ghorbani F, Gheisari E, Dehkordi FS. Genotyping of vacA alleles of Helicobacter pylori strains recovered from some Iranian food items. Tropical Journal of Pharmaceutical Research. 2016 Sep 5;15(8):1631-6.

15. Mashak Z, Jafariaskari S, Alavi I, Shahreza MS, Dehkordi FS. Phenotypic and genotypic assessment of antibiotic resistance and genotyping of vacA, cagA, iceA, oipA, cagE, and babA2 alleles of Helicobacter pylori bacteria isolated from raw meat. Infection and drug resistance. 2020;13:257.

16. Liang CM, Tai WC, Hsu PI, Wu DC, Kuo CH, Tsay FW, Lee CL, Chen KY, Chuah SK. Trend of changes in antibiotic resistance in Helicobacter pylori from 2013 to 2019: a multicentre report from Taiwan. Therapeutic Advances in Gastroenterology. 2020 Dec;13:1756284820976990.

17. Sudhakar U, Anusuya CN, Ramakrishnan T, Vijayalakshmi R. Isolation of Helicobacter pylori from dental plaque: A microbiological study. Journal of Indian Society of Periodontology. 2008;12(3):67.

18. Andrews J. BSAC disc diffusion method for antimicrobial susceptibility testing. 2.1.4 ed. British Society for Antimicrobial Chemotherapy: Birmingham, UK; 2003.

19. NCCLS. Performance Standards for Antimicrobial Susceptibility Testing. Approved Standard M7-A5: Informational Supplement M100- S18. National Committee for Clinical Laboratory Standards: Wayne, PA; 2007.

20. Ranjbar R, Seif A, Dehkordi FS. Prevalence of antibiotic resistance and distribution of virulence factors in the shiga toxigenic Escherichia coli recovered from hospital food. Jundishapur Journal of Microbiology. 2019;12(5):8.

21. Nejat S, Momtaz H, Yadegari M, Nejat S, Safarpour Dehkordi F, Khamesipour F. Seasonal, geographical, age and breed distributions of equine viral arteritis in Iran. Kafkas Univ Vet Fak Derg. 2015 Jan 1;21(1):111-6.

22. Dehkordi FS, Saberian S, Momtaz H. Detection and segregation of Brucella abortus and Brucella melitensis in Aborted Bovine, Ovine, Caprine, Buffaloes and Camelid Fetuses by application of conventional and real-time polymerase chain reaction. The Thai Journal of Veterinary Medicine. 2012 Mar 1;42(1):13.

23. Rahimi E, Yazdanpour S, Dehkordi FS. Detection of Toxoplasma gondii antibodies in various poultry meat samples using enzyme linked immuno sorbent assay and its confirmation by polymerase chain reaction. J Pure Appl Microbiol. 2014;8(1):421-7.

24. Dehkordi FS. Prevalence study of Bovine viral diarrhea virus by evaluation of antigen capture ELISA and RT-PCR assay in Bovine, Ovine, Caprine, Buffalo and Camel aborted fetuses in Iran. AMB express. 2011 Dec;1(1):1-6.

25. Dehkordi FS, Haghighi N, Momtaz H, Rafsanjani MS, Momeni M. Conventional vs real-time PCR for detection of bovine herpes virus type 1 in aborted bovine, buffalo and camel foetuses. Bulgarian Journal of Veterinary Medicine. 2013 Jun 1;16(2).

26. Mirzaie A, Halaji M, Dehkordi FS, Ranjbar R, Noorbazargan H. A narrative literature review on traditional medicine options for treatment of corona virus disease 2019 (COVID-19). Complementary therapies in clinical practice. 2020 Aug 1;40:101214.

27. Halaji M, Farahani A, Ranjbar R, Heiat M, Dehkordi FS. Emerging coronaviruses: first SARS, second MERS and third SARS-CoV-2: epidemiological updates of COVID-19. Infez Med. 2020;28(suppl):6-17.

28. Sheikhshahrokh A, Ranjbar R, Saeidi E, Dehkordi FS, Heiat M, Ghasemi-Dehkordi P, Goodarzi H. Frontier therapeutics and vaccine strategies for sars-cov-2 (COVID-19): A review. Iranian Journal of Public Health. 2020 Oct;49(Suppl 1):18.

29. Ranjbar R, Mahmoodzadeh Hosseini H, Safarpoor Dehkordi F. A review on biochemical and immunological biomarkers used for laboratory diagnosis of SARS-CoV-2 (COVID-19). The Open Microbiology Journal. 2020 Dec 15;14(1).

30. Rahi A, Kazemeini H, Jafariaskari S, Seif A, Hosseini S, Dehkordi FS. Genotypic and phenotypic-based assessment of antibiotic

resistance and profile of staphylococcal cassette chromosome mec in the methicillin-resistant Staphylococcus aureus recovered from raw milk. Infection and drug resistance. 2020;13:273.

31. Muñoz-Ramirez ZY, Pascoe B, Mendez-Tenorio A, Mourkas E, Sandoval-Motta S, Perez-Perez G, Morgan DR, Dominguez RL, Ortiz-Princz D, Cavazza ME, Rocha G. A 500-year tale of co-evolution, adaptation, and virulence: Helicobacter pylori in the Americas. The ISME journal. 2021 Jan;15(1):78-92.

32. Ueda J, Yamaguchi A, Shibasaki K. Occurrence of Helicobacter pylori in saliva from preschool-age children. Oral Science International. 2015;12(1):5-8.

33. Fernández Tilapa G, Axinecuilteco Hilera J, Giono Cerezo S, Martínez Carrillo DN, Illades Aguiar B, Román Román A. vacA genotypes in oral cavity and Helicobacter pylori seropositivity among adults without dyspepsia. Medicina Oral, Patologia Oral, Cirugia Bucal. 2011;16 (2):e175-80.

34. Goud ES, Kannan R, Rao UK, Joshua E, Tavaraja R, Jain Y. Identification of Helicobacter pylori in saliva of patients with and without gastritis by polymerase chain reaction. Journal of Pharmacy & Bioallied Sciences. 2019;11(Suppl 3):S523.

35. Salari Z, Ranjkesh A, Behboudi E. Molecular Identification of Helicobacter pylori and IceA Genes Frequency from Dental Plaques Isolated from People Using PCR Method. International Journal of Medical Laboratory. 2020.;7(3):191-196.

36. Cuyutupac G, Armando I. Dental Biofilm, a reservoir for Helicobacter Pylori in patients with chronic gastritis. Revista de la Facultad de Medicina Humana. 2020;20(4):597-601.

37. Yang J, Zhang Q, Chen M, Wu WZ, Wang R, Liu CJ, et al. Association Between Helicobacter pylori Infection and Risk of Periodontal Diseases in Han Chinese: A Case-Control Study. Medical Science Monitor

38. Rasmussen LT, Labio RW, Gatti LL, Silva LC, Queiroz VF, Smith MD, Payão SL. Helicobacter pylori detection in gastric biopsies, saliva and dental plaque of Brazilian dyspeptic patients. Memorias do Instituto Oswaldo Cruz. 2010;105:326-30.

39. Fauzia KA, Miftahussurur M, Syam AF, Waskito LA, Doohan D, Rezkitha YA, Matsumoto T, Tuan VP, Akada J, Yonezawa H, Kamiya S. Biofilm formation and antibiotic resistance phenotype of Helicobacter pylori clinical isolates. Toxins. 2020;12(8):473.

40. Hanafiah A, Binmaeil H, Ali RA, Rose IM, Lopes BS. Molecular characterization and prevalence of antibiotic resistance in Helicobacter pylori isolates in Kuala Lumpur, Malaysia. Infection and Drug Resistance. 2019;12:3051.

41. Mashak Z, Jafariaskari S, Alavi I, Shahreza MS, Dehkordi FS. Phenotypic and genotypic assessment of antibiotic resistance and genotyping of vacA, cagA, iceA, oipA, cagE, and babA2 alleles of Helicobacter pylori bacteria isolated from raw meat. Infection and Drug Resistance. 2020;13:257.

eISSN 2255-0569

ORIGINAL

Study the roles of health policy makers in drug distribution among pharmacies

Estudiar el papel de los responsables de la política sanitaria en la distribución de medicamentos entre las farmacias

Hiva Farhadi[1]

1. Department of Marketing, Faculty of Business and Economics, Linnaeus University, Sweden

Corresponding author
Hiva Farhadi
Department of Marketing, Faculty of Business and Economics,
Linnaeus University, Sweden
E-mail: hiva.farhadi1612@gmail.com

Received: 16 - IX - 2021
Accepted: 10 - XI - 2021

doi: 10.3306/AJHS.2022.37.01.34

Abstract

Background: Drug distribution network management is one of the most important facilities in the ministry of health. This network is faced with several issues. The present survey was done to assess the roles of health policy makers in drug distribution among pharmacies.
Methods: A Judgmental sampling method was used in this study. Five managers of the Department of Drugs, Food and Narcotics of the Ministry of Health, Tehran, Iran who were determined the country's pharmaceutical policy, were selected in this survey. Designed questionnaire was presented to all 5 health policy makers. The data were stratified and the descriptive analysis method was used to test their partial and general hypotheses. Cronbach's alpha test was used to assess the validity of the questionnaires.
Results: As the Alpha= 0.850 was obtained for questions in the presented questionnaire, they have been approved as reliable. The study hypothesis (the impact of health policymakers' trust on drug distribution marketing strategies) was accepted because 60% of respondents believed in the effect of gaining policymakers' trust in marketing strategy and 35% of them believed gaining the trust of policymakers has a huge impact on marketing strategy.
Conclusion: Findings showed that adhering to pharmacy quotas, provincial distribution criteria for drugs, adhering to approved drug prices, and having effective and efficient management affect marketing strategies. However, to found other factors affected the health policy makers drug distribution, several studies should perform.

Keywords: Health policy makers, roles, drug distribution, pharmacies.

Resumen

Antecedentes: La gestión de la red de distribución de medicamentos es uno de los servicios más importantes del Ministerio de Sanidad. Esta red se enfrenta a varios problemas. La presente encuesta se realizó para evaluar el papel de los responsables de la política sanitaria en la distribución de medicamentos entre las farmacias.
Métodos: En este estudio se utilizó un método de muestreo criterioso. En esta encuesta se seleccionaron cinco gerentes del Departamento de Medicamentos, Alimentos y Narcóticos del Ministerio de Salud de Teherán, Irán, que determinaban la política farmacéutica del país. El cuestionario diseñado se presentó a los cinco responsables de la política sanitaria. Los datos se estratificaron y se utilizó el método de análisis descriptivo para probar sus hipótesis parciales y generales. Se utilizó la prueba alfa de Cronbach para evaluar la validez de los cuestionarios.
Resultados: Al obtenerse un Alfa= 0,850 para las preguntas del cuestionario presentado, éstas han sido aprobadas como fiables. La hipótesis del estudio (el impacto de la confianza de los políticos sanitarios en las estrategias de marketing de la distribución de medicamentos) fue aceptada porque el 60% de los encuestados creía en el efecto de ganarse la confianza de los políticos en la estrategia de marketing y el 35% de ellos creía que ganarse la confianza de los políticos tiene un gran impacto en la estrategia de marketing.
Conclusión: Los resultados mostraron que el cumplimiento de las cuotas de las farmacias, los criterios de distribución provincial de los medicamentos, el cumplimiento de los precios aprobados de los medicamentos y la existencia de una gestión eficaz y eficiente afectan a las estrategias de marketing. Sin embargo, para encontrar otros factores que afecten a la distribución de medicamentos por parte de los responsables de las políticas sanitarias, habría que realizar varios estudios.

Palabras clave: Responsables de la política sanitaria, funciones, distribución de medicamentos, farmacias.

Introduction

Today, with the advancement of medical sciences, many pharmacological and non-pharmacological treatments for various diseases have been developed[1]. Drug treatments are usually made available to pharmacies and then to patients by drug companies through their distribution system. Powerful and integrated drug distribution system can provide a variety of common drugs and treatments to patients in a short time[2]. Although there are many challenges in the drug distribution system, conducting well-codified studies in this area that are often overlooked with several issues can show a good approach to drug distribution to patients in a country[3].

The uncertainty of drug and medical service distribution channels is conditioned by the dynamic and complex market and pharmaceutical environment that leads to the realization of new trends, new products, and services in a short time frame. Nowadays, drug distribution faces some of the toughest challenges in the market[4], such as the growth of new viruses and diseases, new drugs, use of advanced technologies, and increased customer demands. All these challenges generate risks that affect the sustainability of drug distribution, and it is necessary to provide effective support for the pharmaceutical industry[5].

Totally, 11 complications were identified for the drug distribution network in Iran[6]. Drug availability or shortage, supply of near-expiration drugs, supply of counterfeit drugs, over-the-counter drug sales, black market activity, severe price fluctuations, insufficient interaction with the consumer in the pharmacy, high distribution costs, low performance of distribution network in emergency deliveries, long time to search and find medicine (in the case of certain drugs) and poor quality of responding to consumer complaints are some of the identified complications[7-9].

In Iran, the role of health policy makers in drug distribution is so important. In this regard, health policymakers' have a decisive role in the distribution of drugs. In general, decision-makers in the Ministry of Health give the final opinion on drug distribution. Thus, the present survey was conducted to assess the roles of health policy makers in drug distribution among pharmacies.

Materials and methods

Study area

From the year 2008 to 2009, data collected from the Darupakhsh company, Tehran, Iran was used in this study. A questionnaires were answered by 5 health policymakers and experts in the Ministry of Health, Tehran, Iran.

Sampling

A Judgmental sampling method was used for this purpose. In this regard, 5 managers and officials of the Department of Drugs, Food and Narcotics of the Ministry of Health, Tehran, Iran who were determined the country's pharmaceutical policy, were considered to have completed the entire statistical community. For this purpose, a questionnaire was sent for them and all of them answered the questions.

Questionnaire analysis

The data obtained from the questionnaire were stratified and the descriptive analysis method was used to test their partial and general hypotheses. Cronbach's alpha test was used to assess the validity of the questionnaires. In order to design the questionnaire questions, according to the opinions of experts, very detailed and accurate indicators were determined and questions were designed to evaluate each one. The method of answering the questionnaire was determined based on the Likert scale and the respondents were asked to determine the role of each indicator on the subject in the question on marketing strategies. **Table I** shows the general information of the managers who have answered the questionnaires in Darupakhsh Distribution Company.

Table I: General information of the managers who have answered the questionnaires in Darupakhsh Distribution Company.

No	Jobs
1	Executive Vice President of Darupakhsh Holding
2	Deputy Minister of Finance
3	Managing Director
4	Managing Director
5	Strategic Manager
6	Chief financial officer
7	Former CEO of Tamin Pharmaceutical Holding and Head of Syndication of Iranian Pharmaceutical Industries
8	Former Chief executive officer (CEO) of Darupakhsh Holding
9	The current CEO of Darupakhsh Holding
10	Head of Sales and Marketing

Validity test

Cronbach's alpha test was used to determine the validity of questionnaire. This method was used to calculate the internal consistency of measuring instruments, such as questionnaires or tests that measure various characteristics. In this tool, the answer to each question can take different numerical values. To calculate the Cronbach's alpha coefficient, authors must first calculate the variance of the scores of each subset of the questionnaire (or subtest) questions and the total variance. Then, the value of alpha coefficient was calculated using the following formula[10,11]:

Formula No 1

$$r_a = \frac{J}{J-1}\left(1-\frac{\sum S_j^2}{S^2}\right)$$

Whereas:

J = Number of question or test question subsets
Sj2 = Variance following j test
S2 = Total test variance
In this research, in relation to the use of secondary data, an attempt has been made to use reliable data and information that is approved by the organization's monitoring system, so the information is reliable and seems to be far from biases and distortions.

Results

Evaluation of the validity of the questions in questionnaire

For the questionnaire questions, Alpha = 0.850 was obtained. Considering that the alpha value is greater than 0.7, it was concluded that the questionnaire was reliable.

Questionnaire analysis

Table II shows the designed questionnaire and responses given to each question.

According to the results obtained in the table, the research hypothesis (the impact of health policymakers' trust on drug distribution marketing strategies) can be accepted because 60% of respondents believed in the effect of gaining policymakers' trust in marketing strategy and 35% of them believed Gaining the trust of policymakers has a huge impact on marketing strategy (**Table III**).

Discussion

Recently, many diseases have threatened human life[12-21]. However, proper management of drug distribution can avert severe epidemics and can control the diseases expansion in the community.

The social factors of health comprise the health systems under which people live and utilize health services. One social determinant, for which pharmacists are responsible, is designing drug distribution systems that ensure patients have safe and convenient access to medications. The World Health Organization (WHO) describes the health social determinants of as the circumstances in which people are born, grow, live and age and the wider set of forces and systems shaping daily life. These systems comprise economic policies and systems, development agendas, social norms, social policies and political systems[22].WHO makes it obvious that it is significant to address health social determinants that create barriers to good care. This would comprise health systems, of which medication distribution is a fundamental component[23].

The drug distribution network is one of the most important pillars of the Iranian pharmaceutical system which plays a vital role in rapid and easy access to drugs. The purpose of this study is to explain the roles of health policy makers in drug distribution among pharmacies. Findings showed that the adhering to pharmacy quotas, provincial distribution criteria for drugs, adhering to approved drug prices, and having effective and efficient management affect marketing strategies. Totally, we found that the high impact of health policymakers' trust on drug distribution marketing strategies in Iran.

Scarce data are available in this area globally. High role of health policymakers' in drug distribution for the control of corona virus diseases 2019 (COVID-19) in New York showed by Dzierba et al. (2020)[24]. A Serbian survey[1] revealed that the significant roils of health policymakers' in quality and quantity of drug distribution networks. Similar findings were reported from India[25], Australia[26], and United Kingdome[27].

Drug distribution channels are multifaceted and amassed from entities, including logistics organizations, pharmaceutical companies and employees, hospitals, pharmacies, customers, doctors, governmental institutions, and health policymakers'. The role if health policymakers' decisions may be significant, including their extensive attentions to diseases outbreak and dissemination, emotional stability, social support, openness to experience, self-discipline, and cognitive flexibility. Drug distribution is a sequence of procedures envisioned to recover primary care and comprises

Table II: Designed questionnaire in the present study.

No questions	Questions	Number of participants	Responses (%)				
			Very low	Low	Medium	High	Very high
1	Does adhering to pharmacy quotas affect marketing strategies?	5	-	1 (20)	2 (40)	1 (20)	1 (20)
2	Do provincial distribution criteria for drugs affect marketing strategies?	5	-	1 (20)	2 (40)	1 (20)	1 (20)
3	Does adhering to approved drug prices affect marketing strategies?	5	-	1 (20)	1 (20)	1 (20)	2 (40)
4	Does having effective and efficient management affect marketing strategies?	5	-	-	-	2 (40)	3 (60)

Table III: Frequency of the effect of gaining the trust of policy makers on marketing strategies.

Criteria	Frequency	Percent	The cumulative percentage
Very low	0	0	0
Low	3	15	15
Medium	5	25	40
High	5	25	65
Very high	7	35	100

manufacture, procurement, distribution, and waste disposal, storage, transportation, and delivery of drugs[28]. Thus, it is essential to assess the roles of different factors on its quality.

Conclusions

This survey showed that the health policymakers of the Darupakhsh company and also those of the Iranian Ministry of Health have a significant roles in drug distribution. As far as we know, this study is the first report of the roles of health policy makers in drug distribution among pharmacies. Findings showed that adhering to pharmacy quotas, provincial distribution criteria for drugs, adhering to approved drug prices, and having effective and efficient management affect marketing strategies. However, to found other factors affected the health policy makers drug distribution, several studies should perform.

Interests conflict

The researchers declare that they have no conflict of interest.

References

1. Grujić J, Morača S, Fajsi A. Analysis of Risk Factors in the Channels of Drug Distribution: Professional Perspectives. Sustainability. 2020 Jan;12(11):4787.

2. Mohammadshahi M, Alipouri Sakha M, Zarei L, Karimi M, Peiravian F. Factors Affecting Medicine-Induced Demand and Preventive Strategies: A Scoping Review. Shiraz E-Medical Journal. 2019 Oct 31;20(10).

3. Achuora JO, Arasa RM, Nzioki W, Ochiri G, Muangangi P. Factors affecting distribution performance for pharmaceutical products in Kenya public sector. International Journal of Research in Social Sciences. 2013;3(1):118-39.

4. Esmaeillou Y, Asl IM, Tabibi SJ, majid Cheraghali A. Identifying factors affecting the pharmaceutical supply chain management in Iran. Galen Medical Journal. 2017 Dec 29;6(4):346-55.

5. Khazzaka M. Pharmaceutical marketing strategies' influence on physicians' prescribing pattern in Lebanon: ethics, gifts, and samples. BMC health services research. 2019 Dec;19(1):1-1.

6. Sepahi T, Shahbazi M, Roudposhti MS. Drug Distribution System in Iran: A Multi Method Study of Defects and Solutions. Depiction of Health. 2020 Dec 21;11(4):324-43.

7. Kalantari M, Pishvaee M. A Robust Possibilistic Programming Approach to Drug Supply Chain Master Planning. IERPS. 2016; 7(4): 49-67. (Persian)

8. Mojaradi Z, Mozafari M. System Dynamics Simulation in Medicine Supply Chain: A Case Study of Mashhad Razavi Hospital, Iran. Health Information Management. 2017; 14(5): 211-6. (Persian)

9. Ekhtiari S, raeeszadeh M, mostafavi SA. The comparative evaluation of the procurement, distribution and administration of drug in pharmacies of Kermanshah city to the standard of Food and Drug Organization. RJMS. 2017; 24(159): 30-38. (Persian)

10. Tavakol M, Dennick R. Making sense of Cronbach's alpha. International journal of medical education. 2011;2:53.

11. Connelly LM. Cronbach's alpha. Medsurg nursing. 2011 Jan 1;20(1):45-7.

12. Ranjbar R, Farsani FY, Dehkordi FS. Phenotypic analysis of antibiotic resistance and genotypic study of the vacA, cagA, iceA, oipA and babA genotypes of the Helicobacter pylori strains isolated from raw milk. Antimicrobial Resistance & Infection Control. 2018 Dec;7(1):1-4.

13. Dehkordi FS, Haghighi N, Momtaz H, Rafsanjani MS, Momeni M. Conventional vs real-time PCR for detection of bovine herpes virus type 1 in aborted bovine, buffalo and camel foetuses. Bulgarian Journal of Veterinary Medicine. 2013 Jun 1;16(2).

14. Dehkordi FS. Prevalence study of Bovine viral diarrhea virus by evaluation of antigen capture ELISA and RT-PCR assay in Bovine, Ovine, Caprine, Buffalo and Camel aborted fetuses in Iran. AMB express. 2011 Dec;1(1):1-6.

15. Halaji M, Farahani A, Ranjbar R, Heiat M, Dehkordi FS. Emerging coronaviruses: first SARS, second MERS and third SARS-CoV-2: epidemiological updates of COVID-19. Infez Med. 2020;28(suppl):6-17.

16. Rahimi E, Yazdanpour S, Dehkordi FS. Detection of Toxoplasma gondii antibodies in various poultry meat samples using enzyme linked immuno sorbent assay and its confirmation by polymerase chain reaction. J Pure Appl Microbiol. 2014;8(1):421-7.

17. Dehkordi FS, Saberian S, Momtaz H. Detection and segregation of Brucella abortus and Brucella melitensis in Aborted Bovine, Ovine, Caprine, Buffaloes and Camelid Fetuses by application of conventional and real-time polymerase chain reaction. The Thai Journal of Veterinary Medicine. 2012 Mar 1;42(1):13.

18. Sheikhshahrokh A, Ranjbar R, Saeidi E, Dehkordi FS, Heiat M, Ghasemi-Dehkordi P, Goodarzi H. Frontier therapeutics and vaccine strategies for sars-cov-2 (COVID-19): A review. Iranian Journal of Public Health. 2020 Jul 11.

19. Ranjbar R, Seif A, Dehkordi FS. Prevalence of antibiotic resistance and distribution of virulence factors in the shiga toxigenic Escherichia coli recovered from hospital food. Jundishapur Journal of Microbiology. 2019;12(5):8.

20. Nejat S, Momtaz H, Yadegari M, Nejat S, Safarpour Dehkordi F, Khamesipour F. Seasonal, geographical, age and breed distributions of equine viral arteritis in Iran. Kafkas Univ Vet Fak Derg. 2015 Jan 1;21(1):111-6.

21. Rahi A, Kazemeini H, Jafariaskari S, Seif A, Hosseini S, Dehkordi FS. Genotypic and phenotypic-based assessment of antibiotic resistance and profile of staphylococcal cassette chromosome mec in the methicillin-resistant Staphylococcus aureus recovered from raw milk. Infection and drug resistance. 2020;13:273.

22. Social determinants of health. World Health Organization website. http://www.who.int/social_determinants/en/. Updated 2017. Accessed March 2, 2017.

23. Social determinants of health – Evidence on Social Determinants of Health. World Health Organization website. http://www.who.int/social_determinants/themes/en/. Updated 2017. Accessed August 4, 2017.

24. Dzierba AL, Pedone T, Patel MK, Ciolek A, Mehta M, Berger K, Ramos LG, Patel VD, Littlefield A, Chuich T, May HB. Rethinking the Drug Distribution and Medication Management Model: How a New York City Hospital Pharmacy Department Responded to COVID-19. Journal of the American College of Clinical Pharmacy. 2020;3(8):1471-9.

25. Kumar N, Jha A. Quality risk management during pharmaceutical 'good distribution practices'–A plausible solution. Bulletin of Faculty of Pharmacy, Cairo University. 2018;56(1):18-25.

26. Rovers JP, Mages MD. A model for a drug distribution system in remote Australia as a social determinant of health using event structure analysis. BMC health services research. 2017 Dec;17(1):1-3.

27. Macfarlane CL, Dean L, Thomson R, Garner P. Community drug distributors for mass drug administration in neglected tropical disease programmes: systematic review and analysis of policy documents. Journal of global health. 2019 Dec;9(2).

28. Javalgi, R.; Ramsey, R. Strategic issues of e-commerce as an alternative global distribution system. Int. Mark. Rev. 2001, 18, 376–391.

eISSN 2255-0569

ORIGINAL

Repercussion on social networks of the switched keyboard syndrome

Repercusión en redes sociales del síndrome del teclado cambiado

Alfonso Piñana López, María Concepción Alonso García, José López González, David Alejandro Bandrés Herrera, María Teresa Villamor de Santiago, María Concepción Carvajal Lucerga

Área 2 Servicio Murciano de Salud

Corresponding author
Alfonso Piñana López
Área 2 Servicio Murciano de Salud
E-mail: alfonsopl@gmail.com

Received: 20 - IX - 2021
Accepted: 12 - XI - 2021

doi: 10.3306/AJHS.2022.37.01.38

Abstract

Introduction: Covid-19 has caused numerous health problems in the general population and in health professionals. Some of these problems are not well known, as is the case of the changed keyboard syndrome. The aim of this study was to assess this syndrome among health care personnel in the health area of Cartagena.
Methodology: A survey was carried out among 156 health care workers in the health area of Cartagena to assess the changed keyboard syndrome. The repercussion of this syndrome in different social networks was also assessed.
Results: 45.1% of the people who responded to the survey stated that they had suffered from this syndrome at some time. As for the repercussions, 16.6% indicated that they were too concentrated and should stop, 14.1% believed that they were starting to get sick and 17.2% thought that this situation was funny. Some 52.1% stated that it does not happen to them.
Conclusions: Switched keyboard syndrome is a new consequence of the pandemic that should be evaluated in greater depth to see what repercussions it may have on healthcare personnel.

Keywords: Keyboard, telemedicine, telephone, social networks.

Resumen

Introducción: La Covid-19 ha ocasionado numerosos problemas de salud en la población general y en los profesionales sanitarios. Algunos de esos problemas no son demasiado conocidos como es el caso del síndrome del teclado cambiado. El objetivo de este trabajo ha sido valorar este síndrome entre el personal sanitario del área de salud de Cartagena.
Metodología: Se realiza una encuesta en 156 trabajadores sanitarios del área de salud de Cartagena para valorar el síndrome del teclado cambiado. Se valora también la repercusión de este síndrome en diferentes redes sociales.
Resultados: El 45,1% de las personas que respondieron a la encueta manifiestan haber sufrido este síndrome en alguna ocasión. En cuanto a las repercusiones, un 16,6% indican que están demasiado concentrados y que deberían parar, un 14,1% creen que están empezando a enfermar y un 17,2% creen que esta situación es graciosa. Un 52,1% manifiestan que a ellos no les ocurre.
Conclusiones: El síndrome del teclado cambiado es una nueva consecuencia de la pandemia que debería ser evaluada con mayor profundidad para ver las repercusiones que puede tener en el personal sanitario.

Palabras clave: Teclado, telemedicina, teléfono, redes sociales.

Introduction

The covid-19 pandemic, and the increase in positive cases at the most complicated times, has forced hospitals and health centers to close in order to prioritize patient safety. An unprecedented situation that has led to an increase in medical assistance via telephone, telematic consultations or through the Patient Portal, causing a change in habits for users and healthcare professionals.

Among the consequences of this new reality, a team of doctors specializing in Family and Community Medicine at the West Cartagena Teaching Health Center has detected a hitherto unknown syndrome that has been baptized as "switched keyboard syndrome" (SKS), which consists of trying to enter computer data using the telephone keyboard or vice versa, trying to make a telephone call using the computer's expanded keys.

A study reveals that when we are faced with an extraordinary situation and we focus our work on one task we perform actions that distort our reality.

"In the toughest phases of the pandemic, we spend hours on the phone trying to reach everyone, plus you're on the computer all the time entering data or writing electronic prescriptions. And when you realize you are trying to use the computer by pressing the phone keys, then you get scared and think you are going crazy," says Alfonso Piñana, the physician who led the study.

But his was not a unique case and he decided to launch this research by carrying out an extensive questionnaire among other healthcare professionals in Murcia. The results have been surprising, since 4 out of ten doctors and nursing professionals have suffered at some time from this new syndrome. These conclusions were accepted at the 2nd National Multidisciplinary Covid-19 Congress of the Spanish Scientific Societies.

According to those responsible for the study, when we are faced with an extraordinary situation and we focus our work on a task, we sometimes carry out actions that distort our reality.

In this sense, they have also been able to verify that with the return to relative normality, with the return of patients to healthcare centers and the decrease in new positives, the incidence of this syndrome among healthcare professionals is decreasing.

During 2020 the healthcare professionals of the Primary Care teams of the Cartagena Health Area have attended more than 600,000 consultations by telephone:

- 418,834 corresponding to family physicians.
- 53,205 from pediatricians.
- 149,390 from nurses.

The bulk of the activity has been the follow-up of covid-positive patients, almost 15,000 since the beginning of the pandemic, to which must be added their contacts. In total, around 45,000 patients were contacted by telephone from Monday to Sunday.

The aim of the study was to test the impact of the SKS on social networks.

Methodology

A Google search was carried out to assess the impact on the presentation of the paper at the 2nd Covid 19 national interdisciplinary congress on the "switched keyboard syndrome" one week after its presentation. A questionnaire was elaborated, thanks to the google form platform, with 5 questions on age, gender, field of work and whether, when providing health care via telephone, the patient had tried to enter data into the computer using the telephone keyboard or vice versa or tried to make a telephone call using the expanded keyboard of the computer. A final question was asked about what the respondent was thinking when the CTS happened to him/her. All responses were recorded from December 2020 to February 2021. Dissemination was carried out via Twitter, e-mails and WhatsApp groups of Area 2 of the Murcian Health Service.

Results

The results of the work were presented at the 2nd National Interdisciplinary Congress of Covid 19 and consisted of responses from 156 forms. The age distribution was 5.1% (8) under 30 years, 16% (25) between 31 and 40 years, 34% (53) between 41 and 50 years, 30.1% (47) between 51 and 60 years and 14.7% (23) over 60 years of age. 58.3%(91) were female and 41.7%(65) were male. A total of 77.6% (121) were primary care physicians, 10.9% (17) were hospital care physicians, 5.1% (8) were primary care nurses and the remaining 6.4% (10) were other health professionals. In relation to the question of whether they had suffered from the changed keyboard syndrome, 53.3% (83) answered that it had never happened to them, 35.2% (55) answered that it had happened to them on some occasion and 11.5% (18) admitted that SKS had happened to them many times (**Figure 1**).

In response to the last question, "What does the respondent think about when SKS happens to him/her? 51.6% (81) answered that it had never happened to them. Some 17.2% (27) answered that they were too concentrated and should stop, 14.6% (23) answered that they started to get sick and the rest, 16.6% (53) that it was a funny event. These results led to a diffusion in social networks and media, such as press, radio and television

that a week after its publication, by putting in the google search engine: "changed keyboard syndrome" makes all the results of the first page of the search engine are related to the news and part of the results of the second page.

Figure 1: When using telephone consultation in health care, have you ever tried to use your telephone keypad to enter data into the computer or vice versa?

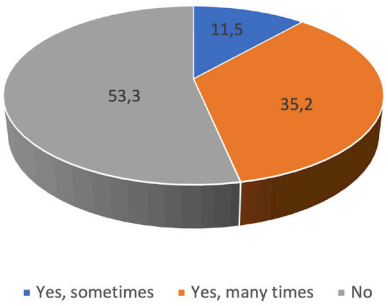
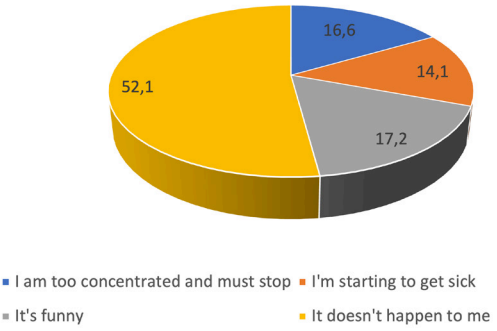


Figure 2: When using telephone consultation in health care, have you ever tried to use your telephone keypad to enter data into the computer or vice versa?



Conclusions

The reality is that when we face a new reality and focus our work on a task, we assume behaviors that distort reality. The work originated from a comment on the situation of wanting to enter computer data with the telephone keyboard, thinking that it was a unique behavior, but that other colleagues began to comment that it also happened to them. Therefore, the SKS can be considered as a consequence of the pandemic times we are living in. Given its repercussion in the media, it should serve us to be open to any new activity that appears in health care and as a warning sign, to stop, take a breath and return to the service of users who demand health care.

Interests conflict

The researchers declare that they have no conflict of interest.

References

https://2congresocovid.es/site/abstract/submission/?s=445&a=115829

https://www.europapress.es/murcia/noticia-medicos-atencion-primaria-detectan-nuevo-sindrometeclado-cambiado-20210412125031.html

https://www.niusdiario.es/sociedad/sanidad/descubren-sindrome-teclado-cambiado-medicosconfunden-teclas-telefono-ordenador_18_3121920223.html

https://www.laverdad.es/murcia/detectan-extrano-sindrome-20210412130938-nt.html

https://www.cope.es/programas/herrera-en-cope/noticias/sindrome-del-teclado-cambiado-quesufren-los-medicos-debido-asistencia-sanitaria-por-telefono-20210414_1237723 14/04/2021 El 40% de sanitarios podría estar sufriendo el llamado síndrome del teclado cambiado

https://twitter.com/cope/status/1382292023961661443

eISSN 2255-0569

ORIGINAL

Investigating the safety and health risks ranking in the hospital using the integrated approach of failure modes and effects analysis (FMEA) and Fuzzy- based Multiple Criteria Decision Making (MCDM) method

Investigación de la clasificación de los riesgos para la seguridad y la salud en el hospital mediante el enfoque integrado del análisis de los modos de fallo y los efectos (FMEA) y el método de toma de decisiones con criterios múltiples (MCDM) basado en Fuzzy

Hossein Armin[1], Somayeh Toussani[2], Seyed Nouredin Hosseini Gousheh[2], Reza Gholamnia[1,3], Shokooh Sadat Khaloo[1]

1. Graduated from Health, Safety and Environment, School of Public Health and Safety, Shahid Beheshti University of Medical Sciences, Tehran, Iran. 2. Social Determinants of Health Research Center, Yasuj University of Medical Sciences, Yasuj, Iran. 3. Workplace Health Promotion Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Corresponding author
Seyed Nouredin Hosseini Gousheh
Yasuj University of Medical Sciences, Yasuj, Iran
E-mail: nh_hse@yahoo.com.

Received: 21 - IX - 2021
Accepted: 14 - XI - 2021

doi: 10.3306/AJHS.2022.37.01.41

Abstract

Introduction: Hospitals are considered as one of the most risky and stressful work environments. Given the importance of the issue, it is necessary to evaluate the various occupational hazards factors to hospital staff in order to make appropriate decisions regarding their management and control. Nowadays, the use of Multiple Criteria Decision Making (MCDM) methods has become widespread in risk assessment and ranking. Therefore, the present study was conducted to determine the importance of occupational hazards and to rank the most important potential health and safety risks in the hospital.

Methods: In the present study, potential failure cases were identified in all wards of Shahid Beheshti Hospital in Yasouj (Yasouj, Iran) using the opinions of experts. The method of analysis of failure factors and its effects is one of the most widely used and traditional methods in risk assessment and management. However, there are limitations such as the same weight of severity indicators, the probability of occurrence and the ability to detect, as well as the same risk priority score. To eliminate the shortcomings in calculating the definite risk score and reduce inconsistencies in decision making as well as achieve more accurate results, the fuzzy TOPSIS method was used and then, the order of priority of different risks was determined using the fuzzy TOPSIS method.

Results: A total of 112 important risks were identified for the 14 main wards of the studied hospital (nursing and clinical wards, laboratory, operating room, CSR, radiology, MRI, kitchen, pharmacy, laundry, facilities, services, waste and administration), which threatens the safety and health of hospital staff. The highest significance of health risks was related to airborne pathogens, blood and other body fluids (including bacteria, viruses and parasites, 35.42% critical). The highest importance of safety risks was related to cuts caused by sharp tools (needle, angiocatheter, suture, razor, knife, 35.09% critical).

Conclusion: Using an integrated approach of failure analysis and its effects along with MCDM methods increases the speed of this process and obtains more reliable results.

Keywords: Risk assessment, failure analysis and its effects, fuzzy hierarchical analysis process, occupational safety and health.

Resumen

Introducción: Los hospitales están considerados como uno de los entornos laborales más arriesgados y estresantes. Dada la importancia del tema, es necesario evaluar los distintos factores de riesgo laboral para el personal de los hospitales con el fin de tomar decisiones adecuadas en cuanto a su gestión y control. En la actualidad, el uso de los métodos de toma de decisiones con criterios múltiples (MCDM) se ha generalizado en la evaluación y clasificación de riesgos. Por lo tanto, el presente estudio se llevó a cabo para determinar la importancia de los riesgos laborales y clasificar los riesgos potenciales más importantes para la salud y la seguridad en el hospital.

Métodos: En el presente estudio, se identificaron los casos de fallos potenciales en todas las salas del Hospital Shahid Beheshti de Yasouj (Yasouj, Irán) utilizando las opiniones de los expertos. El método de análisis de los factores de fallo y sus efectos es uno de los más utilizados y tradicionales en la evaluación y gestión de riesgos. Sin embargo, existen limitaciones como el mismo peso de los indicadores de gravedad, la probabilidad de ocurrencia y la capacidad de detección, así como la misma puntuación de prioridad de riesgo. Para eliminar las deficiencias en el cálculo de la puntuación definitiva de los riesgos y reducir las incoherencias en la toma de decisiones, así como lograr resultados más precisos, se utilizó el método TOPSIS difuso y, a continuación, se determinó el orden de prioridad de los diferentes riesgos mediante el método TOPSIS difuso.

Resultados: Se identificaron un total de 112 riesgos importantes para las 14 salas principales del hospital estudiado (salas de enfermería y clínica, laboratorio, quirófano, RSC, radiología, resonancia magnética, cocina, farmacia, lavandería, instalaciones, servicios, residuos y administración), que amenazan la seguridad y la salud del personal del hospital. La mayor importancia de los riesgos para la salud estaba relacionada con los patógenos transmitidos por el aire, la sangre y otros fluidos corporales (incluidas las bacterias, los virus y los parásitos, 35,42% de importancia crítica). La mayor importancia de los riesgos para la seguridad estaba relacionada con los cortes causados por herramientas afiladas (aguja, angiocatéter, sutura, navaja, cuchillo, 35,09% crítico).

Conclusión: El uso de un enfoque integrado de análisis de fallos y sus efectos junto con los métodos MCDM aumenta la velocidad de este proceso y obtiene resultados más fiables.

Palabras clave: Evaluación de riesgos, análisis de fallos y sus efectos, proceso de análisis jerárquico difuso, seguridad y salud en el trabajo.

Introduction

The hospital is the main and at the same time the most risky center for providing health services. Therefore, hospital staff are exposed to various occupational hazards[1]. In addition to providing the medical needs of patients, hospitals are also a place for education and research. Therefore, there are a large number of potential hazards such as: radiation, chemicals, toxins, biological hazards, heat, sound, dust and stress... in the hospital[2]. Due to the special conditions in the hospital in terms of crowds, the existence of complex equipment and devices as well as chemicals, exposure to hazardous factors in the workplace will be inevitable, if the principles of safety are not observed[3,4]. One of the main factors in health and safety management is risk assessment, which examines the status of the organization in order to ensure the success of health and safety programs[5]. Risk management is the creation of a culture and infrastructure in a logical and systematic way that enables the organization to minimize losses and maximize benefits[6].

Risk assessment is a valuable tool that can help managers and employees in various health sectors to improve the provision of care services. If health organizations identify, assess, and manage risks and hazards at a certain level in a certain way, then they will be able to reduce real and potential risks and identify opportunities for improving the health system[7]. Failure analysis and its effects is an engineering technique that is widely used to design, identify, and eliminate the potential or known risks, problems and errors from the system. This method provides a framework for analyzing the cause and effect of potential product defects[8]. In fact, analyzing failure modes and their effects is a powerful preventive method for risk management[9]. One of the most important problems in the risk assessment process is the existence of several parameters that affect the amount of risk. This leads to incorrect assessment of the level of risk. Therefore, it is necessary to use Multiple Criteria Decision Making (MCDM) methods to eliminate the effects of individual judgments of evaluators in the evaluation process[10].

The TOPSIS method was first proposed in 1981 and considered as one of the best multiple criteria decision making models in order to solving real-world problems[11]. This method is based on the concept that the selected option should have the shortest distance to the positive ideal solution (best possible case) and the maximum distance to the negative ideal solution (worst possible case). In this method, it is assumed that the desirability of each index is increasing or decreasing uniformly. The distance of an option from the positive or negative ideal is calculated through the Euclidean distance or as the absolute value of the linear distances, which depends on the exchange rate and the exchange between the indices[12]. However, in studies such as the study of Kutlu and Ekmekçioglu (2012), they used a combination of AHP, fuzzy FMEA and TOPSIS methods for risk assessment using D, O and S methods. In this method, the weight of three fuzzy AHP indices is calculated and the final ranking of failure cases is done by TOPSIS method[11]. In the study of Emblemsvåg and Kjølstad (2002), the factors influencing the risk assessment factors and resolve the ambiguity of the assessment process were investigated using fuzzy sets[13]. Jiang et al. (2017) proposed failure modes and effects analysis method based on a new fuzzy method that examines risk factors with fuzzy membership degree[14]. But in general, few studies have been conducted on risk assessment in the proposed method, especially in a hospital setting. Among the studies conducted in this field is the study of Dağsuyu et al. (2016) with the aim of comparing the traditional FMEA method and fuzzy FMEA[15]. In the study of Chanamool and Naenna (2016), failure factors were evaluated and prioritized using the fuzzy FMEA method[16]. Jamshidi et al. (2015) also suggested choosing the best strategy for maintaining sensitive devices in important wards of the hospital[17]. The risk assessment method in the present study was a comprehensive method, so that a widely used and appropriate method was used to initially identify risk centers, and then the best available software (BT Fuzzy Topsis Solver, which corresponds to mathematical equations) was used to model and determine the weight of criteria and ranking options[18].

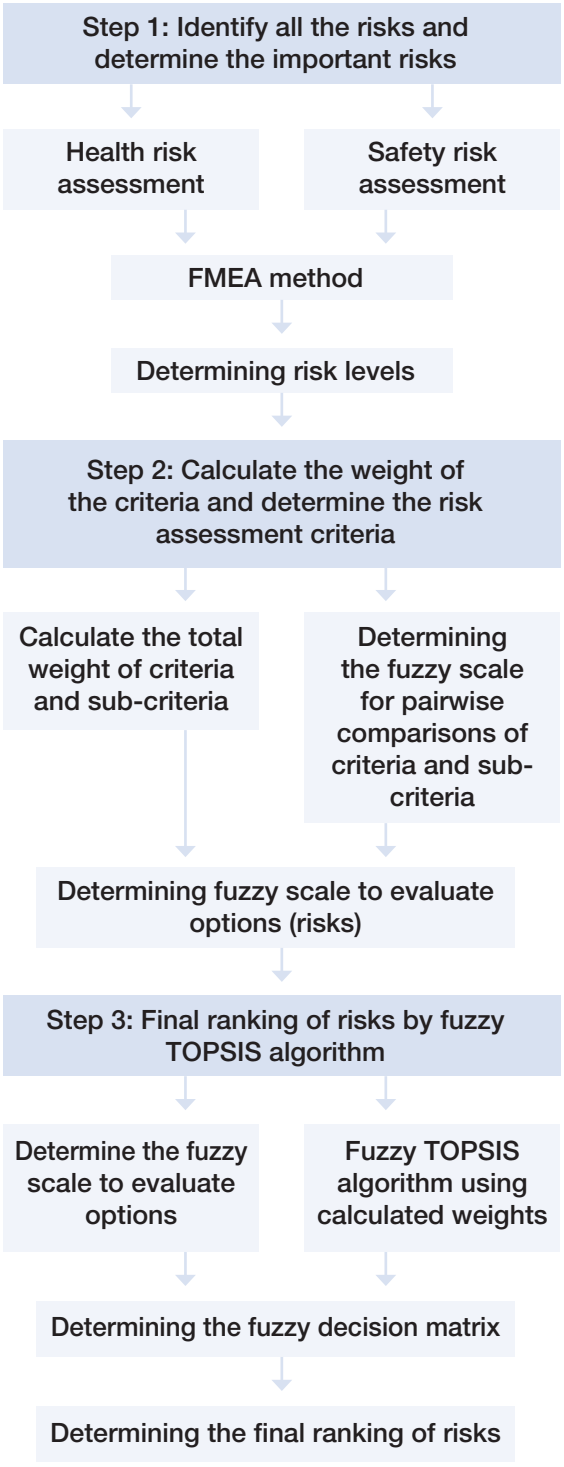
Although several studies have been conducted on the use of failure modes and effects analysis method in different work environments, however, this method has some limitations. Therefore, researchers have tried to compensate for its weaknesses by combining failure modes and effects analysis with other methods, such as multiple criteria decision making. In the present study, the primary foci of risk were first identified by the FMEA method. Then, the fuzzy logic method was used to determine the weight of the criteria and the order of priority of risks in Shahid Beheshti Hospital in Yasouj (Yasouj, Iran).

Materials and methods

Figure 1 shows the research method used in this study.

The present study was performed using the FMEA method in the hospital to assess occupational safety and health risks. At first, the risks of all hospital units were classified into two groups of health and safety risks in each hospital unit based on the literature review, observation and interview. Safety and health risks were identified and classified based on occupational injuries and occupational diseases, respectively. For this purpose, activities and resources have been identified through field visits and interviews with occupational health experts, and then the results of scoring and prioritizing risks have been performed according to the mentioned method

Figure 1: Research method.



(**Figure 1**). This method is based on the calculation and evaluation of risk scores, which are displayed by three tables of effect intensity, probability of occurrence and detectability. This method can only be used as a guide, so in the present study, the fuzzy approach allows experts to use verbal variables in order to evaluate the parameters of the risk assessment technique. Finally, the distance of options in the weighted matrix from the ideal - positive and negative points were determined as well as the final score of each option was determined (percentage of risk criticality)[19].

In order to estimate the risk values by FMEA method, the risk priority number (RPN) was calculated by multiplying the effect severity, occurrence probability and detectability (Equation 1).

[Equation 1]: RPN= S x O x D, where: (S) severity, (O) occurrence and (D) detectability.

In calculating the PRN number, it should be noted that the determination of numbers should be based on the type of activity of the organization. Corrective action should be considered mainly for hazards with high severity and occurrence rates. Given that individuals' judgments about preferences are often opaque in estimating the exact numerical value, fuzzy logic is useful for obtaining problems of ambiguity and uncertainty. Implementation of fuzzy TOPSIS technique in this research was performed in six stages. The decision matrix was created in the first stage.

$$\tilde{D} = \begin{bmatrix} \tilde{x}_{11} & \tilde{x}_{12} & \cdots & \tilde{x}_{1n} \\ \tilde{x}_{21} & \tilde{x}_{22} & \cdots & \tilde{x}_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ \tilde{x}_{m1} & \tilde{x}_{m2} & \cdots & \tilde{x}_{mn} \end{bmatrix} \quad i = 1,2,\dots,m;\ \ j = 1,2,\dots,n$$

Each column represents a measurement index and each row represents an option. Xij represents the quantity of the "I" option under the" J" sub-criterion. Also, the sub-criteria may be negative or positive depending on the effect on the options. In this study, verbal expressions and fuzzy numbers of **table I** have been used to evaluate the options for each criterion[20].

In the second step, the decision matrix was normalized. At this point we need to convert the fuzzy decision matrix of people's opinions into a matrix without fuzzy scale (R˜). In order to obtain the matrix R., it is sufficient to normalize the decision matrix based on the equation 3-1 and 3-2.

$$\tilde{R} = [\tilde{r}_{ij}]_{m\times n}$$

$$\tilde{r}_{ij} = \left(\frac{a_{ij}}{c_j^*}, \frac{b_{ij}}{c_j^*}, \frac{c_{ij}}{c_j^*}\right) \ and\ c_j^* = \max_i c_{ij} \qquad [4]$$

$$\tilde{r}_{ij} = \left(\frac{a_j^-}{c_{ij}}, \frac{a_j^-}{b_{ij}}, \frac{a_j^-}{a_{ij}}\right) \ and\ a_j^- = \min_i a_{ij} \qquad [5]$$

In the third step, a normal weight matrix was created: generate a matrix without fuzzy weight scale V˜ with the assumption of the vector W˜_ij based on the equation:

$$i = 1,2,\dots,m \quad j = 1,2,\dots,n \quad \tilde{V} = [\tilde{v}_{ij}]_{m\times n}$$

$$\tilde{v}_{ij} = \tilde{r}_{ij}.\tilde{w}_j \qquad [6]$$

Table I: Verbal expressions and fuzzy numbers for pairwise comparisons.

	Priorities			Fuzzy equivalent of priorities
	O	S	D	Low limit (L)
1	Almost impossible	None	Almost certain	(1,1,1)
2	Unlikely	Very low	Very much	(1,2,3)
3	Low	Insignificant	Much	(2,3,4)
4	Relatively low	Low	Relatively high	(3,4,5)
5	Medium	Medium	Medium	(4,5,6)
6	Relatively high	Significant	Low	(5,6,7)
7	High	High	Very low	(6,7,8)
8	Duplicate defects	Severe	Unlikely	(7,8,9)
9	Much	Dangerous with warnings	Very unlikely	(8,9,10)
10	Extremely high	Dangerous without warning	Almost impossible	(9,10,10)

In the fourth step, the values of positive and negative ideal were determined. In this step, positive and negative ideals were determined based on Equations 7 and 8[26]:

$$A^{+} = (\tilde{v}_1^{*}, \tilde{v}_2^{*}, \dots, \tilde{v}_n^{*}) \ where \ \tilde{v}_j^{*} = (\tilde{c}_j^{*}, \tilde{c}_j^{*}, \tilde{c}_j^{*}) \ and \ \tilde{c}_j^{*} = \max_i\{\tilde{c}_{ij}\} \quad [7]$$

$$A^{-} = (\tilde{v}_1^{-}, \tilde{v}_2^{-}, \dots, \tilde{v}_n^{-}) \ where \ \tilde{v}_j^{-} = (\tilde{a}_j^{-}, \tilde{a}_j^{-}, \tilde{a}_j^{-}) and \ \tilde{a}_j^{-} = \min_i\{\tilde{a}_{ij}\} \quad [8]$$

$$\forall i = 1,2,\dots,m; \quad j = 1,2,\dots,n$$

In the fifth step, the distance between the options and the ideals was calculated. The calculation of the sum of the distances of each component from the positive fuzzy ideal and the negative fuzzy ideal was obtained by the following equation (A and B are two fuzzy numbers):

$$\tilde{A} = (a_1, b_1, c_1)\tilde{B} = (a_2, b_2, c_2)$$

$$D(A,B) = \sqrt{\frac{1}{3}[(a_2 - a_1)^2 + (b_2 - b_1)^2 + (c_2 - c_1)^2]} \quad [9]$$

According to the above explanations on how to calculate the distance between two fuzzy numbers, we get the distance of each component from the ideal and anti-ideal:

$$d_i^{*} = \sum_{j=1}^{n} d(\tilde{v}_{ij} - \tilde{v}_j^{*}) \qquad i = 1,2,\dots,m \quad [10]$$

$$d_i^{-} = \sum_{j=1}^{n} d(\tilde{v}_{ij} - \tilde{v}_j^{-}) \qquad i = 1,2,\dots,m \quad [11]$$

In the sixth step, the similarity index to the ideal option (CL) was calculated using Equation 12:

$$Cl_i = \frac{d_i^{-}}{d_i^{*} + d_i^{-}} \qquad i = 1,2,\dots,m \quad [12]$$

In the seventh stage, the options were ranked in descending order of CL[21].

Results

Fuzzy TOPSIS

In the present study, the fuzzy TOPSIS method was used to rank hospital risks in two categories: health and safety. Therefore, risks were initially identified in 14 hospital wards. It was then scored by the 1 to 10 fuzzy spectrum of **table I** based on three criteria: risk severity (S), probability of occurrence (O) and detectability (D). This is the formation of the decision matrix and is given in **tables II** and **III**. Then, using Equations 4 and 5, the evaluation matrix was normalized and by Equation 6, the normal matrix was multiplied by the weight of the criteria to obtain the weighted matrix. Positive and negative ideals were then identified by Equations 7 and 8. Finally, the distance of the options in the weighted matrix from the positive and negative ideals was determined by equations 10 and 11. Equation 12 was used to determine the final score of each option (percentage of risk criticality). The results are given in **tables II** and **III**.

Discussion

Different modes of failure and its causes were identified in all wards of the hospital in the present study. Then, to evaluate and prioritize them, in addition to the three traditional indicators used in FMEA (severity, occurrence, and detection), we used a fuzzy integrated approach to rank hazards using fuzzy real-world numbers instead of definite numbers[22]. Then, in total, 112 important types of risks were identified separately from a large number of different risks in 14 sections and in 2 groups of safety and health risks and were classified using fuzzy TOPSIS method. According to the results of the in-class ranking of risk assessment, in the group of health risks, the highest risk scores were related to the following: pathogens (35.42%), night shift (32.08%), ergonomic factors (32.05%) and psychological factors (32.03%). In the group of safety risks, the highest final weights of the risks extracted from the results of the combined method were: Injuries caused by sharp objects (35.09%), electric shock (35.01%), slipping and falling (32.71%) and fire and burns (32.20%), respectively.

It should be noted that the overall ranking of the most important risks was obtained in all wards of the hospital, and accordingly, in order to manage the risks, a grouping was proposed according to the critical situation of each risk. It should be noted that risk management is not able to eliminate all risks simultaneously and can only suggest appropriate solutions to manage them. Therefore, each risk

Table II: Health risks.

Wards (sections)	The most important risk	S	O	D	Percentage of criticality	Rank
Clinical departments (Nursing)	Ergonomic (heavy workload, incorrect posture)	(2,3,4)	(3,4,5)	(5,6,7)	24.40%	3
	Airborne, blood and other body fluids pathogens (bacteria, viruses, parasites)	(2,3,4)	(4,5,6)	(6,7,8)	28.66%	1
	Night shift	(1,2,3)	(4,5,6)	(4,5,6)	32.08%	4
	Psychological factors (job stress-chronic fatigue)	(2,3,4)	(5,6,7)	(3,4,5)	32.05%	2
Clinical departments (Practical Nurse)	Ergonomic (improper posture - patient transport)	(2,3,4)	(4,5,6)	(5,6,7)	29.42%	2
	Night shift	(1,2,3)	(4,5,6)	(4,5,6)	24.31%	3
	Airborne, blood and other body fluids pathogens (bacteria, viruses, parasites)	(2,3,4)	(4,5,6)	(6,7,8)	31.55%	1
	Latex sensitivity	(1,2,3)	(2,3,4)	(2,3,4)	14.72%	4
Laboratory	Airborne, blood and other body fluids pathogens (bacteria, viruses, parasites)	(2,3,4)	(5,6,7)	(6,7,8)	35.42%	1
	Hazardous chemicals (solvents-acid and base)	(2,3,4)	(2,3,4)	(2,3,4)	18.28%	3
	Ergonomic (improper workstation, repetitive work, improper work tool)	(2,3,4)	(3,4,5)	(5,6,7)	28.02%	2
	Psychological factors (job stress-chronic fatigue)	(2,3,4)	(2,3,4)	(2,3,4)	18.28%	3
Operating room	Hazardous chemicals (anesthetic gases: N2O)	(3,4,5)	(3,4,5)	(5,6,7)	32.00%	1
	Ergonomic (heavy workload, incorrect posture)	(2,3,4)	(4,5,6)	(5,6,7)	28.29%	2
	Psychological factors (job stress-chronic fatigue)	(3,4,5)	(2,3,4)	(4,5,6)	24.03%	3
	Ionized and non-ionizing rays (X, alpha, laser, ultraviolet, beta, gamma)	(2,3,4)	(2,3,4)	(3,4,5)	19.00%	4
CSR	Hazardous chemicals (ethylene oxide - glutaraldehyde- mercury)	(2,3,4)	(3,4,5)	(6,7,8)	28.37%	2
	Airborne, blood and other body fluids pathogens (bacteria, viruses, parasites)	(2,3,4)	(3,4,5)	(5,6,7)	26.27%	3
	Ergonomic (improper posture - patient transport)	(2,3,4)	(4,5,6)	(5,6,7)	28.78%	1
	Latex sensitivity	(1,2,3)	(2,3,4)	(3,4,5)	16.57%	4
Radiology	Ionizing rays (X-rays and radioactive isotopes)	(2,3,4)	(4,5,6)	(6,7,8)	30.74%	1
	Night shift	(1,2,3)	(5,6,7)	(5,6,7)	28.23%	2
	Ergonomic (improper workstation, repetitive work)	(2,3,4)	(3,4,5)	(4,5,6)	23.97%	3
	Magnetic and electric fields	(2,3,4)	(2,3,4)	(2,3,4)	17.07%	4
MRI	Magnetic and electric fields	(2,3,4)	(4,5,6)	(6,7,8)	33.77%	1
	Non-ionizing radiation of radio waves	(2,3,4)	(2,3,4)	(4,5,6)	23.59%	3
	Psychological factors (job stress)	(2,3,4)	(2,3,4)	(2,3,4)	18.75%	4
	Ergonomic (improper workstation, repetitive work)	(2,3,4)	(3,4,5)	(3,4,5)	23.90%	2
Pharmacy	Ergonomic (long standing and sitting, repetitive tasks)	(2,3,4)	(3,4,5)	(3,4,5)	26.63%	2
	Psychological factors (disturbance of mental and physical balance due to repeated exposure)	(1,2,3)	(2,3,4)	(3,4,5)	20.21%	4
	Night shift	(1,2,3)	(5,6,7)	(3,4,5)	29.23%	1
	Contact with hand-made drugs or narcotics - drug abuse	(2,3,4)	(3,4,5)	(2,3,4)	23.94%	3
Kitchen	Ergonomic (pulling and lifting and repetitive tasks)	(2,3,4)	(4,5,6)	(4,5,6)	30.27%	2
	Foodborne Diseases (Escherichia coli, Salmonella, Staphylococcus aureus ..)	(2,3,4)	(2,3,4)	(2,3,4)	19.51%	3
	Thermal stress (increase in body temperature, excessive transpiration, workload, decrease in capacity and adaptation)	(3,4,5)	(3,4,5)	(4,5,6)	30.70%	1
	Psychological factors (job stress)	(2,3,4)	(2,3,4)	(2,3,4)	19.51%	3
Laundry	Hazardous chemicals (disinfectants-detergents)	(2,3,4)	(3,4,5)	(3,4,5)	23.76%	2
	Thermal stress (increase in body temperature, excessive transpiration, workload, decrease in capacity and adaptation)	(1,2,3)	(4,5,6)	(3,4,5)	23.46%	3
	Ergonomic (long standing, incorrect posture and excessive force)	(3,4,5)	(4,5,6)	(4,5,6)	32.05%	1
	Noise	(1,2,3)	(3,4,5)	(3,4,5)	20.73%	4
Waste	Ergonomic (prolonged standing work, incorrect posture and excessive force)	(2,3,4)	(4,5,6)	(6,7,8)	27.56%	2
	Hazardous infectious and chemical wastes	(3,4,5)	(5,6,7)	(6,7,8)	32.21%	1
	Thermal stress (cold and heat)	(1,2,3)	(4,5,6)	(4,5,6)	21.23%	3
	Noise	(1,2,3)	(3,4,5)	(4,5,6)	19.00%	4
Installations	Noise	(2,3,4)	(5,6,7)	(5,6,7)	30.18%	1
	Gases and vapors from welding and cutting	(2,3,4)	(3,4,5)	(4,5,6)	24.86%	3
	Thermal stress (cold and heat)	(2,3,4)	(2,3,4)	(2,3,4)	17.70%	4
	Ergonomic (incorrect posture and excessive force)	(3,4,5)	(2,3,4)	(4,5,6)	25.26%	2
Administrative	Ergonomic (long standing and sitting, repetitive tasks)	(2,3,4)	(4,5,6)	(3,4,5)	30.69%	1
	Light and brightness	(2,3,4)	(2,3,4)	(2,3,4)	25.82%	2
	Psychological factors (job stress)	(1,2,3)	(3,4,5)	(1,2,3)	22.33%	3
	Thermal stress (cold and heat)	(1,2,3)	(1,2,3)	(1,2,3)	15.15%	4
Services	Ergonomic (heavy carrying-patient handling)	(4,5,6)	(4,5,6)	(5,6,7)	31.39%	1
	Chemicals (disinfectants-detergents)	(2,3,4)	(5,6,7)	(3,4,5)	24.42%	3
	Airborne, blood and other body fluids pathogens (bacteria, viruses, parasites)	(2,3,4)	(3,4,5)	(6,7,8)	25.89%	2
	Dust (cleaning)	(2,3,4)	(4,5,6)	(1,2,3)	18.30%	4

should be controlled or eliminated, after identifying, analyzing and evaluating the risks. It should be noted that if this is not possible, they should be reduced to an acceptable level[23].

Conclusion

In this study, a new approach to prioritize failure modes was investigated in order to improve the risk priority number. The results obtained from the failure modes and effects analysis method used in this study show that if two or more failure modes have the same risk priority number, it is possible to evaluate and ranking the failure modes using risk prioritization codes. On the other hand, an attempt was made to determine the weight for each of the indicators of severity, probability of occurrence and detectability based on their importance using the method of hierarchical analysis process in fuzzy environment and

Table II: Safety risks.

Wards (sections)	The most important risk	S	O	D	Percentage of criticality	Rank
Clinical departments (Nursing)	Cutting and tearing caused by sharp tools (needle, angiocatheter, suture, razor, knife)	(2,3,4)	(3,4,5)	(2,3,4)	23.13%	3
	Electric shock	(2,3,4)	(2,3,4)	(2,3,4)	20.05%	4
	Slip and fall	(2,3,4)	(3,4,5)	(5,6,7)	31.02%	1
	Oxygen gas fire in case of leakage and burns	(3,4,5)	(2,3,4)	(3,4,5)	25.80%	2
Clinical departments (Practical Nurse)	Cutting and tearing caused by sharp tools (needle, angiocatheter, suture, razor, knife)	(2,3,4)	(4,5,6)	(2,3,4)	26.70%	2
	Slip and fall	(2,3,4)	(3,4,5)	(5,6,7)	32.71%	1
	Electric shock	(2,3,4)	(2,3,4)	(2,3,4)	20.49%	4
	Falling people (patient from bed or in elevator)	(4,5,6)	(1,2,3)	(1,2,3)	21.10%	3
Laboratory	Electric shock	(2,3,4)	(2,3,4)	(1,2,3)	19.56%	4
	Cutting and tearing caused by sharp tools (needle, angiocatheter, suture, razor, knife)	(2,3,4)	(4,5,6)	(4,5,6)	35.09%	1
	Burns and blisters (hot surfaces of sterile objects)	(2,3,4)	(2,3,4)	(2,3,4)	22.38%	3
	Slip and fall	(2,3,4)	(3,4,5)	(1,2,3)	22.98%	2
Operating room	Leakage and explosion of compressed and anesthetic gases	(3,4,5)	(1,2,3)	(3,4,5)	26.48%	2
	Cutting and tearing caused by sharp tools (needle, angiocatheter, suture, razor, knife)	(2,3,4)	(2,3,4)	(3,4,5)	26.36%	3
	Slip and fall	(2,3,4)	(3,4,5)	(2,3,4)	26.83%	1
	Electric shock	(2,3,4)	(2,3,4)	(1,2,3)	20.32%	4
CSR	Cutting and tearing caused by sharp tools (needle, angiocatheter, suture, razor, knife)	(2,3,4)	(3,4,5)	(2,3,4)	26.44%	1
	Slip and fall	(2,3,4)	(3,4,5)	(2,3,4)	26.44%	1
	electric shock	(3,4,5)	(2,3,4)	(1,2,3)	23.53%	4
	Elevator crash	(4,5,6)	(1,2,3)	(1,2,3)	23.60%	3
Radiology	Electric shock	(2,3,4)	(2,3,4)	(1,2,3)	23.95%	2
	Fire and burns	(2,3,4)	(2,3,4)	(1,2,3)	23.95%	2
	Conflict with moving parts of equipment and devices	(2,3,4)	(2,3,4)	(1,2,3)	23.95%	2
	Slip and fall	(2,3,4)	(3,4,5)	(1,2,3)	28.14%	1
MRI	Electric shock	(2,3,4)	(3,4,5)	(2,3,4)	29.66%	1
	Contact with sharp and win objects	(2,3,4)	(2,3,4)	(1,1,1)	18.23%	4
	Conflict with moving parts of equipment and devices	(2,3,4)	(2,3,4)	(2,3,4)	25.71%	3
	Slip and fall	(2,3,4)	(3,4,5)	(1,2,3)	26.39%	2
Pharmacy	Falling objects	(1,2,3)	(2,3,4)	(1,1,1)	18.60%	3
	Slip and fall	(2,3,4)	(2,3,4)	(1,2,3)	28.88%	2
	Electric shock	(2,3,4)	(3,4,5)	(1,2,3)	33.93%	1
	Cutting and tearing caused by winning tools	(1,2,3)	(2,3,4)	(1,1,1)	18.60%	3
Kitchen	Fire and burns caused by hot surfaces	(2,3,4)	(3,4,5)	(1,2,3)	23.31%	3
	Slip and fall	(2,3,4)	(4,5,6)	(1,2,3)	26.69%	1
	Unprotected equipment	(2,3,4)	(4,5,6)	(1,2,3)	26.69%	1
	Electric shock	(2,3,4)	(3,4,5)	(1,2,3)	23.31%	3
Laundry	Slip and fall	(2,3,4)	(2,3,4)	(1,2,3)	30.57%	1
	Electric shock	(2,3,4)	(4,5,6)	(4,5,6)	20.75%	3
	Elevator crash	(3,4,5)	(3,4,5)	(4,5,6)	27.92%	2
	Fire and burns	(1,2,3)	(2,3,4)	(2,3,4)	20.75%	3
Waste	Electric shock	(3,4,5)	(2,3,4)	(3,4,5)	17.94%	3
	Fire and burns	(4,5,6)	(1,2,3)	(2,3,4)	32.20%	2
	Cutting and tearing caused by winning tools	(3,4,5)	(2,3,4)	(2,3,4)	32.33%	1
	Slip and fall	(2,3,4)	(3,4,5)	(3,4,5)	17.53%	4
Installations	Electric shock	(3,4,5)	(1,2,3)	(1,2,3)	26.36%	1
	Danger of boiler explosion	(2,3,4)	(2,3,4)	(1,2,3)	23.66%	3
	Fire of heating devices, storage of flammable materials, defective wiring system	(2,3,4)	(1,2,3)	(1,2,3)	23.62%	4
	Throwing metal objects and particles, smoke	(3,4,5)	(3,4,5)	(3,4,5)	26.36%	1
Administrative	Fire	(2,3,4)	(3,4,5)	(2,3,4)	30.47%	1
	Electric shock	(3,4,5)	(3,4,5)	(1,2,3)	32.01%	2
	Slip and fall	(2,3,4)	(4,5,6)	(3,4,5)	29.35%	3
Services	Fire and explosion of cylinders	(2,3,4)	(2,3,4)	(1,2,3)	35.01%	1
	Elevator crash	(2,3,4)	(4,5,6)	(4,5,6)	22.14%	4
	Contact greasy hand of service with oxygen cylinder	(3,4,5)	(3,4,5)	(4,5,6)	22.64%	3
	Equipment and patient collide with cylinders	(1,2,3)	(2,3,4)	(2,3,4)	27.56%	2

formation of paired comparison matrix. This causes each of the indicators to effect on each failure mode based on their importance[24]. Fuzzy values were used to scoring three indices for each failure mode[25]. The use of an integrated approach leads to an increase in the efficiency of the FMEA method and greater confidence in the results[25]. Fuzzy Multi-criteria Risk Assessment method has been proposed to deal with obstacles and difficulties in calculating the definite risk score and reducing inconsistencies in decision making. In the present study, it has been tried to compensate the weaknesses of the case failure modes and effects analysis method by presenting new concepts and combining the FMEA method with Fuzzy- based Multiple Criteria Decision Making (MCDM) method. Therefore, in this respect, it is a completely new, comprehensive and accurate method that can be used by researchers, relevant officials, employers, companies, etc.

Interests conflict

The researchers declare that they have no conflict of interest.

References

1.Tziaferi SG, Sourtzi P, Kalokairinou A, Sgourou E,Koumoulas E, Velonakis E. Risk assessment of physical hazards in greek hospitals combining staff's perception, experts' evaluation and objective measurements. Safety and health at work. 2011;2(3):260-72.

2. United States Department of Labor, Occupational Safety & Health Administration. Safety and health topics: healthcare. Available at: https://www.osha, gov/SLTC/health carefacilities/index.html. Accessed August 5, 2014.

3. Omidvari M, Zareie M, Shahbazi D. HSE in hospitals. Fanavaran publication.2014 [Persian].

4. Charney W. Handbook of Modern Hospital Safety. 2nd ed. London: CRC Press; 2009: 1-226.

5. Alizadeh M, Tayebi AM, Falah MS. HSEQ-R total management system, 1stedn. Tehran;I.R.T.C.I.publication, 2008, 154-156 [Persian].

6. AS/NZS.Risk Management Standard, AS/NZS 4360: 2004. Jointly published by Standards Australia International Ltd., Sydney and Standards New Zealand, Wellington, (2004).

7. Mosallanezhad B, AhmadiA. Using fuzzy FMEA to increase patient safety in fundamental processes of operating room. Industrial and Systems Engineering.2018;11(3):146-66.

8. Chin, K. S., Chan, A., & Yang, J. B. (2008). Development of a fuzzy FMEA based product design system. The International Journal of Advanced Manufacturing Technology, 36(7-8), 633-49.

9. Kusler-Jensen J WAJ. FMEA An idea whose time hascome.SSM. 2003 Jun;9(3):30

10.Shahbazi D. Assessing and prioritizing health, safety and environmental risks in hospitals (Case study: ShahidBeheshti University of Medical Sciences). scientific journal of Ilam university of medical sciences. 2016;24(1):43-54.

11. Kutlu AC, Ekmekçioglu M. Fuzzy failure modes and effects analysis by using fuzzy TOPSIS-based fuzzy AHP. ExpSyst Appl. 2012;39(1):61-7. DOI: 10.1016/j.eswa.2011.06.044.

12. Onüt K, Kara S, Isik E. Long term supplier selection using a combined fuzzy MCDM approach: A case study for a telecommunication company. ExpSyst Appl. 2009;36(2):3887-96. DOI:10.1016/j.eswa.2008.02.045

13. EmblemsvågJ.,Kjølstad L.E. Strategic risk analysis a field version, Management Decision; 2002, 40 (9): 842-52

14. Jiang, W., Xie, C., Zhuang, M., & Tang, Y. (2017). Failure mode and effects analysis based on a novel fuzzy evidential method. Applied Soft Computing, 57, 672-83.

15.Dağsuyu C, Göçmen E, Narlı M, Kokangül A. Classical and fuzzy FMEA risk analysis in a sterilization unit. Computers & Industrial Engineering. 2016;101:286-94.

16.Chanamool N, Naenna T. Fuzzy FMEA application to improve decision-making process in an emergency department. Applied Soft Computing. 2016;43:441-53.

17. Jamshidi A, Rahimi SA, Ait-kadi D, Ruiz A. A comprehensive fuzzy risk-based maintenance framework for prioritization of medical devices. Applied Soft Computing. 2015;32:322-34.

18. 10.Omidvari M. Safety Risk Assessment in Motor Vehicle Industries by using William Fine and ANP-DEMATEL. Iran Occupational Health. 2017;14(1):57-70.

19. Sharma, R.K., D. Kumar, and P. Kumar,Systematic failure mode effect analysis(FMEA) using fuzzy linguistic modelling.International Journal of Quality &ReliabilityManagement, 2005. 22 (9): p. 986-1004

20. Yoon, K. and Hwang, C.L. \Manufacturing plant location analysis by multiple attribute decision making: Part II, Multi-plant strategy and plant relocation", International Journal of Production Research, 23(2), pp. 361-70 (1985).

21. Wang, Y.M. and Elhag, T.M.S. \Fuzzy TOPSIS method based on alpha level sets with an application to bridgerisk assessment", Expert Systems with Applications, 31, pp. 309-319 (2006).

22. Moradi A, Nadershahi M.A Fuzzy Multi-criteria Risk Assessment Based on Decision Matrix Technique: A Case Study in One of the Steel Industries.joheb. 2019; 6(2) :9-18

23. Mahdevari S, Shahriar K, Esfahanipour A. Human health and safety risks management in underground coal mines using fuzzy TOPSIS. Sci Total Environ. 2014;488:85-99. DOI: 10.1016/j.scitotenv.2014.04.076

24. Sabet Motlagh M, Ayazi SA, Hosseini Dehshiri SJ, Presenting a Combined Approach to Assessing and Ranking Failure Modes Using Violated FMEA and Fuzzy Hierarchical Analysis Process. JR_SQM. 2017;7(3)-002:19-30

25. Kamali A, Bozorgi-Amiri A,Shakibaei H. Risk Assessment and Ranking through Integration Failure Mode and Effects Analysis and Multiple-Criteria Decision-Making in an Interval Valued Fuzzy Environment: A Case Study in Hydraulic Pump Industry.joheb. 2020; 7(1) :1-10. .

eISSN 2255-0569

ORIGINAL

Results of a health intervention program in 1094 bolivian mining workers

Resultados de un programa de intervención en salud en 1094 trabajadores de mineria bolivianos

Vahid Mohebbi Ortuño[1], Ronald Lagrava Burgoa[2], Andrés Aramayo Quiroga[3], Cleyvis Liceras Escalante[4], Boris Apaza Quevedo[5]

1. Especialista en Medicina de Trabajo. Supervisor de Salud Ocupacional en Minera San Cristóbal S.A. Potosí. Bolivia.
2. Magister en Salud Publica. Superintendente Senior de Salud en Minera San Cristóbal S.A.
3. Magister en Salud Pública. Supervisor de Programas y Servicios en Minera San Cristóbal S.A. Potosí. Bolivia.
4. Diplomado en Seguridad industrial y Salud en el Trabajo. Médico General de Salud Ocupacional en Minera San Cristóbal S.A.
5. Diplomado en Gestión de la Salud. Analista de Gestión de Información de Salud en Minera San Cristóbal.

Corresponding author
Vahid Mohebbi Ortuño
Supervisor de Salud Ocupacional Minera San Cristóbal.
Potosí. Bolivia
E-mail: vmohebbi@gmail.com

Received: 23 - IX - 2021
Accepted: 15 - XI - 2021

doi: 10.3306/AJHS.2022.37.01.48

Abstract

Background: It is known that health intervention programs that include lifestyle changes usually have a beneficial effect on cardiovascular health. The aim of this study was to assess the impact of a health intervention program in Bolivian mining workers.
Materials and methods: A total of 1094 workers of a Bolivian mining company completed a healthy habits modification program that included diet, physical activity and smoking cessation during 2016 and 2019. The changes obtained in different scales related to cardiovascular risk such as vascular age, atherogenic indices, obesity and body fat were assessed.
Results: Significant improvements were observed both in the mean values and in the prevalence of altered values of all the scales analyzed in practically all the periods studied (2016-2017, 2017-2018 and 2018-2019).
Conclusion: The scales related to cardiovascular risk analyzed in this study have significantly improved after the implementation of this health intervention program.

Keywords: Health intervention programs, cardiovascular disease, obesity.

Resumen

Antecedentes: Se conoce que los programas de intervención en salud que incluyen cambios en el estilo de vida suelen tener un efecto beneficioso en la salud cardiovascular. El objetivo de este estudio fue valorar el impacto de un programa de intervención sanitaria en trabajadores de la minería boliviana.
Materiales y métodos: Un total de 1094 trabajadores de una empresa minera de Bolivia completaron un programa de modificación de hábitos saludables que incluía dieta, actividad física y abandono del consumo de tabaco durante los años 2016 y 2019. Se valoraron los cambios obtenidos en diferentes escalas relacionadas con riesgo cardiovascular como edad vascular, índices aterogénicos, obesidad y grasa corporal.
Resultados: Se observan mejorías significativas tanto en los valores medios como en la prevalencia de valores alterados de todas las escalas analizadas en prácticamente todos los periodos estudiados (2016-2017, 2017-2018 y 2018-2019).
Conclusión: Las escalas relacionadas con riesgo cardiovascular analizadas en este estudio han mejorado significativamente después de la implantación de este programa de intervención en salud.

Palabras clave: Programas de intervención en salud, enfermedad cardiovascular, obesidad.

Introduction

It is essential to know that the evaluation of any health program will make it possible to know and measure the results obtained, its possible usefulness and also its potential impact on health. It is not possible to know how a health intervention program will evolve if the appropriate evaluation methods are not available to establish strategies, implement changes, optimize available resources and facilitate decision-making based on the results obtained[1].

There are two possible ways to evaluate a health intervention program, one is the formative evaluation that will allow us to change and adjust the programs and the other is the summative evaluation that will assess the programs already completed. This summative evaluation will allow us to define important changes if necessary or to continue or modify the program according to the correlation that exists between the objectives that were set, the way in which they were executed and the results that were obtained[2,3].

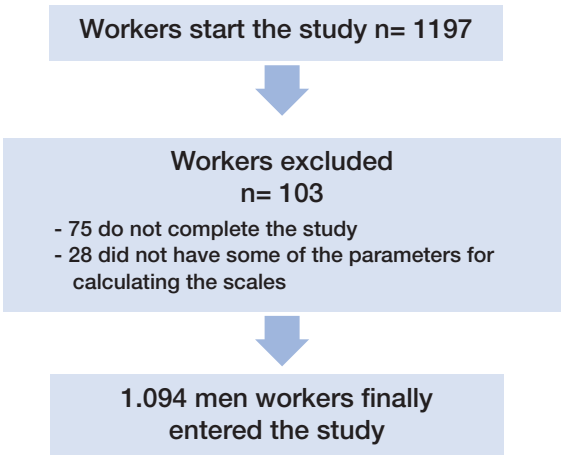
Knowing that the evaluation component of any program is fundamental, it is necessary that the people involved in the design and implementation plan from the beginning the evaluation methodology to be used[4,5].

The objective of this study is to evaluate the results of a health intervention program carried out in Bolivian mining workers.

Material and methods

Intervention study conducted in 1197 male workers of a mining company in Bolivia between the years 2016-2019. 103 workers were excluded from the study for different reasons (see flowchart in **Figure 1**) so the total number of people finally included in the study was 1094.

Figure 1: Flow chart of participants.



Four controls were carried out in 2016, 2017, 2018 and 2019. In each of the controls, the analytical, anthropometric, and clinical variables necessary to calculate the variables related to cardiovascular risk included in the study were determined.

Parameters included in the study

The different measurements (anthropometric, clinical, and analytical) were performed by health personnel from the participating occupational health units after homogenizing the measurement techniques.

Weight (in kilograms) and height (in cm) were obtained with a SECA 700 measuring scale with a capacity of 200 kg, which incorporated a SECA 220 telescopic measuring rod with millimetric division and a 60-200 cm interval.

Abdominal circumference were measured with a SECA model 200 tape measure with the person in a standing position with their feet together and trunk erect, abdomen relaxed, and upper limbs hanging on both sides of their body.

Blood pressure was obtained with an OMRON M3 automatic sphygmomanometer with the person in the supine position after 10 minutes of rest. Three measurements were taken at one-minute intervals and the mean of the three was obtained. Blood tests were obtained after 12 hours of fasting. Samples were sent to reference laboratories. Glycemia, total cholesterol and triglycerides use automated enzymatic methods, and the values are expressed in mg/dl. HDL was determined by precipitation with dextran sulfate Cl2Mg, and values are also expressed in mg/dl. LDL was calculated using the Friedewald formula (provided that triglycerides were less than 400 mg/dl). Values are expressed in mg/dl.

Friedewald formula: LDL= total cholesterol – HDL – triglycerides/5

The different atherogenic indices have different cutoff points[6]:

Total cholesterol/HDL-c index: low risk: < 5, moderate risk: between 5 and 9 and high risk: > 9 in men. LDL-c/HDL-c ratio: low risk: < 3 and high risk ≥ 3. Triglycerides/HDL-c ratio is considered high risk from 3%. Cholesterol-HDL-c index: high risk as from 130.

BMI is calculated by dividing weight by height in meters squared. Obesity is considered to be over 30.

CUN BAE[7] (Clínica Universidad de Navarra Body Adiposity Estimator) The formula is:

-44.988 + (0.503 x age) + (10.689 x gender) + (3.172 x BMI) - (0.026 x BMI2) + (0.181 x BMI x gender) - (0.02 x BMI x age) - (0.005 x BMI2x gender) + (0.00021 x BMI2 x age).

Where male sex equals 0 and female sex equals 1.

The CUN BAE cut-off points for obesity are from 25% in men and 35% in women.

An interesting concept that can also be applied to vascular ages, which we will see below, is avoidable lost life years (ALLY)[8] which can be defined as the difference between chronological age (CA) and vascular age (VA).

ALLY = Vascular age – Chronological age

As the meaning of ALLY is different according to the value of the CA, the ratio of ALLY to CA is defined as the ratio of avoidable lost life years (RALLY).

RALLY = ALLY / Chronological age

In order to calculate vascular age with the Framingham model[9], we used age, sex, HDL-c, total cholesterol, systolic blood pressure values, antihypertensive treatment, smoking, and diabetes. The scale can be calculated from the age of 30 years.

Since there are no cut-off points for vascular age, high values are set at five years of age and older.

A smoker was a person who regularly consumed at least 1 cigarette/day (or the equivalent in other types of consumption) in the previous month, or had stopped smoking in the preceding 12 months.

Protocol of intervention.

The intervention protocol included dietary advice to improve nutritional habits. Different levels of physical activity were recommended according to the characteristics of each worker. Smoking cessation was facilitated. Oral and written information on each of these activities was given at each of the visits.

Workers could visit the occupational health unit whenever they needed to increase adherence to the program.

Statistical analysis

A descriptive analysis of the categorical variables was performed, calculating the frequency and distribution of responses for each of them. For quantitative variables, the mean and standard deviation were calculated, and for qualitative variables, the percentage was calculated. The paired samples T-test was used to assess the difference in means. The McNemar test was used to assess the difference in proportions. Statistical analysis was performed with the SPSS 27.0 program, with an accepted statistical significance level of 0.05.

Ethical considerations and aspects

The study was approved by the Clinical Research Ethics Committee of the La Paz. All procedures were performed in accordance with the ethical standards of the institutional research committee and with the 2013 Declaration of Helsinki. All patients signed written informed consent documents before participating in the study.

Results

An improvement is observed in the mean values of all the parameters analysed, vascular age, atherogenic indices, BMI and CUN BAE as the programme progresses. The differences observed between each of the periods are always statistically significant except for RALLY for vascular age between 2018-2019. The full data are presented in **table I**.

Table I: Mean values of the different parameters in each of the years of the study and differences observed between them.

	year 2016 Mean (SD)	year 2017 Mean (SD)	year 2018 Mean (SD)	year 2019 Mean (SD)	dif (2016-17) Mean (p-value)	dif (2017-18) Mean (p-value)	dif (2018-19) Mean (p-value)
ALLY vascular age	2.04 (6.26)	-0,65 (5.32)	-1.18 (6.25)	-1.55 (4.77)	2.69 (<0.0001)	0.53 (0.001)	0.37 (0.01)
RALLY vascular age	0.046 (0.15)	-0.019 (0.12)	-0.032 (0.14)	-0.037 (0.10)	0.065 (<0.0001)	0.013 (0.001)	0.05 (0.082)
Total cholesterol/HDL-c	5.32 (1.50)	4.97 (1.28)	4.69 (1.35)	4.26 (0.97)	0.35 (<0.0001)	0.27 (<0.0001)	0.43 (<0.0001)
LDL-c/HDL-c	3.52 (1.18)	3.34 (1.06)	3.11 (1.08)	2.75 (0.74)	0.18 (<0.0001)	0.23 (<0.0001)	0.36 (<0.0001)
Triglycerides/HDL-c	5.29 (3.78)	4.97 (3.35)	4.62 (3.03)	4.15 (2.82)	0.32 (0.001)	0.35 (<0.0001)	0.47 (<0.0001)
Total cholesterol-HDL-c	164.28 (42.86)	157.67 (37.20)	154.03 (43.17)	150.21 (38.47)	6.61 (<0.0001)	3.63 (0.001)	3.83 (<0.0001)
BMI	27.46 (3.21)	27.05 (3.27)	26.86 (3.26)	26.70 (3.30)	0.41 (<0.0001)	0.18 (<0.0001)	0.17 (<0.0001)
CUNBAE	26.89 (4.53)	26.45 (4.68)	26.33 (4.65)	26.17 (4.88)	0.44 (<0.0001)	0.12 (0.006)	0.16 (0.007)

Table II: Prevalence of elevated values of the different parameters in each of the study years and differences observed between them.

	year 2016 %	year 2017 %	year 2018 %	year 2019 %	dif (2016-17) % (p-value)	dif (2017-18) % (p-value)	dif (2018-19) % (p-value)
ALLY vascular age ≥ 5	27.4	12.6	11.8	5.9	14.8 (<0.0001)	0.8 (0.529)	5.9 (<0.0001)
Total cholesterol/HDL-c moderate-high	54.8	46.3	40.5	35.3	8.5 (<0.0001)	5.8 (<0.0001)	5.2 (<0.0001)
LDL-c/HDL-c high	64.5	60.4	53.3	42.7	4.1 (0.004)	7.1 (<0.0001)	10.6 (<0.0001)
Triglycerides/HDL-c high	72.2	68.3	67.5	62.5	3.9 (0.002)	0.8 (0.591)	5.0 (0.001)
Total cholesterol-HDL-c high	79.8	79.4	70.5	70.4	0.4 (0.817)	8.9 (<0.0001)	0.1 (0.968)
BMI obesity	20.4	17.5	15.9	15.1	2.9 (<0.0001)	1.6 (0.048)	0.8 (0.281)
CUNBAE obesity	66.6	62.3	60.9	60.0	4.3 (<0.0001)	1.4 (0.125)	0.9 (0.282)

Table II shows the prevalence of altered values and the differences observed in each of the periods analysed, in all cases an improvement is observed as the programme progresses, although the differences observed are not always statistically significant.

Discussion

Both the mean values and the prevalence of elevated values of all the variables included in the study improve over the course of the health intervention programme carried out in Bolivian mining workers.

Similar data to ours were found in the study by Sammito[10] in German soldiers in which a decrease in BMI values was observed after an intervention programme. Other authors such as Liu, on the other hand, in a study conducted in 2015 in 2660 Taiwanese, observed no differences in BMI values before and after the lifestyle intervention[11].

A study conducted in a Spanish population[12] , although focusing particularly on physical activity, showed an improvement in anthropometric parameters as well as in lipid profile and cardiovascular risk. Similar results were obtained in a Croatian study[13].

We have not found any studies assessing the effect of a health intervention programme on atherogenic indices or vascular age, so we cannot compare our results with those obtained by other authors.

The strengths of the study include the large sample size (more than 1000 workers), the variety of scales calculated and the long duration of the programme (3 years).

The limitations of the study are that it was carried out in a specific geographical area and in a working population, which makes it impossible to generalise the results to other countries and to the general population. Another limitation is that a control group without intervention has not been established.

Interests conflict

The researchers declare that they have no conflict of interest.

References

1. Gnecco AT, Plaza RV. Evaluación de programas de salud. Rev Fac Cienc Salud Univ Cauca 2008;10(2): 48-55

2. De Salazar L, Díaz C. La evaluación-sistematización: una propuesta metodológica para la evaluación en promoción de la salud. Un estudio de caso en Cali, Colombia. Ciencia & Saude Colectiva 2004;9(3): 545-55

3. Habitcht JP, Victoria CG, Vaughan JP. Evaluation designs for adequacy, plausibility and probability for public health programme performance and impact. IJE 1999;28(1):10-18

4. De Salazar L. Evaluación de efectividad en promoción de la salud. Guía de evaluación rápida. Universidad del Valle, CEDETES, Cali 2004

5. Bergonzoli G. Propuesta: La epidemiología y la planificación local: medidas para la evaluación del impacto potencial. Colomb Med 2005;36: 44-9

6. López González ÁA, Rivero Ledo YI, Vicente Herrero MT, Gil Llinás M, Tomás Salvá M, Riutord Fe B. Índices aterogénicos en trabajadores de diferentes sectores laborales del área mediterránea española. Clin Investig Arterioscler. 2015;27(3):118-28

7. Gómez-Ambrosi J, Silva C, Catalán V, Rodríguez A, Galofré JC, Escalada J, et al. Clinical usefulness of a new equation for estimating body fat. Diabetes Care 2012;35(2):383-8.

8. Cuende JI. Edad vascular, RR, ALLY, RALLY y velocidad de envejecimiento, basados en el SCORE: relaciones entre nuevos conceptos de prevención cardiovascular. Rev Esp Cardiol. 2018;71:399-400

9. Ramírez M. La edad vascular como herramienta de comunicación del riesgo cardiovascular. Centro Integral para la Prevención de Enfermedades Crónicas. 2010. Disponible en: http://pp.centramerica.com/pp/bancofotos/267-2570.pdf

10. Sammito S. Obesity intervention during a work health promotion: the Obesity Intervention Program of the German military forces. J Occup Environ Med. 2013 Jul;55(7):728-31.

11. Liu CC, Hung CL, Shih SC, Ko HJ, Chang RE. Effects of health intervention program on cardiometabolic risk profiles from health evaluation center in Asian population: a longitudinal study and propensity analysis. Health Qual Life Outcomes. 2015;13:132.

12. Arija V, Villalobos F, Pedret R, Vinuesa A, Timón M, Basora T, et al. Effectiveness of a physical activity program on cardiovascular disease risk in adult primary health-care users: the "Pas-a-Pas" community intervention trial. BMC Public Health. 2017 Jun 15;17(1):576.

13. Francula-Zaninovic S, Nola IA. Management of Measurable Variable Cardiovascular Disease' Risk Factors. Curr Cardiol Rev. 2018;14(3):153-63.

eISSN 2255-0569

ORIGINAL

Values of body roundness index according different sociodemographic characteristics and healthy habits in caucasians

Valores del índice de redondez corporal según diferentes características sociodemográficasy hábitos saludables en los caucásicos

Yuri Shengeliya[1], Nataliya Shengeliya[2], Sofiya Shengeliya[3], Manana Uchaneyshvilli[4], Bárbara Altisench Jané[2], José Ignacio Ramírez Manent[2,5]

1. Policlinica nº 22, Filial 25 Moscú 2. Atención Primaria de Mallorca 3. Lechebni Center Moscú 4. Policlinica Ministerstva Oborini nº 9 Moscú 5. Universidad de las Islas Baleares

Corresponding author
Yuri Shengeliya
Policlinica n.º 22 filial 25, Moscú. Rusia
E-mail: n.u.s@mail.ru

Received: 24 - IX - 2021
Accepted: 18 - XI - 2021

doi: 10.3306/AJHS.2022.37.01.52

Abstract

Introduction: Obesity is a chronic disease characterized by an increase in fat mass and consequently by weight gain. The increase in the prevalence of obesity implies an increase in the prevalence of several obesity-related comorbidities. Several indices have been developed to determine obesity. The BRI is a new index to assess obesity. So far, only a few studies have been done using BRI. To learn more about this new index, a study is proposed whose objective was to analyze, in a large population, the relationship between a new index to assess obesity, the LBBB, and different sociodemographic parameters and healthy habits.

Methods: Descriptive and cross-sectional study in 60,799 Caucasian adult workers in which the BRI (Body Roundness Index) has been evaluated as a measure of obesity and its relationship with different parameters of age, sex, social class and educational level and healthy habits such as tobacco consumption. physical activity, dietary consumption of fruits and vegetables, and alcohol consumption.

Results: Male sex, age 50 years and older, social classes II-III, non-university studies, smokers, poor diet and low physical activity increase the risk of presenting elevated BRI, the highest OR being for alcohol consumption OR: 75.77 (73.98-77.56) in women and OR: 80.65 (79.71-81.58) in men, and not physical exercise with OR: 8.97 (8.49-9.46) in women and OR: 11.02 (10.53-11.52) in men.

Conclusion: Unhealthy habits, especially alcohol consumption and a somewhat less low level of physical activity and unhealthy eating, greatly increase the risk of developing high LBBB values.

Keywords: Obesity, alcohol consumption, unhealthy habits, physical activity.

Resumen

Introducción: La obesidad es una enfermedad crónica que se caracteriza por el aumento de la masa grasa y, en consecuencia, por el aumento de peso. El aumento de la prevalencia de la obesidad implica un aumento de la prevalencia de varias comorbilidades relacionadas con la obesidad. Se han desarrollado varios índices para determinar la obesidad. El BRI es un nuevo índice para evaluar la obesidad. Hasta ahora, sólo se han realizado unos pocos estudios con el BRI. Para conocer mejor este nuevo índice, se propone un estudio cuyo objetivo fue analizar, en una población amplia, la relación entre un nuevo índice para valorar la obesidad, el BRI, y diferentes parámetros sociodemográficos y hábitos saludables.

Métodos: Estudio descriptivo y transversal en 60.799 trabajadores adultos caucásicos en el que se ha evaluado el BRI (Índice de Redondez Corporal) como medida de obesidad y su relación con diferentes parámetros de edad, sexo, clase social y nivel educativo y hábitos saludables como el consumo de tabaco, actividad física, consumo dietético de frutas y verduras y consumo de alcohol.

Resultados: El sexo masculino, la edad de 50 y más años, las clases sociales II-III, los estudios no universitarios, los fumadores, la mala alimentación y la baja actividad física aumentan el riesgo de presentar un BRI elevado, siendo la OR más alta la del consumo de alcohol OR: 75,77 (73,98-77,56) en mujeres y OR: 80,65 (79,71-81,58) en hombres, y la del ejercicio físico no con OR: 8,97 (8,49-9,46) en mujeres y OR: 11,02 (10,53-11,52) en hombres.

Conclusión: Los hábitos poco saludables, especialmente el consumo de alcohol y un nivel algo menos bajo de actividad física y una alimentación poco saludable, aumentan en gran medida el riesgo de desarrollar valores elevados de BRI.

Palabras clave: Obesidad, consumo de alcohol, hábitos no saludables, actividad física.

Introduction

Obesity is defined as a chronic disease characterized by an increase in fat mass and consequently by an increase in weight[1]. Due to continuous increase in prevalence in all ages and its serious health consequences[2], obesity has become one important public health problem.

In worldwide more than a billion adults are overweight and 300 million of them are obese. In Spain, according to the National Health Survey of 2017, obesity affects 17,4% of the adult population (18% of men and 16% of women) and if added also the percentage of overweight affect a 54,57%[3].

The increase in prevalence of obesity involves an increase in the prevalence of several obesity-related comorbidities[4-6]. Among others, adiposity is supposed to be the physiological characteristic of obese and overweight individuals, which puts such individuals at-risk for cardiovascular disease[7-8]. In fact, the relationship between overall adiposity and risk for cardiovascular disease is well documented[9-10]. Furthermore, several studies, including the Framingham heart study[11], shows the relation between the adipose tissue accumulation and the incidence of adverse metabolic events and, also, with a higher risk for developing metabolic diseases[12-14]. Obesity also increases the risk of diabetes and certain types of cancer[15].

In addition to the consequences of their illness on the health of individual, it has been estimated that obesity and the diseases related to it, are a health cost of 2% to 7%[16].

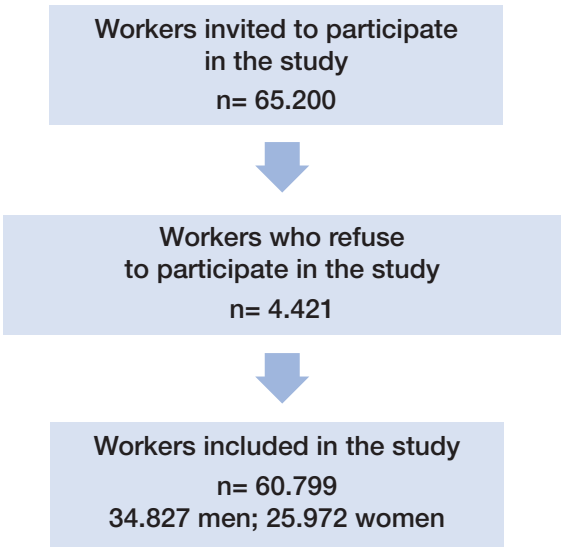
Several indices have been developed for determining obesity. Among others, the body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR) and waist-to-height ratio (WtHR). The BMI is the most widely used and accepted index for classifying overweight and obesity in clinical practice[17]. However, BMI presents some important and well documented limitations, such as: a different behavior in men and women, limited usefulness in children and athletes, differences between ethnic groups and especially in determining the composition and distribution of body fat, which can represent a limitation in epidemiological studies or clinical practice. Among other errors, the above indicated limitations could lead to classify individuals with high muscle mass as overweight or obese. On the other hand, subjects with BMI in the normal range may have a high percentage of fat. In last years they have emerged new indices to determine obesity, among them we can highlight the body adiposity index (BAI) and the body roundness index (BRI). The BAI was developed by Bergman et al[8] in African Americans and Mexican Americans and is determined from measurements of hip circumference and height. This index showed a high correlation with the measured body fat using DXA ($r = 0.85$; $p < 0.001$). However, a recent study in Spanish Mediterranean population suggested that BAI does not exceed the limitations of BMI[18]. The BRI is a new index to value the obesity, was developed in 2013 by Thomas et al[19] and to estimate waist circumference and height are needed. BRI values range from 1 to 16, and rounder individuals tend to have large values. Up to now, only a few studies have been conducted using the BRI. To know more this new index is proposed a study whose objective was to analyze, in a large population, the relationship between a new index to value the obesity, the BRI, and different socio demographic parameters as age, gender, social class and educational level and healthy habits as tobacco consumption, physical activity, dietary consumption of fruits and vegetables and alcohol consumption.

Material and methods

Subjects and Study Protocol

A cross-sectional study with Caucasians adult workers (ages, 20-69 years) was performed. All subjects were from Russia and belong to different productive sectors. Participants in the study were systematic selected during their work health periodic examination between January and December 2019. Every day each worker was assigned a number and half of the examined workers were randomly selected using a random number table. Thus, from a total population of 130.487 workers, 65.200 of them were invited to participate in the study. 4.421 (6.8%) refused to participate, being the final number of participants 60.799 (93.2%), with 25.972 women (42.7%) and 34.827 men (57.3%).

Figure 1



The mean of age of participants in the study was 39.98 years (SD±10.36). All participants were informed of the purpose of this study before they provided written informed consent to participle. Following the current legislation,

members of the Health and Safety Committees were informed as well. The study protocol was in accordance with the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee. After acceptance, a complete medical history, including family and personal history was recorded.

Inclusion criteria:

- Age between 18 and 69 (working age population),
- Agreement to participate in the study and to be gainfully employed.
- Subjects who did not meet any of the inclusion criteria and those who refused to participate were excluded from the study.

Measurements and Calculations

All anthropometric measurements were made in the morning, after an overnight fast, at the same time (9 a.m.), and according to the recommendations of the International Standards for Anthropometric Assessment (ISAK)[20]. Furthermore, all measurements were performed by well trained technicians or researchers to minimize coefficients of variation. Each measurement was made three times and the average value was calculated. Weight and height were determined according to recommended techniques mentioned above. Body weight was measured to the nearest 0.1 kg using an electronic scale (Seca 700 scale, Secagmbh, Hamburg). Height was measured to the nearest 0.5 cm using a stadiometer (Seca 220 (CM) Telescopic Height Rod for Column Scales, Seca gmbh, Hamburg). BMI was calculated as weight (kg) divided by height (m) squared (kg/m^2). Criteria to define overweight were the ones of the World Health Organization (WHO)21 which considers obesity when BMI ≥ 30 kg/m^2. Abdominal waist was measured using a flexible steel tape (Lufkin Executive Thinline W 606). The plane of the tape was perpendicular to the long axis of the body and parallel to the floor. Waist circumference was measured at the level of the umbilicus and the superior iliac crest. The measurement was made at the end of a normal expiration while the subject stood upright, with feet together and arms hanging freely at the sides. Waist circumference (WC) circumference (HC) was measured using a tapeline at the level midway between the lateral lower rib margin and iliac crest as well as at the levels of trochanters. WHtR was calculated by dividing WC by height in cm.

The BRI was calculated using the equation 364.2-365.5 x $\sqrt{1-((WC/2\pi)^2/(0.5\ height)^2)}$ developed by Thomas et al19 The cut off for normal and abnormal values was calculated with ROC curve.

Venous blood samples were taken from the antecubital vein with suitable vacutainers without anticoagulant to obtain serum. Blood samples were taken following a 12 h overnight fast. Participants were seated at rest for at least 15 minutes before blood samples were taken. Serum was obtained after centrifugation (15 min, 1,000 g, 4°C) of blood samples. Serum was stored at -20°C and analyses were performed within 3 days. Concentrations of glucose, cholesterol and triglycerides were measured in serum by standard procedures used in clinical biochemistry laboratory.

Blood pressure was determined after a resting period of 10 minutes in the supine position using an automatic and calibrated sphygmomanometer. As indicated for the anthropometrical measures, blood pressure was measured three times with a one-minute gap between each measurement and an average value was calculated.

For social class, the 2011 National Classification of Occupations (CNO-11) was used with the proposal made by the social determinants group of the Spanish Society of Epidemiology[22], classifying in 3 categories: Class I: Directors/managers, university professionals, athletes, and artists; Class II: Intermediate occupations and self-employed workers without employees; and Class III: Unskilled workers.

Smoking, diet, and physical activity were assessed by clinical interview. Tobacco was considered a dichotomous variable, being able to have the value of yes/no. A smoker was the person who had regularly consumed at least 1 cigarette/day (or the equivalent in other types of consumption) in the previous month or had stopped smoking less than a year before. Healthy eating included a daily consumption of vegetables and fruits; physical activity was considered adequate when performing at least 30 minutes a day or 150 minutes a week of moderate intensity aerobic physical activity or 75 minutes a week of vigorous activity.

Quantification of consumption in standard drinking units is currently the reference method at all levels of care. Assessment of consumption in standard drinking units allows a rapid quantification of consumption and its easy conversion into grams of pure alcohol[23]. The value of standard drinking units in Russia is set at 10 g of alcohol and is equivalent to one consumption of wine (100 ml), champagne (100 ml), or beer (200 ml) and half a consumption of spirits or mixed drinks (25 ml). If a man exceeds 35 standard drinking units in a week and a woman over 20 in a week, there is a significant risk to their long-term health[24].

Statistical Analyses

All the data were tested for their normal distribution (Kolmogorov-Smirnov test). Results are expressed as means and standard deviations (SD) and, when required, in percentages. Student t test for unpaired data was used to evaluate differences in anthropometric and biochemical characteristics between genders. Chi-square test was used for the difference of proportions.

The statistical method of ROC curves (Receiver operating characteristic) curves were used to determine BRI discriminatory capacity of obesity). Cutoff values were derived mathematically from the ROC curves. Statistical analysis was carried out using IBM SPSS Statistics 20.0 software (SPSS/IBM, Chicago, IL, USA). Significance was accepted at $p<0.05$.

Results

The sociodemographic, analytical and clinical characteristics of the population are shown in **table I**.

The mean BRI values increase with age in both sexes. There is also an increase in the BRI in the most disadvantaged social classes and the lower the level of studies. People with a healthy diet and who do physical activity regularly have lower mean LBBB values. All data is presented in **table II**.

The **figure 1** shows the area under the BRI curve for both men and women to detect obesity, establishing the cut-off points:

- Men cut-off 3.84 (sensitivity 0.762 specificity 0.762 Youden index 0.524.
- Women cut-off 3.17 (sensitivity 0.793 specificity 0.793 Youden index 0.586

In **table III** we observe that the prevalences of high BRI values in both sexes follow a similar trend to that observed with the mean values, that is, there is an increase in prevalence as age increases and as social class decreases. and the level of studies. Higher prevalences are also observed in people with unhealthy habits (smokers, poor diet and low level of physical activity). In all cases, as shown in **table III**, the prevalences are higher in men.

In the multivariate analysis using binary logistic regression, male sex, age 50 years and older, social classes II-III, non-university studies, smokers, poor diet and low physical activity were established as covariates. **Figure 3** shows how all the covariates increase the risk of presenting elevated BRI, the highest OR being for alcohol consumption and not physical exercise.

Table I: Sociodemographic, analytical and clinical characteristics of the population.

Characteristics	Women (n=25972)	Men (n=34827)	Total (n=60799)	p-value
Age (years)	39.45 ± 10.17	40.38 ± 10.48	39.98 ± 10.36	<0.0001
Weight (kg)	161.29 ± 6.52	81.28 ± 13.89	168.48 ± 9.23	<0.0001
Height (cm)	65.05 ± 13.08	173.85 ± 7.05	74.35 ± 15.75	<0.0001
BMI (kg/m²)	25.03 ± 4.91	26.88 ± 4.23	26.09 ± 4.63	<0.0001
Waist circumference (cm)	75.39 ± 9.82	88.58 ± 9.69	82.95 ± 11.73	<0.0001
Waist-to-height ratio	0.47 ± 0.06	0.51 ± 0.06	0.49 ± 0.06	<0.0001
Systolic BP (mmHg)	114.59 ± 15.11	125.35 ± 15.68	120.75 ± 16.33	<0.0001
Diastolic BP (mmHg)	70.43 ± 10.41	76.00 ± 10.84	73.62 ± 11.01	<0.0001
Total cholesterol (mg/dl)	192.97 ± 36.39	196.89 ± 38.69	195.22 ± 37.77	<0.0001
HDL-C (mg/dl)	54.97 ± 9.17	50.50 ± 7.61	52.41 ± 8.60	<0.0001
LDL-C (mg/dl)	120.47 ± 36.89	121.78 ± 37.25	121.22 ± 37.10	<0.0001
Triglycerides (mg/dl)	87.87 ± 45.96	125.30 ± 88.76	109.31 ± 75.88	<0.0001
Glycaemia (mg/dl)	85.21 ± 15.08	90.62 ± 21.20	88.31 ± 19.02	<0.0001

Table II: Values of BRI according sociodemographic variables and healthy habits by sex.

	Women	Men	Total	
Characteristics	Mean ± SD	Mean ± SD	Mean ± SD	p-value
20-29 years	2.48 ± 0.95	3.14 ± 0.93	2.84 ± 0.99	<0.0001
30-39 years	2.67 ± 1.08	3.45 ± 1.06	3.11 ± 1.13	
40-49 years	3.02 ± 1.25	3.75 ± 1.13	3.43 ± 1.24	
50-59 years	3.27 ± 1.26	4.00 ± 1.21	3.72 ± 1.28	
60-69 years	3.35 ± 1.22	4.10 ± 1.19	3.83 ± 1.26	
Social class I	2.53 ± 1.02	3.52 ± 1.09	2.94 ± 1.16	<0.0001
Social class II	2.91 ± 1.35	3.67 ± 1.15	3.29 ± 1.31	
Social class III	2.90 ± 1.09	3.60 ± 1.13	3.34 ± 1.16	
Elementary	3.02 ± 1.21	3.60 ± 1.12	3.41 ± 1.19	<0.0001
High School	2.75 ± 1.15	3.63 ± 1.16	3.16 ± 1.24	
University	2.52 ± 1.03	3.57 ± 1.11	2.96 ± 1.18	
Non smokers	2.89 ± 1.19	3.65 ± 1.12	3.32 ± 1.21	<0.0001
Smokers	2.77 ± 1.15	3.53 ± 1.14	3.23 ± 1.20	
Physical activity	2.30 ± 0.63	2.99 ± 0.65	2.67 ± 0.72	<0.0001
Non physical activity	3.45 ± 1.34	4.10 ± 1.19	3.85 ± 1.29	
Correct feeding	2.31 ± 0.62	2.99 ± 0.65	2.66 ± 0.72	<0.0001
Non correct feeding	3.40 ± 1.35	4.02 ± 1.20	3.79 ± 1.29	
Non alcohol consumption	2.74 ± 1.06	3.37 ± 0.96	3.08 ± 1.05	<0.0001
Alcohol consumption	4.39 ± 1.61	4.90 ± 1.11	4.78 ± 1.27	

Figure 1: ROC curve.

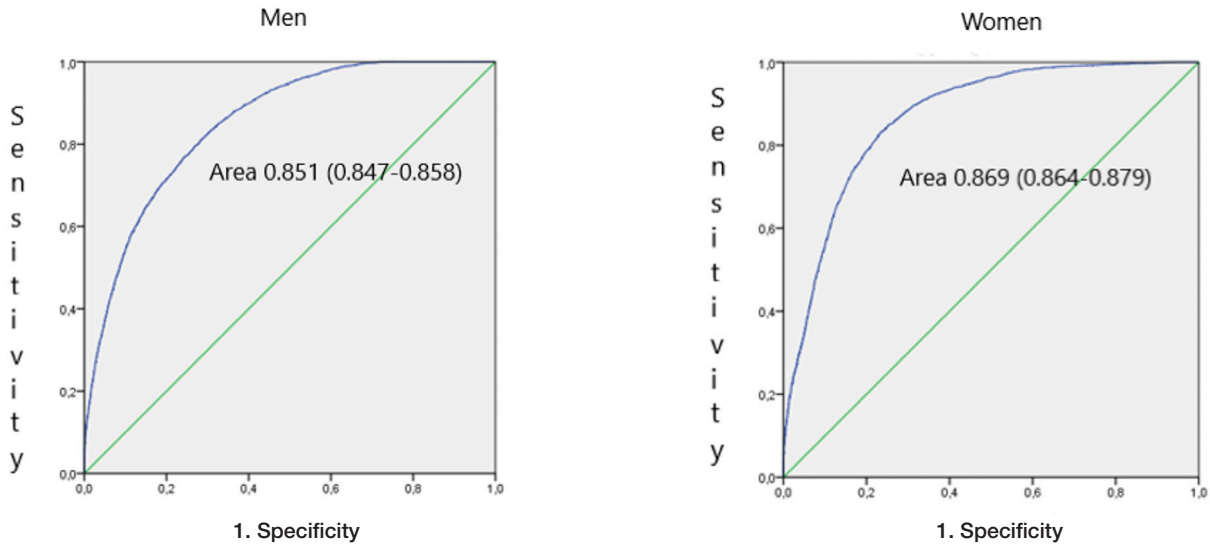
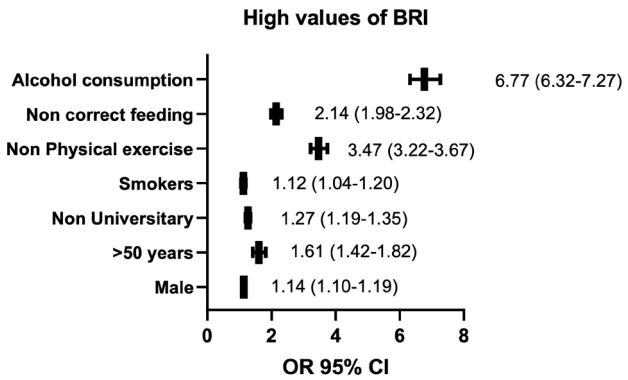


Table III: Prevalence of high values of BRI according sociodemographic variables and healthy habits by sex.

	Women			Men		
	n	High BRI	p-value	n	High BRI	p-value
Social class I	3670	18.88 (17.62-20.15)	<0.0001	2582	32.26 (30.46-34.07)	<0.0001
Social class II	8482	29.68 (28.70-30.65)		8173	36.46 (35.42-37.51)	
Social class III	13820	31.68 (30.90-32.45)		24071	34.22 (33.62-34.82)	
Elementary	12240	34.98 (34.13-35.82)	<0.0001	23670	34.60 (33.99-35.20)	<0.0001
High School	10517	25.65 (24.82-26.49)		8882	34.83 (33.84-35.83)	
University	3215	18.94 (17.59-20.30)		2274	33.73 (31.78-35.67)	
20-29 years	4950	17.01 (15.96-18.06)	<0.0001	5892	18.11 (17.13-19.09)	<0.0001
30-39 years	8435	23.71 (22.80-24.62)		11019	28.41 (27.56-29.25)	
40-49 years	7840	34.38 (33.32-35.43)		10399	39.22 (38.28-40.15)	
50-59 years	4096	42.75 (41.23-44.27)		6339	49.65 (48.41-50.88)	
60-69 years	651	46.08 (42.24-49.92)		1177	53.56 (50.50-56.21)	
Non smoker	17541	30.85 (30.16-31.53)	<0.0001	22081	36.16 (35.49-36.76)	<0.0001
Smoker	8431	31.82 (30.89-32.76)		12745	36.97 (36.16-37.78)	
Physical activity	12410	51.34 (50.46-52.22)	<0.0001	19483	53.17 (52.47-53.87)	<0.0001
Non physical activity	13562	8.97 (8.49-9.46)		15343	11.02 (10.53-11.52)	
Correct feeding	12829	49.88 (49.01-50.75)	<0.0001	20870	50.46 (49.78-51.13)	<0.0001
Non correct feeding	13143	9.05 (8.56-9.54)		13956	10.89 (10.37-11.41)	
Non alcohol consumption	23768	24.90 (24.35-25.45)	<0.0001	28011	23.40 (22.90-23.89)	<0.0001
Alcohol consumption	2204	75.77 (73.98-77.56)		6815	80.65 (79.71-81.58)	

Figure 3: Binary logistic regression.



Discussion

Our results show a higher prevalence of BRI in men compared to women, which is consistent with studies carried out by other authors[25]. The mean values of systolic and diastolic blood pressure were also higher for men than for women, which was to be expected due to the hormonal effect that progesterone and estrogens produce on the regulation of blood pressure in women[26].

We found that unhealthy eating habits are associated with a higher percentage of BRI in both sexes with a small, albeit positive, effect of healthy eating on BRI, which is consistent with the study by Ching et al conducted in Malaysia. Although in this study what was valued was the percentage of metabolic syndrome between vegetarians and non-vegetarians, in the latter a lower percentage

of obesity was revealed[27]. These vegetarian diets are more similar to healthy eating patterns characterized by the consumption of foods high in vitamins, minerals, antioxidants, fiber, MUFA (monounsaturated fatty acids) and n-3 fatty acids. In fact, greater adherence to healthy dietary patterns is associated with a lower risk of glucose intolerance, weight gain, inflammation, insulin resistance, and a higher level of HDL cholesterol[28].

In our study, alcohol appears as one of the unhealthy lifestyle habits that is most related to obesity. Taking into account that 1 gram of alcohol provides 7.1 kcal and that the energy created by alcohol is added to that of other foods, the energy increase from alcohol consumption can produce a positive energy balance with weight gain[29]. In addition, different studies support the fact that habitual alcohol consumption modifies dietary intake and this is dose dependent. This effect on diet affects the intake of specific macronutrients differently. Thus, when alcohol consumption is related to higher dietary intake, the most frequent is fat and protein intake and, less frequently, carbohydrate intake[30].

Physical exercise promotes the reduction of body fat and the increase of lean mass. Aerobic exercise is the most recommended; however, the addition of resistance exercises is essential to increase strength and prevent loss of fat-free mass[31]. In our work, the lack of physical exercise on a regular basis is the second cause that is most related to a high BRI value. Although the way to evaluate the amount of fat tissue is different from that of other studies, our results coincide with these, finding a higher proportion of fat tissue in those with a low level of physical activity[32].

In our literature search, we have not found in the different databases studies examining the influence of sociodemographic variables on BRI values, therefore we can not compare our results with those obtained by other authors. Regarding healthy habits and their influence on BRI values, Sánchez et al studied it in the ILERVAS[33] project carried out in 6672 middle-aged people and observed a beneficial effect of physical activity and the Mediterranean diet, just like us.

Strengths and limitations

As strengths of the study, we will highlight the large sample size, more than 60,000 people, the large number of variables analyzed and the establishment of cut-off points for the BRI.

As limitations, it should be noted that our data is based on the Russian population, so it cannot be extrapolated to other countries and only those patients who have attended the company's medical check-ups are included. Another limitation is that physical activity and diet have not been determined through validated scales, but rather through a survey.

Finally, as it is a cross-sectional study, it does not allow establishing causal relationships between the assessed factors.

Conclusions

In our work, the main conclusion is that unhealthy habits, especially alcohol consumption and somewhat less low level of physical activity and unhealthy eating, greatly increase the risk of presenting high LBBB values. Sociodemographic variables such as age, sex, and educational level have a much smaller effect.

Interests conflict

The researchers declare that they have no conflict of interest.

References

1. Barbany M, Foz M. Obesidad: concepto, clasificación y diagnóstico. An Sist Sanit Navar. 2002;25 Suppl 1: 3-6.

2. Hetherington MM, Cecil JE. Gene-environment interactions in obesity. Forum Nutr. 2010; 63: 195-203.

3. ENSE 2017 https://www.mscbs.gob.es/estadEstudios/estadisticas/encuestaNacional/encuesta2017.htm

4. Dietz WH, Robinson TN. Clinical practice. Overweight children and adolescents. N Engl J Med. 2005; 352: 2100-9.

5. Must A, Spadano J, Coakley EH, Field AE, Colditz G, et al. The disease burden associated with overweight and obesity. JAMA.1999; 282: 1523-9.

6. Ross R, Berentzen T, Bradshaw AJ, Janssen I, Kahn HS, et al. Does the relationship between waist circumference, morbidity and mortality depend on measurement protocol for waist circumference? Obes Rev. 2008; 9: 312-25.

7. Piché ME, Tchernof A , and Després JP. Obesity Phenotypes, Diabetes, and Cardiovascular Diseases. Circ Res. 2020;126(11):1477-1500. https://doi.org/10.1161/CIRCRESAHA.120.316101

8. Bergman RN, Stefanovski D, Buchanan TA, Sumner AE, Reynolds JC, et al. A better index of body adiposity. Obesity (Silver Spring).2011; 19: 1083-9.

9. Katzmarzyk PT, Gagnon J, Leon AS, Skinner JS, Wilmore JH, et al. Fitness, fatness, and estimated coronary heart disease risk: the HERITAGE Family Study. Med Sci Sports Exerc.2001; 33: 585-90.

10. Tanaka H, Clevenger CM, Jones PP, Seals DR, DeSouza CA. Influence of body fatness on the coronary risk profile of physically active postmenopausal women. Metabolism.1998; 47: 1112-20.

11. Kannel WB, Dawber TR, Kagan A, Revotskie N, Stokes J. Factors of risk in the development of coronary heart disease–six year follow-up experience. The Framingham Study. Ann Intern Med. 1961;55: 33-50.

12. Eckel RH, Alberti KG, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet.2010; 375: 181-3.

13. Mathieu P, Poirier P, Pibarot P, Lemieux I, Despres JP. Visceral obesity: the link among inflammation, hypertension, and cardiovascular disease. Hypertension.2009; 53: 577-84.

14. Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet.2009;373: 1083- 96.

15. Heber D. An integrative view of obesity. Am J Clin Nutr.2010; 91 (1): 280S-283S.

16. Low S, Chin MC, Deurenberg-Yap M. Review on Epidemic of Obesity. Ann Acad Med Singapore 2009; 38 (1): 57-9.

17. Bouchard C. BMI, fat mass, abdominal adiposity and visceral fat: where is the 'beef'? Int J Obes (Lond).2007; 31: 1552-3.

18. Lopez AA, Cespedes ML, Vicente T, Tomas M, Bennasar-Veny M, et al. Body adiposity index utilization in a Spanish Mediterranean population: comparison with the body mass index. PLoS One.2012; 7: e35281.

19. Thomas DM, Bredlau C, Bosy-Westphal A, Mueller M, Shen W, Gallagher D, et al. Relationships between body roundness with body fat and visceral adipose tissue emerging from a new geometrical model. Obesity.2013;21(11):2264-71

20. Bioelectrical impedance analysis in body composition measurement: National Institutes of Health Technology Assessment Conference Statement. Am J Clin Nutr. 1996;64:524S-532S.

21. Organization WH. Obesity: preventing and managing the global epidemic. Report of a WHO Consultation. 2000. Ginebra:WHO

22. Domingo-Salvany A, Bacigalupe A, Carrasco JM, Espelt A, Ferrando J, Borrell C. Propuesta de clase social neoweberiana y neomarxista a partir de la Clasificación Nacional de Ocupaciones 2011. Gac Sanit 2013;27(3):263-72

23. Silla Stoel M, Rosón Hernández B. Evaluación del consumo de alcohol y diagnóstico de patrón de consumo. Trastornos Adictivos. 2009;11(3):191-9

24. Rodríguez-Martos A, Gual A, Llopis Llacer JJ. La unidad de bebida estándar: un registro simplificado del consumo de bebidas alcohólicas. Med Clin (Barc) 1999; 112: 446-50

25. Nkwana MR, Monyeki KD, Lebelo SL. Body Roundness Index, A Body Shape Index, Conicity Index, and Their Association with Nutritional Status and Cardiovascular Risk Factors in South African Rural Young Adults. Int J Environ Res Public Health. 2021 Jan 1;18(1):281. doi: 10.3390/ijerph18010281.

26. Wenner MM, Stachenfeld NS Regulación de la presión arterial y el agua: comprensión de los efectos de las hormonas sexuales dentro y entre hombres y mujeres. J. Physiol. 2012; 590 : 5949–5961. doi: 10.1113 / jphysiol.2012.236752.

27. Ching YK, Chin YS, Appukutty M, Gan WY, Chan YM. Comparisons of conventional and novel anthropometric obesity indices to predict metabolic syndrome among vegetarians in Malaysia. Sci Rep. 2020 Nov 30;10(1):20861. doi: 10.1038/s41598-020-78035-5.

28. Fung TT, Willett WC, Stampfer MJ, Manson JE, Hu FB Dietary patterns and the risk of coronary heart disease in women. Arco. Interno. Medicina. 2001; 161 : 1857–1862. doi: 10.1001 / archinte.161.15.1857.

29. Yeomans MR. Alcohol, appetite and energy balance: is alcohol intake a risk factor for obesity? Physiol Behav. 2010;100:82–9. doi: 10.1016/j.physbeh.2010.01.012

30. Cummings JR, Gearhardt AN, Ray LA, Choi AK, Tomiyama AJ. Experimental and observational studies on alcohol use and dietary intake: a systematic review. Obes Rev. 2020 Feb;21(2):e12950. doi: 10.1111/obr.12950. Epub 2019 Nov 5.

31. Swift DL, McGee JE, Earnest CP, Carlisle E, Nygard M, Johannsen NM. The Effects of Exercise and Physical Activity on Weight Loss and Maintenance. Prog Cardiovasc Dis. 2018 Jul-Aug;61(2):206-213. doi: 10.1016/j.pcad.2018.07.014. Epub 2018 Jul 9.

32. Xiao T, Fu YF. Resistance training vs. aerobic training and role of other factors on the exercise effects on visceral fat. Eur Rev Med Pharmacol Sci. 2015 May;19(10):1779-84.

33. Sánchez M, Sánchez E, Hernández M, González J, Purroy F, Rius F et al. Dissimilar impact of a Mediterranean diet an physical activity on anthropometric indice: a cross-sectional study from the ILERVAS-Project. Nutrients 2019;11(6):1359

eISSN 2255-0569

ORIGINAL

Evaluation of the neck lymph node involvement in outcome of iranian patients with maxillofacial squamous cell carcinoma

Evaluación de la afectación de los ganglios linfáticos del cuello en los pacientes iraníes con carcinoma maxilofacial de células escamosas

Hossein Danesteh[1], Azita Sadeghzadeh[2], Farshad Dehghani[3]

1. Department of Oral and Maxillofacial Surgery, School of Dentistry, Shiraz University of Medical Sciences, Shiraz, Iran.
2. Oral and Dental Disease Research Center, Department of Oral and Maxillofacial Medicine, School of Dentistry, Shiraz University of Medical Sciences, Shiraz, Iran.
3. Undergraduate Student, School of Dentistry, Shiraz University of Medical Sciences, Shiraz, Iran.

Corresponding author
Azita Sadeghzadeh
Oral and Dental Disease Research Center, Department of Oral and Maxillofacial Medicine, School of Dentistry, Shiraz University of Medical Sciences, Shiraz, Iran
E-mail: a_sadeghzade@sums.ac.ir

Received: 27 - IX - 2021
Accepted: 22 - XI - 2021

doi: 10.3306/AJHS.2022.37.01.59

Abstract

Background: Oral squamous cell carcinoma (OSCC) is the predominant malignancy of oral cavity (about 90% of oral malignant lesions). This study aimed to evaluate the long-term extent of lymph node involvement of the neck among patients with maxillofacial SCC after the surgery.
Methods: In this cross-sectional study, 32 patients with maxillofacial SCC who underwent surgery were evaluated for any type of lymph node involvement (necrotic, reactive, or metastatic) at 3, 6, 12, and 24 months. Data was acquitted through clinical and paraclinical examinations such as CT scan, ultrasound of the neck area, pathology and histology.
Results: The SCC of posterior mandible had more lymph node involvement (P=0.02). Compared to moderately/poorly differentiated cases, patients with well-differentiated histopathological grade had lower lymph node involvement (P=0.01). TNM stage had no influence on lymph node involvement (P>0.05). Patients with neck dissection and reconstruction (P=0.003) as well as those who received postoperative radiotherapy or chemotherapy/radiotherapy together (P=0.001 and 0.005 respectively) had lower degree of lymph node involvement. Post-operative lymph node involvement was significantly more in patients with the positive CT scan status of bilateral metastatic lymphadenopathy in zones 1, 2 and 3 before the operation in comparison to other statuses like bilateral benign lymph nodes (p=0.001) or lymphadenopathy in just one or two zones (1and/or 2) (P>0.05).
Conclusion: We determined the effect of different parameters on lymph node involvement and determined some positive and negative correlations. Furthermore, some parameters like age, gender, and TNM staging had no influence on the mentioned outcome.

Keywords: OSCC; lymph node involvement; TNM staging.

Resumen

Antecedentes: El carcinoma oral de células escamosas (CCE) es la neoplasia maligna predominante de la cavidad oral (alrededor del 90% de las lesiones malignas orales). El objetivo de este estudio es evaluar la extensión a largo plazo de la afectación de los ganglios linfáticos del cuello entre los pacientes con CCE maxilofacial después de la cirugía.
Métodos: En este estudio transversal, 32 pacientes con CCE maxilofacial sometidos a cirugía fueron evaluados para cualquier tipo de afectación ganglionar (necrótica, reactiva o metastásica) a los 3, 6, 12 y 24 meses. Los datos se absolvieron mediante exámenes clínicos y paraclínicos como la tomografía computarizada, la ecografía de la zona del cuello, la patología y la histología.
Resultados: El CCE de la mandíbula posterior tenía más afectación de los ganglios linfáticos (P=0,02). En comparación con los casos moderadamente/pobremente diferenciados, los pacientes con grado histopatológico bien diferenciado tenían menor afectación ganglionar (P=0,01). El estadio TNM no influyó en la afectación de los ganglios linfáticos (P>0,05). Los pacientes con disección y reconstrucción del cuello (P=0,003), así como los que recibieron radioterapia postoperatoria o quimioterapia/radioterapia conjuntamente (P=0,001 y 0,005 respectivamente) tuvieron menor grado de afectación ganglionar. La afectación ganglionar postoperatoria fue significativamente mayor en los pacientes con el estado positivo en la TC de linfadenopatía metastásica bilateral en las zonas 1, 2 y 3 antes de la operación en comparación con otros estados como los ganglios linfáticos benignos bilaterales (p=0,001) o la linfadenopatía en sólo una o dos zonas (1y/o 2) (P>0,05).
Conclusión: Determinamos el efecto de diferentes parámetros sobre la afectación ganglionar y determinamos algunas correlaciones positivas y negativas. Además, algunos parámetros como la edad, el sexo y el estadiaje TNM no influyeron en el resultado mencionado.

Palabras clave: CCE; afectación de los ganglios linfáticos; estadiaje TNM.

Introduction

Oral squamous cell carcinoma (OSCC) as the most common malignant epithelial neoplasm of the oral cavity comprises 2%-4% of all cancer cases[1]. A group of neoplasms affecting any region of the oral cavity, pharynx and salivary glands are called oral cancer. However, this term and OSCC tend to be used interchangeably, as the latter comprises more than 90% of all oral neoplasms. Despite the new therapeutic approaches, morbidity and mortality from OSCC have not changed significantly during the last 30 years. It seems that its incidence, however, has been increasing among young white individuals (especially women) aged 18 to 44 years. The five-year survival of patients with OSCC is between 40-50%; its clinical manifestations in advanced stages are so characteristic that misdiagnosis rarely happens. In contrast, incorrect diagnosis is quite possible in the early stages, which may explain why OSCC is usually diagnosed in the advanced stages regardless of easy access to the oral cavity for clinical examination[2].

Tobacco and alcohol are the greatest risk factors for OSCC in the western world[3] and seem to have synergic effect[4]. The use of areca nuts (also called betel quid)[5] and narcotics are other risk factors[6]. OSCC mostly occurs in older men and people with low socioeconomic status[7]. Immune deficiency, body inability to repair damaged DNA and reduce carcinogens, and vitamin deficiency are represent important risk factors[8].

The most common symptoms in patients with oral cancer are discomfort and pain which can vary from mild discomfort to severe pain[9]. Some other symptoms are dysphagia, difficulty in breathing and speech, teeth mobility, trismus and paresthesia[10]. The tongue and mouth floor are the most common sites for OSCC accounting for more than 50% of cases in the West[11]. Biopsy and histopathological evaluation are always necessary for diagnosis[12]. Evaluating the histological characteristics of the tumor and its adjacent tissues, are essential for devising the treatment plan and predicting the outcome[13]. The factors that mainly affect the prognosis of OSCC include size and site, tumor thickness histopathologic grade, perineural invasion, lympho vascular invasion, tumor suppressor gene impairment (e.g., p53) and the quality of treatment[14]. It is crucial to determine the status of lymph nodes after the diagnosis of OSCC. Before requesting paraclinical assessments, a thorough clinical investigation should be done. However this may not be accurate because the tumor cells spread into the adjacent tissues before any clinical symptoms develop[15]. The clinical method for detecting regional cervical lymph node involvement is palpation[16], though computed tomography (CT)[17], ultrasonography (US)[18] and biopsy are paraclinical investigations that may be essential in the detection of cervical lymph node involvement. Head and neck cancers usually spread through lymph nodes rather than hematogenously. The size and site of the primary tumor play an important role in lymph node involvement[19]. Proper treatment for early-stage (T1/T2) squamous cell carcinoma (SCC) of the oral cavity is a controversial issue. Surgery and radiotherapy are often used to control the primary tumor, but failure often occurs because of recurrence in cervical lymph nodes[20]. In this study, we aimed to investigate the long-term extent of lymph node involvement of the neck after surgery among patients with maxillofacial SCC.

Materials and Methods

Study procedure

In this cross-sectional study, 32 patients with maxillofacial SCC who were referred to Rajaei Trauma Hospital affiliated to Shiraz University of Medical Sciences, Shiraz, Iran from 2014-2018 were studied. The protocol of this study was approved by the local Ethics Committee of Shiraz University of Medical Sciences (approval ID: IR.SUMS.DENTAL.REC.1399.117).

The patients underwent surgery and were evaluated for lymph nodes involvement of any type (necrotic, reactive, or metastatic) at 3 months, 6 months, 1 year, and 2 years after the operation. Data was acquitted through the clinical examination as well as the neck CT scan with contrast, ultrasound of the neck area and pathology and histology sheets. In the ultrasound and CT scan, changes in the form, size and the number of lymph nodes were noted. The diagnosis of metastasis was made based on the pathology and radiology reports as well as observations made during the operation. Inclusion criteria were patients below the age of 75 years with primary SCC in the maxillofacial zone. Exclusion criteria were patients with recurrent SCC, end-stage disease, facial involvement, distant metastasis (including the lung and brain), or systemic conditions. According to the data obtained through ultrasound, radiology and clinical examinations, we determined the TNM stage, which indicates the number and size of involved lymph nodes and presence or absence of metastasis (**Table I**).

Table I: The TNM staging system for patients with maxillofacial squamous cell carcinoma.

TNM Stage	Tumor	Node involvement	Metastasis
Stage 0	T is	N0	M0
Stage I	T 1	N0	M0
Stage II	T.2	N0	M0
Stage III	T.3	N0	M0
	T.1	N1	M0
	T.2	N1	M0
	T.3	N1	M0
Stage IVA	T.4a	N0	M0
	T.4a	N1	M0
	T.1	N2	M0
	T.2	N2	M0
	T.3	N2	M0
	T 4a	N2	M0
Stage IVB	Any T	N3	M0
	T 4b	Any N	M0
Stage IVC	Any T	Any N	-----

Statistical analysis

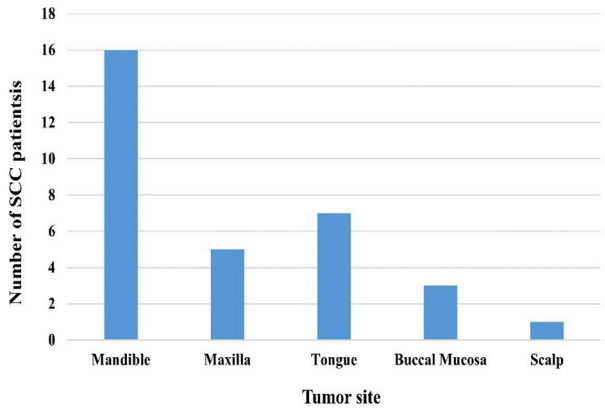
All statistical analyses were carried out using the SPSS software package (SPSS Inc., Chicago, USA). Continuous and normally distributed data were expressed as mean ± standard deviation (SD). One-way analysis of variance (ANOVA) and the post-hoc Tukey tests were used to compare the differences among experimental groups. A p-value of less than 0.05 was considered statistically significant.

Results

Overall, 32 proven cases of maxillofacial SCC were eligible for the analysis. The patient group consisted of 20 males (62.5%) and 12 females (37.5%). For more insight to the data, the patients were divided into four age groups: below 50 years (n=7), 51-60 years (n=9), 61-70 years (n=13), and older than 70 years (n=3). There was no statistically significant difference in the SCC prevalence between different age groups (P=0.9) and genders (P=0.15). The lymph node involvement did not differ with respect to age (P=0.25) and sex (P=0.18).

As shown in **figure 1**, the mandible (n=16, 50%) was the most common site affected by the OSCC in both males and females.

Figure 1: Sites affected by the OSCC in both males and females' groups.

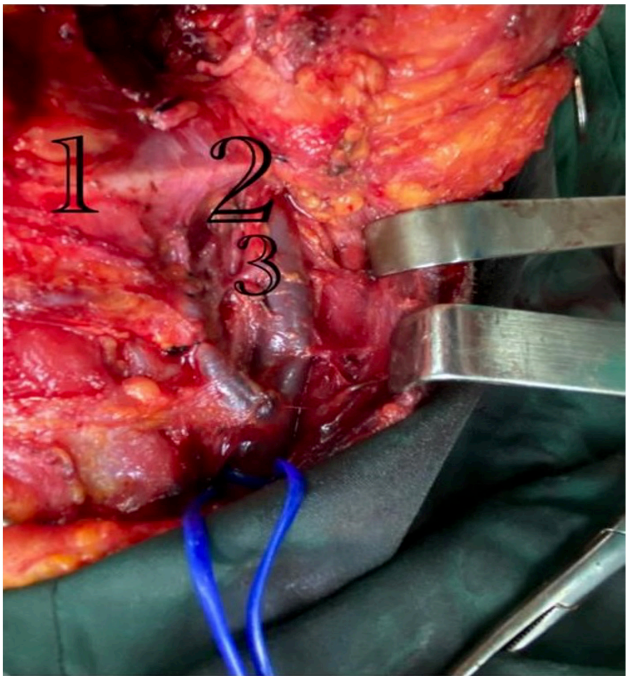


The SCC of the posterior mandible had significantly more lymph node involvement compared with other sites (P=0.02). Most patients had well-differentiated tumors (n=23, 71.9%) while the remaining (n=9, 28.1%) were moderately or poorly differentiated. Lymph node involvement in patients with well-differentiated histopathological grade was significantly lower than moderately and poorly differentiated cases (P=0.01), but the difference between moderately and poorly differentiated tumors was not statistically significant. Mandibular SCC is presented in **figure 2**.

Figure 2: Mandibular squamous cell carcinoma.

In accordance with the TNM classification system, 4 (12.5%), 11 (34.4%), 12 (37.5%), and 5 (15.6%) cases were diagnosed at stage I, II, III, and IV, respectively. Most of the studied patients were diagnosed in stage II and III. Different TNM stage had no remarkable influence on long-term lymph node involvement after surgery (P>0.05), though patients with neck dissection (zones 1, 2 and 3) and reconstruction (**Figure 3**) had less lymph node involvement in comparison with cases without neck dissection and reconstruction (P=0.003).

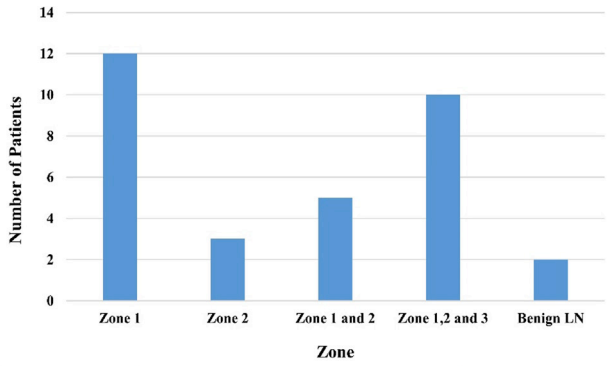
Figure 3: Patient with neck dissection (zones 1, 2 and 3).



There was a significantly lower degree of lymph node involvement among patients visited by an oncologist and those who regularly attended follow-up sessions in comparison with the patients who ignored their follow

up sessions at 1 year and 2 years' evaluation (P<0.05). Patients who received postoperative radiotherapy alone or chemotherapy and radiotherapy together had a significantly lower degree of lymph node involvement (P=0.001 and 0.005, respectively) than those who didn't receive any adjunctive therapy or who received chemotherapy alone. In fact, postoperative chemotherapy was associated with no significant changes in the mentioned variable. Zone 1 involvement was most seen in CT scan followed by zone 1, 2 and 3 and zone 1 and 2 involvement in the two-year follow-up (**Figure 4**).

Figure 4: Zone involvement of patients with maxillofacial squamous cell carcinoma in CT scans.



Post-operative lymph node involvement was significantly more observed in patients with the positive CT scan status of bilateral metastatic lymphadenopathy in zones 1, 2 and 3 before the operation in comparison to other statuses like bilateral benign lymph nodes (P=0.001), lymphadenopathy in just one or two zones (1and/or 2) (P>0.05), bilateral reactive lymph nodes of zones 1, 2, and 3 (P=0.001), or unilateral reactive lymph nodes of zones 1, 2, and 3 (P=0.003) and bilateral and unilateral necrotic lymph nodes of zones 1, 2 and 3 (P=0.002 and 0.003, respectively). Patients with positive sonography for reactive lymph nodes before surgery had statistically more lymph node involvement in two year follow up period in comparison with the benign lymph node situation. However, there was no significant difference in the outcome of patients with unilateral or bilateral lymphadenopathy of any type (reactive, necrotic or metastatic) found in sonography before the operation (P>0.05). Different zones of lymph node involvement found in preoperative sonography had no significant influence on the outcome of patients (P>0.05). Pathological findings of lymph node involvement after surgery coincided with preoperative CT scan findings, but not sonographic details.

Discussion

Originating from oral epithelial cells, OSCC represents the predominant malignancy of the oral cavity, accounting for about 90% of all malignant oral lesions. In primary OSCC invasion of the deeper layers below the epithelium and drainage to regional lymph nodes may occur[21]. To establish the diagnostic and prognostic parameters of OSCC, we must determine the histological differentiation degree, tumor size, invasion to nearby tissues and metastasis[22]. The most important prognostic factor is the lymph node status of the neck[23]. Although CT and magnetic resonance image (MRI) are used to localize and characterize head and neck tumors, they do not perform well in the evaluation of lymph node metastasis[24]. Given the immense effect of achieving an accurate pre-operative estimation of invasiveness and nodal metastasis on OSCC patient management and prognosis, novel clinical indicators and advanced radiological techniques are required.

In this study, no relation was found between SCC occurrence, age and gender, but some previous studies have shown different prevalence of SCC among different age groups[25] and genders[26]. Although some studies suggested that sex and age may be prognostic in SCCs[27], our findings showed no significant difference in lymph node involvement with respect to age and sex which is in line to some reports[28]. In the current study, the mandible was the most common site affected by oral SCC in both males and females which is in contrast with the results of previous studies who found the tongue to be the predominant site[29]. These differences could be due to the different study populations and different sample sizes. We also found that patients with posterior mandibular SCC had more post-operative lymph node involvement in the two-year follow-up compared with SCCs of other regions. Though Sharma et al.[30] found SCCs of the posterior maxillary and mandibular areas to have more lymph node involvement both before and after surgery. Uchiyama et al.[31] and Tajmirriahi et al.[32] also found the posterior areas to be more prone to metastasis, which emphasizes the importance of tumor location in lymph node involvement.

Histopathological assessment of the surgical resection specimen always provides useful information which is essential for identifying the post-operative treatment needs and prognosis for individuals with oral/oropharyngeal SCC[13]. In line with our study, Tzu et al.[33] and Amaral et al.[34] reported that moderately and poorly differentiated tumors caused more lymph node involvement than well-differentiated tumors, which can be related to the more aggressive nature of cancerous cells in less differentiated ones. The clinical stage is another prognostic factor in the survival rate for SCC patients. However, our study revealed no significant prognostic difference on long-term lymph node involvement between stage II and III OSCC. This limited prognostic value of TNM staging was also shown in the study of Bankfalvi et al.[35], though this finding contrasts with that of Amaral et al.[34].

In terms of management, there has been conflicting ideas regarding radical neck dissection vs. wait and

watch over the last decades[36]. It is currently believed that extensive neck dissections cause higher morbidity without offering a better long-term outcome[36]. We found that patients with neck dissection (zone 1, 2 and 3) and reconstruction had significantly less lymph node involvement in the two-year follow-up relative to the cases without neck dissection, which is in line with some previous studies[37] and in contrast with others[38]. Patients who cared for their regular follow-up sessions had less lymph node involvement in the follow up period which can be due to the prompt detection of any changes by their physicians. The same finding was reported in the study of Kumaran et al.[39]. Patients with the history of OSCC must visit their doctors every 1-3 months in the first two years and every 3-6 months thereafter. They can be visited yearly if no recurrence occurs after the first five years. Arun et al.[40] found that patients who visited their oncologist and received adjunctive treatments after surgery had less lymphadenopathy in the follow up period, which coincides with our findings regarding patients who received radiotherapy, (but not chemotherapy) as an adjunctive treatment. It seems that radiotherapy of any type (e.g. teletherapy or brachytherapy) can eradicate the remnant cancerous cells[41]. In the current study, there was an accurate relationship between the radiologic findings in the (CT scan, but not sonography) with lymph node involvement. It was shown that compared the efficacy and accuracy of different methods of radiology in detecting lymph node involvement, sonography alone is insufficient[30]. Sismanis et al.[42] were probably the first who report the usefulness of ultrasonography in the assessment of neck node metastasis and reported that ultrasonography changed the stage in 28% of their patients and was beneficial even in patients with palpable metastasis. Hajec et al.[43] reported similar findings and concluded that sonography of the neck changed the treatment plan in more than half of their patients. In contrast to these studies and in line with our study, John et al.[44] reported that sonography provided no additional data in patients with palpable metastasis and declared its inaccuracy in the detection of lymph node involvement. Zone 1 involvement was the most commonly reported zone in CT scan status followed by zone 1, 2 and 3 and zone 1 and 2 involvement in the two-year follow-up. It seems that zone 2 involvement alone can rarely happen, as an interesting finding.

This study has some important limitations due to methodological flaws such as no prior sample size estimation; therefore, we used as many cases as possible. However, due to the relatively small number of participants in our study and limited reports in the Iranian population, further studies with larger sample size and post-operative follow-ups are highly warranted.

Discussion

This study successfully evaluated the lymph node involvement of the neck in the two-year follow-up period for patients who had undergone surgery for maxillofacial SCC. We determined the effect of different parameters on lymph node involvement and some positive and negative correlations and found that parameters like age, gender and TNM staging had no influence on the outcome of patients.

Interests conflict

The researchers declare that they have no conflict of interest.

References

1. Siddiqui IA, Farooq MU, Siddiqui RA, Rafi ST. Role of toluidine blue in early detection of oral cancer. Pakistan Journal of Medical Sciences. 2006;22(2):184-7.

2. Scott S, Grunfeld E, Main J, McGurk M. Patient delay in oral cancer: a qualitative study of patients' experiences. Psycho-Oncology. 2006;15(6):474-85.

3. de Freitas Cordeiro-Silva M, Oliveira ZFL, de Podestá JRV, Gouvea SA, Von Zeidler SV, Louro ID. Methylation analysis of cancer-related genes in non-neoplastic cells from patients with oral squamous cell carcinoma. Molecular Biology Reports. 2011;38(8):5435-41.

4. Ogden GR. Alcohol and oral cancer. Alcohol. 2005;35(3):169-73.

5. Subapriya R, Thangavelu A, Mathavan B, Ramachandran CR, Nagini S. Assessment of risk factors for oral squamous cell carcinoma in Chidambaram, Southern India: a case-control study. European Journal of Cancer Prevention. 2007;16(3):251-6.

6. Thavarajah R, Rao A, Raman U, Rajasekaran ST, Joshua E, Hemalatha R, et al. Oral lesions of 500 habitual psychoactive substance users in Chennai, India. Archives of Oral Biology. 2006;51(6):512-9.

7. Markopoulos AK. Current aspects on oral squamous cell carcinoma. The Open Dentistry Journal. 2012;61(1):126-30.

8. Kulkarni DP, Wadia PP, Pradhan TN, Pathak AK, Chiplunkar SV. Mechanisms involved in the down-regulation of TCR ζ chain in tumor versus peripheral blood of oral cancer patients. International Journal of Cancer. 2009;124(7):1605-13.

9. Scully C, Bagan J. Oral squamous cell carcinoma overview. Oral oncology. 2009;45(4/5):301-8.

10. Haya-Fernández MC, Bagan J, Murillo-Cortés J, Poveda-Roda R, Calabuig C. The prevalence of oral leukoplakia in 138 patients with oral squamous cell carcinoma. Oral Diseases. 2004;10(6):346-8.

11. Jovanovic A, Schulten EA, Kostense PJ, Snow GB, van der Waal I. Tobacco and alcohol related to the anatomical site of oral squamous cell carcinoma. Journal of Oral Pathology and Medicine. 1993;22(10):459-62.

12. Rapidis AD, Gullane P, Langdon JD, Lefebvre JL, Scully C, Shah JP. Major advances in the knowledge and understanding of the epidemiology, aetiopathogenesis, diagnosis, management and prognosis of oral cancer. Oral Oncology. 2009;45(4-5):299-300.

13. Woolgar JA. Histopathological prognosticators in oral and oropharyngeal squamous cell carcinoma. Oral Oncology. 2006;42(3):229-39.

14. Conceição Pereira M, Oliveira DT, Landman G, Kowalski LP. Histologic subtypes of oral squamous cell carcinoma: prognostic relevance. Journal of the Canadian Dental Association. 2007;73(4):339-44.

15. Jank S, Robatscher P, Emshoff R, Strobl H, Gojer G, Norer B. The diagnostic value of ultrasonography to detect occult lymph node involvement at different levels in patients with squamous cell carcinoma in the maxillofacial region. International Journal of Oral and Maxillofacial Surgery. 2003;32(1):39-42.

16. Bergman SA, Ord RA, Rothman M. Accuracy of clinical examination versus computed tomography in detecting occult lymph node involvement in patients with oral epidermoid carcinoma. Journal of Oal and Maxillofacial Surgery. 1994;52(12):1236-9.

17. Close LG, Merkel M, Vuitch MF, Reisch J, Schaefer SD. Computed tomographic evaluation of regional lymph node involvement in cancer of the oral cavity and oropharynx. Head and Neck. 1989;11(4):309-17.

18. Woolgar JA, Scott J. Prediction of cervical lymph node metastasis in squamous cell carcinoma of the tongue/floor of mouth. Head and Neck. 1995;17(6):463-72.

19. de Bree R, Leemans CR, Silver CE, Robbins KT, Rodrigo JP, Rinaldo A, et al. Paratracheal lymph node dissection in cancer of the larynx, hypopharynx, and cervical esophagus: the need for guidelines. Head and Neck. 2011;33(6):912-6.

20. Kligerman J, Lima RA, Soares JR, Prado L, Dias FL, Freitas EQ, et al. Supraomohyoid neck dissection in the treatment of T1/T2 squamous cell carcinoma of oral cavity. American Journal of Surgery. 1994;168(5):391-4.

21. Leusink FK, van Es RJ, de Bree R, de Jong RJB, van Hooff SR, Holstege FC, et al. Novel diagnostic modalities for assessment of the clinically node-negative neck in oral squamous-cell carcinoma. Lancet Oncology. 2012;13(12):554-61.

22. Massano J, Regateiro FS, Januário G, Ferreira A. Oral squamous cell carcinoma: review of prognostic and predictive factors. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology. 2006;102(1):67-76.

23. Atula TS, Grénman R, Varpula MJ, Kurki TJ, Klemi PJ. Palpation, ultrasound, and ultrasound-guided fine-needle aspiration cytology in the assessment of cervical lymph node status in head and neck cancer patients. Head and Neck. 1996;18(6):545-51.

24. Vandecaveye V, De Keyzer F, Vander Poorten V, Dirix P, Verbeken E, Nuyts S, et al. Head and neck squamous cell carcinoma: value of diffusion-weighted MR imaging for nodal staging. Radiology. 2009;251(1):134-46.

25. Alves AM, Correa MB, Silva KDd, Araújo LMAd, Vasconcelos ACU, Gomes APN, et al. Demographic and clinical profile of oral squamous cell carcinoma from a service-based population. Brazilian Dental Journal. 2017;28(3):301-6.

26. Lin N-C, Hsu J-T, Tsai K-Y. Difference between Female and Male Patients with Oral Squamous Cell Carcinoma: A Single-Center Retrospective Study in Taiwan. International Journal of Environmental Research and Public Health. 2020;17(11):3978-85.

27. Mahmood N, Hanif M, Ahmed A, Jamal Q. Impact of age at diagnosis on clinicopathological outcomes of oral squamous cell carcinoma patients. Pakistan Journal of Medical Sciences. 2018;34(3):595-9.

28. Kapila SN, Natarajan S, Boaz K. A comparison of clinicopathological differences in oral squamous cell carcinoma in patients below and above 40 years of age. Journal of Clinical and Diagnostic Research. 2017;11(9):46-50.

29. Agrawal KH, Rajderkar S. Clinico-epidemiological profile of oral cancer: A hospital based study. Indian Journal of Community Health. 2012;24(2):80-5.

30. Sharma A, Kim J-W, Paeng J-Y. Clinical analysis of neck node metastasis in oral cavity cancer. Journal of the Korean Association of Oral and Maxillofacial Surgeons. 2018;44(6):282-8.

31. Uchiyama Y, Sasai T, Nakatani A, Shimamoto H, Tsujimoto T, Kreiborg S, et al. Distant metastasis from oral cavity—correlation between histopathology results and primary site. Sarcoma. 2020;11(122):142-51.

32. Tajmirriahi N, Razavi SM, Shirani S, Homayooni S, Gasemzadeh G. Evaluation of metastasis and 5-year survival in oral squamous cell carcinoma patients in Isfahan (2001–2015). Dental Research Journal. 2019;16(2):117-21.

33. Chao A, Wang TH, Lee YS, Hsueh S, Chao AS, Chang TC, et al. Molecular characterization of adenocarcinoma and squamous carcinoma of the uterine cervix using microarray analysis of gene expression. International journal of cancer. 2006;119(1):91-8.

34. Amaral TMP, da Silva Freire AR, Carvalho AL, Pinto CAL, Kowalski LP. Predictive factors of occult metastasis and prognosis of clinical stages I and II squamous cell carcinoma of the tongue and floor of the mouth. Oral Oncology. 2004;40(8):780-6.

35. Bankfalvi A, Piffko J. Prognostic and predictive factors in oral cancer: the role of the invasive tumour front. Journal of Oral Pathology and Medicine. 2000;29(7):291-8.

36. Hamoir M, Schmitz S, Gregoire V. The role of neck dissection in squamous cell carcinoma of the head and neck. Current treatment options in oncology. 2014;15(4):611-24.

37. Guo CB, Feng Z, Zhang JG, Peng X, Cai ZG, Mao C, et al. Supraomohyoid neck dissection and modified radical neck dissection for clinically node-negative oral squamous cell carcinoma: a prospective study of prognosis, complications and quality of life. Journal of Cranio-Maxillofacial Surgery. 2014;42(8):1885-90.

38. Fakih AR, Rao RS, Borges AM, Patel AR. Elective versus therapeutic neck dissection in early carcinoma of the oral tongue. American Journal of Surgery. 1989;158(4):309-13.

39. Kumaran PS, Thangaswamy SV, Navaneetham A. The need for early detection of neck nodal metastasis in squamous cell carcinoma of oral cavity. Journal of Pharmacy and Bioallied Sciences. 2012;4(2):341-3.

40. Arun I, Maity N, Hameed S, Jain PV, Manikantan K, Sharan R, et al. Lymph node characteristics and their prognostic significance in oral squamous cell carcinoma. Head and Neck. 2020.

41. Wang J-s, Wang H-j, Qian H-l. Biological effects of radiation on cancer cells. Military Medical Research. 2018;5(1):20-30.

42. Sismanis A, Merriam J, Yamaguchi KT, Shapshay SM, Strong MS. Diagnostic value of fine needle aspiration biopsy in neoplasms of the head and neck. Otolaryngology Head and Neck Surgery. 1981;89(1):62-6.

43. Hajek PC, Salomonowitz E, Turk R, Tscholakoff D, Kumpan W, Czembirek H. Lymph nodes of the neck: evaluation with US. Radiology. 1986;158(3):739-42.

44. John D, Williams SR, Ahuja A, Evans R, To K, King W, et al. Palpation compared with ultrasound in the assessment of malignant cervical lymph nodes. Journal of Laryngology and Otology. 1993;107(9):821-3.

eISSN 2255-0569

ORIGINAL

Correlation between heart age and other scales and parameters related to cardiovascular risk

Correlación entre edad del corazón y otras escalas y parámetros relacionados con riesgo cardiovascular

Karina Lisbell Arias Rebolledo[1], Flavio J. Leguen[2], Rosa González Casquero[3], Juan Antonio Roberto Martín[3], Pere Riutord Sbert[4], María Gil Llinás[3]

1. Current Workplace: International Clinic, Lima-Perú
2. Florida International University. Miami. Florida. USA
3. Unidad Docente Multiprofesional de Salud Laboral de Baleares
4. ADEMA University School. Palma. Balearic Island. Spain

Corresponding author
Karina Lisbell Arias
Current Workplace: International Clinic, Lima-Perú
E-mail: klar25384@gmail.com

Received: 28 - IX - 2021
Accepted: 24 - XI - 2021

doi: 10.3306/AJHS.2022.37.01.65

Abstract

Background: To assess the use of heart age as new tool to evaluate cardiovascular risk, measuring correlation with classical tools (REGICOR, SCORE) and with other cardio-vascular parameters.
Methods: An observational, transversal and descriptive study was conducted in 6788 volunteers (3885 women and 2903 men, 35 - 65 years) between January 2018 and December 2019. The "Heart age calculator" considered the following parameters: age, sex, height, weight, waist perimeter, familiar history of cardiovascular disease, presence of diabetes, tobacco consumption, levels of total and HDL cholesterol and systolic blood pressure values. Cardiovascular risk was assessed using Framingham calibrated for Spanish population (REGICOR) and SCORE models.
Results: Overweight, obesity, adiposity, metabolic syndrome and diabetes were significantly more prevalent in men than in women ($p < 0.05$). A high correlation was observed between heart age and cardiovascular risk (absolute and relative) measured according to REGICOR model, with correlation coefficients of 0.6 - 0.8, higher in men than in women. As relative risk increased, heart age was worsening. Finally, a relationship between heart age and cardiovascular parameters (waist perimeter, BMI, adiposity and metabolic syndrome) was also established.
Conclusions: Heart age can be a useful tool to assess the cardiovascular risk, at least in these peruvian population.

Keywords: Heart age, cardiovascular disease, obesity, metabolic syndrome, diabetes.

Resumen

Introducción: Para evaluar el uso de la edad del corazón como nueva herramienta para valorar el riesgo cardiovascular, se determina la correlación con las herramientas clásicas (REGICOR y SCORE) y con otros parámetros cardiovasculares.
Métodos: Estudio observacional, transversal y descriptivo, realizado en 6.788 voluntarios (3.885 mujeres y 2.903 hombres) de 35 a 65 años entre Enero de 2018 y diciembre de 2019.
La "Calculadora de edad del Corazón" considera los siguientes parámetros: edad, sexo, altura, peso, perímetro de la cintura, historia familiar de enfermedad cardiovascular, presencia de diabetes, consumo de tabaco, niveles de colesterol total y HDL y presión sistólica. El riesgo cardiovascular se evaluó a través de Framingham calibrada para la población española (REGICOR) y el modelo SCORE.
Resultados: El sobrepeso, la obesidad, la grasa corporal, el síndrome metabólico y la diabetes fueron significativamente más frecuente en hombres que en mujeres ($p < 0,05$). Una alta correlación fue observada entre la edad del corazón y el riesgo cardiovascular (absoluto y relativo), medido de acuerdo al modelo REGICOR, con coeficientes de corre-lación de 0,6 - 0,8, mayor en hombres que en mujeres. A medida que aumenta el riesgo relativo, la edad del corazón va empeorando. Por último, se estableció una relación entre la edad del corazón y los parámetros cardiovasculares (perímetro de cintura, índice de masa corporal, obesidad y síndrome metabólico).
Conclusiones: La edad del corazón puede ser una herramienta útil para evaluar el riesgo cardiovascular, al menos en esta población peruana.

Palabras clave: Edad del corazón, enfermedad cardiovascular, obesidad, síndrome metabólico, diabetes.

Introducción

Cardiovascular disease is a public health problem in most countries and not only in industrialised countries, with almost 80% of cardiovascular disease deaths in 2005 occurring in countries traditionally considered as non-affluent[1]. The high prevalence of certain risk factors is the cause of this situation.

Hypertension currently affects about 800 million people worldwide[2] and is expected to affect 1.56 billion by 20253. Unhealthy diets high in saturated fats and low in polyunsaturated fats increase cholesterol levels. The WHO predicts a significant increase in LDL-cholesterol concentrations in the populations of many developing countries by 2020[2].

Globally, more than 1.6 billion adults are overweight and at least 400 million of them are obese. Since 1980 the rate of obesity has tripled or more in many parts of the world[4].

Over the last decade smoking has declined in many Western countries, but prevalence remains high in many others and, globally, the number of smokers is expected to rise to between 1.4 and 1.8 billion by 2030[2].

It is therefore of great medical and especially public health importance to be able to catalogue cardiovascular risk using the different existing scales, as this stratification will enable appropriate prevention and treatment policies to be established. In our environment, the most widely used scales are the Framingham scale, which assesses morbidity and mortality, and the SCORE scale, which determines mortality.

For several authors, the Framingham scales overestimate the risk in those southern European countries where the incidence of cardiovascular problems is lower[5-10], a situation that led to the need to create their own scales[11-12], and so in Spain the Framingham scale was calibrated to create the REGICOR scale[13-14].

The main advantage of the age of the heart over the classic risk scales (Framingham, SCORE) is that patients and health professionals find it more comprehensible to speak of a numerical value (years), with which they are more familiar, than to speak of a percentage of risk.

The aim of this study is to assess whether heart age (CE) as a new tool in the study and approach to cardiovascular risk correlates well with the classic tools (REGICOR, SCORE) and with other related parameters (BMI, waist circumference, body fat or metabolic syndrome).

Methods

A descriptive and cross-sectional study is conducted in 6788 people (3885 women and 2903 men) from different regions of Peru between January 2018 and December 2019. The age range of the participants is 35 to 65 years.

The people were recruited during occupational medical examinations in different companies. As medical examinations are mandatory in these companies, selection bias is avoided. All workers between 35 and 65 years of age who attended the medical examinations were included, except those who did not want to participate. All participants were asked to sign an informed consent form.

To calculate the age of the heart, the tool called "Heart age calculator" was used, which in its Spanish version is available on the web page: www.quiereatucorazon.com. This tool was developed by Unilever in collaboration with researchers from the Framingham Study at Boston University. The weight of each of the parameters analysed on the age of the heart is similar to that of the same factors in the determination of cardiovascular risk according to the Framingham model.

The calculation of all heart ages is performed twice, by a different person, to avoid errors.

The parameters necessary to calculate the age of the heart are the following: age, sex, height (in centimetres), weight (in kilograms), waist circumference (in centimetres), history of cardiovascular disease in the mother or father and their age when they first suffered from it, presence or absence of diabetes, tobacco consumption (if they do not currently smoke, they are also asked whether they have stopped smoking in the last year), total cholesterol and HDL cholesterol values and finally systolic pressure values and whether they are currently receiving antihypertensive treatment. With all these parameters a numerical value in years is obtained which has to be compared with the biological age. The final result will be the number of years gained (represented by a minus sign in front and indicating that the heart age is lower than the biological age) or lost (heart age worse than the biological age).

To determine the different anthropometric parameters, international recommendations are followed. BMI was obtained using the Quetelet index. Height and weight were determined using an approved scale-measuring device. Abdominal waist circumference was calculated with a tape measure placed parallel to the ground at the level of the last floating rib, i.e. the natural waist circumference measured between the top of the hip bone (iliac crests) and the lower rib, measured during normal breathing with the subject standing and with the abdomen relaxed.

Total cholesterol and triglycerides were determined by automated enzymatic methods, HDL-C was determined by precipitation with dextran-sulphate Cl2Mg and glucose by an enzymatic method. Blood collection was performed at the same session and at the same location, after an overnight fast of 12 hours. Samples were sent

to the reference laboratory and processed within a maximum of 48-72 hours, stored at -20ºC.

Blood pressure was determined after a resting period of about 10 minutes in the supine position using a calibrated OMRON M3 automatic sphygmomanometer.

Body fat values were determined using the Tanita BF-350 Body Composition Analyzer bioimpedance meter with two stainless steel electrodes located on the lower platform for Body Compartment analysis. The patient stands on the electrodes with bare feet and in 15 seconds the results are obtained. To obtain reliable results, the manufacturer's instructions were followed.

To classify people according to parameters associated with overweight, the recommendations of the different scientific societies are followed:

- SEEDO[15] (Spanish Society for the Study of Obesity) criteria according to BMI values.
- NCEP ATPIII[16] (National Cholesterol Educational Program Adult Treatment Panel III) criteria for metabolic syndrome (MS). MS was considered when at least three of these criteria were present.
- Body fat values were classified according to the criteria established by Gallagher[17] as low, normal, high and very high.
- High waist circumference values were established according to the criteria established in the metabolic syndrome16 (≥ 88 cm in women and ≥ 102 cm in men).

Measurements in all three centres are performed by specially trained healthcare personnel to avoid interobserver bias as much as possible. The sphygmomanometers used are of the same brand and are perfectly calibrated, as are the bioimpedance meters and the scales. The analytical determinations were performed in two laboratories using similar equipment as they belonged to the same company.

Cardiovascular risk according to the Framingham model calibrated for the Spanish population is called the REGICOR scale and is calculated using the computer tool available at: http://www.regicor.org. This scale is applicable from the age of 35 years and uses age, sex, total cholesterol, HDL cholesterol, systolic and diastolic blood pressure, diabetes and tobacco consumption as parameters. Both absolute and relative risk are determined. Relative risk is calculated by dividing the absolute risk of the individual by the theoretical risk of an individual of the same age and sex with optimal exposure to cardiovascular risk factors.

Cardiovascular risk using the SCORE scale is determined by using the calculator available at http://registrocardioib.com/public/testCalculadora.aspx

In the descriptive analysis, after testing for normal distribution using the Kolmogorov-Smirnov method, the mean value, standard deviation and 95% confidence interval were used. For the analysis of two parametric variables, the mean difference (Student's t-test) was used. The chi-square test with 95% confidence level was used to test proportions. To assess the correlation between cardiac age and cardiovascular risk values according to the REGICOR and SCORE models, Pearson's correlation coefficient was used. All analyses were performed with the SPSS 27.0 statistical package.

The study was approved by the research ethics committee. All participants signed the informed consent form.

Results

Table I shown the characteristics of the people who participated in the study in relation to the different parameters related to cardiovascular risk.

Table I: Characteristics of the sample according to the different parameters related to cardiovascular risk.

	Women (n 3885)			Men (n 2903)			
	Mean	SD	95% CI	Mean	SD	95% CI	p-value
Age (years)	45.2	6.8	45-45.4	46.7	7.4	46.4-46.9	< 0.05
SBP (mm Hg)	117.6	16.2	117.1-118.2	132	17.2	131.4-132.6	< 0.05
DBP (mm Hg)	74.5	10.4	74.2-74.9	81.6	11.1	81.2-82	< 0.05
Weight (kg)	64.7	11.9	64.3-65.1	82.2	13.1	81.8-82.7	< 0.05
Height (cm)	160.9	6.3	160.7-161.1	173	7.1	172.8-173.3	< 0.05
BMI (kg/m²)	25	9.4	24.7-25.3	27.5	4.5	27.1-27.8	< 0.05
Total Cholesterol (mg/dl)	197.2	36	196-198.4	208.2	36.9	206.9-209.6	< 0.05
HDL-c (mg/dl)	58	12	57.6-58.4	47.8	9.9	47.4-48.2	< 0.05
% Smokers	32.5		31-34	33.6		31.9-35.3	> 0.05
% Diabetes	3.5		2.9-4.1	8.9		7.9-9.9	< 0.05
Waist circumference (cm)	81.2	12.6	80.8-81.6	95.2	11	94.8-95.6	< 0.05
% body fat very high	16.7		15.1-18.3	27.1		25-29.2	< 0.05
% Metabolic syndrome	6.7		5.9-7.5	15		13.7-16.3	< 0.05
Heart age	1.2	9.8	0.9-1.5	3.7	2.3	3.6-3.8	< 0.05
REGICOR absolute risk	1.1	0.6	1.1-1.2	1.7	0.9	1.6-1.7	< 0.05
REGICOR relative risk	0.3	0.6	0.2-0.3	1.9	1.9	1.8-1.9	< 0.05
SCORE scale(*)	1.2	9.8	0.9-1.5	7.7	8.1	7.4-8	< 0.05

(*) The SCORE scale can only be calculated from 40 years of age onwards.

As a first step we determine the cardiac age of the people in our study and, more importantly, we quantify how many years they have gained or lost. Years gained, i.e. when the heart age is lower than the biological age, are expressed as negative, while years lost (heart age higher than the biological age) are expressed as positive.

As indicated above, heart age calculations are based on the data obtained in the Framingham study, so it is reasonable to think that there should be a good correlation between the two instruments for measuring cardiovascular risk. To support this, in our study we performed a correlation study using logistic regression, calculating the Pearson correlation coefficient between heart age data and cardiovascular risk data, both in absolute risk and relative risk, according to the Framingham model calibrated for the Spanish population (REGICOR).

In a first analysis, heart age is compared with the relative risk of the REGICOR scale. The data for this correlation are shown in **table II**.

In order to confirm the relationship between the relative risk of the REGICOR scale and the age of the heart more reliably, the years gained or lost are studied in both women and men according to the value of the relative risk. It can thus be seen that, in both sexes, the higher the relative risk, the worse the determination of the heart age parameter (**table III**). In the table, the mean, standard deviation and confidence interval refer to the difference in years between heart age and biological age.

Pearson's correlation index between heart age and absolute cardiovascular risk is also calculated with the REGICOR and SCORE scales in men and women and according to age groups. The results are shown in **table IV**.

It is also interesting to know the relationship between heart age values and the different parameters related to cardiovascular risk, i.e. waist circumference, BMI,

Table II: Pearson correlation index between heart age and relative risk according to the REGICOR scale.

	Heart age		
	Total	Women	Men
Total	0.7225	0.6637	0.7561
35-39 years	0.7528	0.6344	0.7919
40-44 years	0.7032	0.6405	0.7737
45-49 years	0.7454	0.7184	0.7715
50-54 years	0.69	0.6222	0.7271
≥ 55 years	0.6482	0.6002	0.6705

Table III: Relationship between heart age and relative risk according to the Framingham model calibrated for Spain by sex.

Relative risk	Women			Men		
REGICOR	Mean	SD	95% CI	Mean	SD	95% CI
< 1	-5.2	6.1	-5.5;-4.9	-2	4.8	-2.5;-1.4
1-1,99	1	8.3	0.6;1.4	4.5	5.8	4.2;4.8
2-2,99	13.3	6.5	12.8;13.8	13.8	5.1	13.5;14.2
≥3	18.6	5.5	17.3;20	19	2.5	18.7;19.3

Table IV: Pearson correlation index between the age of the heart and the REGICOR and SCORE scales.

	REGICOR						SCORE					
	Women	n	Men	n	Total	n	Women	n	Men	n	Total	n
35-39 years	0.63	941	0.79	605	0.72	1546	no*	941	no*	605	no*	1546
40-44 years	0.65	991	0.79	636	0.69	1627	0.13	991	0.72	636	0.52	1627
45-49 years	0.72	928	0.8	599	0.75	1527	0.54	928	0.61	599	0.56	1527
50-54 years	0.65	598	0.73	544	0.69	1142	0.61	598	0.62	544	0.54	1142
55-59 years	0.64	324	0.7	406	0.66	730	0.58	324	0.65	406	0.52	730
≥ 60 years	0.61	103	0.58	113	0.62	216	0.46	103	0.60	113	0.53	216

(*) The SCORE scale can only be calculated from the age of 40.

Table V: Relationship between heart age and other parameters related to cardiovascular risk.

		Women					Men				
		Mean	SD	95% CI	n	p-value	Mean	SD	95% CI	n	p-value
Waist circumference	**Risk**	5.5	9.9	4.8-6.1	1023	< 0.05	10.5	7.9	9.9-11.1	666	< 0.05
	No risk	-0.3	9.2	-0.7;0	2862		6.9	8	6.6-7.2	2237	
Metabolic syndrome	**Yes**	13.8	7.7	12.8-12.8	260	< 0.05	15.4	5.9	14.9-16	434	< 0.05
	No	0.3	9.2	0-0.6	3625		6.4	7.7	6.1-6.7	2467	
	Underweight	-2.7	8.4	-3.6;-1.8	343	< 0.05	5.2	8.9	1.9-8.6	28	< 0.05
Body mass index	**Normal**	-0.8	9.1	-1.2;-0.4	1933		5.3	8	4.8-5.9	789	
	Overweight	3.4	9.8	2.8-4	1118		7.9	7.9	7.5-8.3	1433	
	Obesity	6.8	9.6	6-7.4	481		10.4	7.8	9.8-11	653	
	Low	-2.4	9.6	-4.2;-2.5	217	< 0.05	5.1	8.6	2.1-8	60	< 0.05
Body fat	**Normal**	-1.4	9.3	-2;-0.8	1810		6.6	8.3	5.9-7.3	1033	
	High	1	9.9	0.2-1.8	1208		8.6	8.3	7.9-9.3	1023	
	Very high	4.4	10.1	3.4-5.5	650		9.7	8.1	9-10.5	787	

body fat and metabolic syndrome. For this purpose, the number of years of heart age gained or lost is calculated according to the value of the different parameters under study. **Table V** shows that in all cases the heart age values worsen as the parameters related to cardiovascular risk also worsen. This occurs in both women and men. In all cases there are statistically significant differences. In the table, the mean, standard deviation and confidence interval refer to the difference in years between heart age and biological age.

Discussion

The main conclusion of the study is that the heart age values calculated using the Heart age calculator tool correlate very well with the values obtained with the Framingham equation, in this case with the Framingham modality calibrated for the Spanish population, a fact that was expected, since both models have a similar basis for calculating risk. The comparative data with the SCORE scale suggest that there is a relationship, although it is somewhat lower. In both cases the correlations are higher in men than in women.

It is also interesting to note the close relationship observed between heart age and other parameters related to cardiovascular risk and overweight such as BMI, body fat, waist circumference and metabolic syndrome.

One of the strengths of the study is that it is the first to make comparisons between heart age and other validated and widely used tools for estimating cardiovascular risk. This fact will prevent the results from being compared with those obtained by other authors, but it will allow this work to constitute a starting point for future studies and allow this tool to enter into the work methodology of other authors when assessing cardiovascular risk parameters.

The fact that there are no previous studies with data on heart age forces us to compare our results with those of other authors who assess the correlation between other cardiovascular risk scales. Thus, several studies consulted show good correlation between classic Framingham and REGICOR[18-20] and between classic Framingham and SCORE[21]. However, the data from all these studies must be evaluated with caution as it is difficult to compare them since the methodology used has not always been the same and the characteristics of the population also differ. In general, most of the studies focus on populations with a predominantly high cardiovascular risk, which implies an initial bias in terms of the target population.

With the data obtained indicating initially a good correlation with the classical cardiovascular risk scales as well as with the other parameters studied, we believe that heart age can be a useful tool for assessing cardiovascular risk, at least in our population. However, in order to extrapolate this situation to other populations, further studies are needed.

Interests conflict

The researchers declare that they have no conflict of interest.

References

1. World Health Organization. The global burden of disease: 2004 update. Geneva, World Health Organization, 2008. Consultado 8 de Septiembre de 2010. Disponible en http://www.who.int

2. Mckay J, Mensah G. Atlas of heart disease and stroke. Geneve, World Health Organization, 2004.

3. Kanavos P. High blood pressure and health policy: where we are and where we need to go next, 2007.

4. World Health Organization. Obesity and overweight fact sheet number 311, Geneve, World Health Organization, September 2006. Disponible en: http://www.who.int

5. Menotti A, Lanti M, Puddu PE, Kromhout D. Coronary heart disease incidence in Northern and Southern European populations: a reanalysis of the seven countries study for an European coronary risk chart. Heart. 2000;84:238-44.

6. Menotti A, Puddu PE, Lanti M. Comparison of the Framingham risk function-based coronary chart risk function from an Italian population study. Eur Hearth J. 2000;21:365-70.

7. Tomás L, Vares C, Pérez I, Puig T, Balaguer I. Factores de riesgo y morbimortalidad coronaria en una cohorte laboral mediterránea seguida durante 28 años. Estudio Manresa. Rev Esp Cardiol. 2001;54:1146-54.

8. Kuulasmaa K, Tunstall-Pedoe H, Dobson A, Fortmann S, Sans S, Tolonen H, et al. Estimation of contribution of changes in classic risk factors to trends in coronary-event rates across the WHO MONICA Project populations. Lancet. 2000;355:675-87.

9. Pérez G, Pena A, Sala J, Roset PN, Masiá R, Marrugat J, and the REGICOR investigators. Acute myocardial infarction case fatality, incidence and mortality rates in a population registry in Girona, Spain, 1990-1992. Int J Epidemiol. 1998;27:599-604.

10. Masiá R, Pena A, Marrugat J, Sala J, Villa JS, Pavesi M, et al. High prevalence of cardiovascular risk factors in Girona, Spain, a province with low myocardial infarction incidence. J Epidemiol Community Health. 1998;52:707-15.

11. D'Agostino RB, Grundy S, Sullivan LM, Wilson P. Validation of the Framingham Coronary Heart Disease Prediction Scores: results of a multiple ethnic groups investigation. JAMA. 2001;286: 180-7.

12. Hense HW, Schulte H, Lowel H, Assman G, Keil U. Framingham risk function overestimates risk of coronary heart disease in men and women from Germany: results of the MONICA Augsburg and the PROCAM cohorts. Eur Hearth J. 2003;24:937-45.

13. Marrugat J, Solanas P, D'Agostino R, Sullivan L, Ordovas J, Cordón F, et al. Estimación del riesgo coronario en España mediante la ecuación de Framingham calibrada. Rev Esp Cardiol. 2003;56:253-61.

14. Marrugat J, D'Agostino R, Sullivan L, Elosua R, Wilson P, Ordovás J, et al. An adaptation of the Framingham risk function to southern Europe Mediterranean areas. J Epidemiol Community Health. 2003;57:634-8.

15. Rubio MA, Salas-Salvadó J, Barbany M, Moreno B, Aranceta J, Bellido D, Blay V et al. Consenso SEEDO 2007 para la evaluación del sobrepeso y la obesidad y el establecimiento de criterios de intervención terapéutica. Revista Española de Obesidad. 2007;7-48

16. Grundy S. Diagnosis and Management of the Metabolic Syndrome. Circulation. 2005; 112(17):2735-2752.

17. Gallagher D, Heymsfield SB, Heo M, Jebb SA, Murgatroyd PR, Sakamoto Y. Healthy percentage body fat ranges: an approach for developing guidelines based on body mass index. Am J Clin Nutr 2000;72(3):694-701

18. Baena JM, Del Val JL, Salas LH, Sánchez R, Altes E, Deixens B, Amatller M, Núñez DK. Comparación de los modelos SCORE Y REGICOR para el cálculo del riesgo cardiovascular en sujetos sin enfermedad cardiovascular atendidos en un centro de salud de Barcelona. Rev. Esp. Salud Pública. 2005; 79(4):453-64.

19. Ramos R, Solanas P, Cordón F, Rohlfs I, Elosua R, Sala J et al. Comparación de la función Framingham original y la calibrada del REGICOR en la predicción del riesgo coronario poblacional. Med Clin (Barc). 2003; 121: 521-26.

20. Cristóbal J, Lago F, De la Fuente J, González-Juanatey JR, Vázquez-Bellés P, Vila M. Ecuación de Framingham de Wilson y ecuación de REGICOR. Estudio comparativo. Rev Esp Cardiol.2005;58: 910-15.

21. Álvarez A, Díaz L, López V, Prieto MA, Suárez S. Comparación de los modelos Score y Framingham en el cálculo de alto riesgo cardiovascular para una muestra de varones de 45 y 65 años de Asturias. Rev. Esp. Salud Pública. 2005; 79(4):465-73.

eISSN 2255-0569

ORIGINAL

Values of different anthropometric indices associated with obesity according to findrisc test values

Valores de diferentes índices antropométricos asociados a la obesidad según los valores del test de findrisc

Mayerith Carolina Torreyes Reyes[1], Mayra Alejandra Useche Barrios[2], Ingrid Fabiola Tirado Chacón[3], Mark Indalecio Salas Rodrigues[4], Johana Tahiry Alvarez Maza[4], Katrina Riera Routon[5]

1. Unidad Dermatológica Barinas. Barinas Venezuela. 2 Centro Médico Sigma. Merida. Venezuela
3. Hospital I Lagunillas. Mérida. Venezuela 4. Servicio Balear de Prevención. Palma. España 5. Pharmaceuticals

Corresponding author
Mark Indalecio Salas Rodrigues
Servicio Balear de Prevención
Camino Reis, 308 - Edif. Clínica Palmaplanas, 07010, Palma
E-mail: marcksalas@hotmail.com

Received: 30 - IX - 2021
Accepted: 25 - XI - 2021

doi: 10.3306/AJHS.2022.37.01.71

Abstract

Introduction and objective: Obesity is a metabolic disorder characterized by excessive accumulation of adipose tissue in the body and is associated with the development of abnormalities in blood glucose metabolism, either pre-diabetes or type 2 diabetes. There are different scales that assess the risk of diabetes, the most widely used being the Findrisc scale. The aim of this study is to determine the relationship of various scales of overweight and obesity with the values of the Findrisc scale.
Methods: A descriptive, cross-sectional study of 48,366 Spanish workers in which the risk of type 2 diabetes was determined using the Findrisc scale. Different scales of overweight and obesity such as BMI, waist/height, waist/hip, body adiposity index and abdominal volume index were also assessed.
Results: The prevalence of high values of all the scales analyzed in this study are much higher in those people who are at high risk of type 2 diabetes. This prevalence is higher in men.
Conclusion: There is a clear relationship between the values of the Findrisc scale and the values of all the overweight and obesity scales analyzed.

Keywords: Obesity, Findrisc score, body adiposity index, abdominal volume index, body mass index.

Resumen

Introducción y objetivo: La obesidad es un trastorno metabólico que se caracteriza por la acumulación excesiva del tejido adiposo en el cuerpo y guarda relación con la aparición de alteraciones en el metabolismo de la glucemia, ya sea prediabetes o diabetes tipo 2. Existen diferentes escalas que valoran el riesgo de diabetes, siendo la más utilizada la de Findrisc. El objetivo de este estudio es conocer la relación de varias escalas de sobrepeso y obesidad con los valores de la escala de Findrisc.
Material y métodos: Estudio descriptivo y transversal en 48.366 trabajadores españoles en los que se determina el riesgo de padecer diabetes tipo 2 mediante la escala Findrisc. También se valoran diferentes escalas de sobrepeso y obesidad como IMC, cintura/altura, cintura/cadera, índice de adiposidad corporal e índice de volumen abdominal.
Resultados: La prevalencia de valores elevados de todas las escalas analizadas en este estudio son mucho mayores en aquellas personas que presentan un alto riesgo de padecer diabetes tipo 2. Esta prevalencia es mayor en los hombres.
Conclusión: Existe una clara relación entre los valores de la escala de Findrisc y los valores de todas las escalas de sobrepeso y obesidad analizadas.

Palabras clave: Obesidad escala Findrisc, índice de adiposidad visceral, índice de volumen abdominal, índice de masa corporal.

Introduction

Obesity is a chronic and complex disease which is defined as an excess of body fat. Due to continuous increase in prevalence in adults, adolescents and children and its serious health consequences[1], obesity has become one of the most important public health problems.

According to the latest data available, worldwide more than a billion adults are overweight and 300 million of them are obese. In Spain, in 2019, overweight and obesity affects 53% of the adult population[2].

The increase in prevalence of obesity involves an increase in the prevalence of several obesity-related comorbidities[3-4]. Among others, adiposity is supposed to be the physiological characteristic of obese and overweight individuals, which puts such individuals at-risk for cardiovascular disease[5]. In fact, the relationship between overall adiposity and risk for cardiovascular disease is well documented[6-7]. Furthermore, several studies, including the Framingham heart study[8], shows the relation between the adipose tissue accumulation and the incidence of adverse metabolic events and, also, with a higher risk for developing metabolic diseases[9-11]. In Spain Framingham equation has been adjusted to allow its utilization as an effective predictor for cardiovascular risk[12-13]. Obesity also increases the risk of diabetes and certain types of cancer[14].

In addition to the consequences of their illness on the health of individual, it has been estimated that obesity and the diseases related to it, are a health cost of 2 to 7%[15].

Thus, body fat content and, mainly, the fat distribution or adiposity could be considered as important indicators of health risk. Several techniques have been developed for assessing and/or determining body fat or adiposity. Among others, these methodologies include the body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR), waist-to-height ratio (WHtR), skinfold thickness, dual-energy X-ray absorption (DXA) and hydrostatic densitometry. The BMI, an index of relative weight, is the most widely used and accepted index for classifying overweight and obesity in clinical practice, providing a simple approach to characterize obesity in individuals[16]. However, BMI presents some important and well documented limitations, such as: a different behavior in men and women, limited usefulness in children and athletes, differences between ethnic groups and especially in determining the composition and distribution of body fat, which can represent a limitation in epidemiological studies or clinical practice. Among other errors, the above indicated limitations could lead to classify individuals with high muscle mass as overweight or obese. On the other hand, subjects with BMI in the normal range may have a high percentage of fat.
In recent years they have emerged new indices to determine obesity, among them we can highlight the body adiposity index (BAI) and the abdominal volume index (AVI). The BAI was developed by Bergman et al and is determined from measurements of hip circumference and height. This index showed a high correlation with the measured body fat using DXA ($r = 0.85$; $p < 0.001$). In his study, performed only in African Americans and Mexican Americans, Bergman et al. found that this correlation was greater than that between BMI and body fat measured using DXA when together men and women were considered[5].The authors concluded that the BAI is a useful predictor of obesity and suggested that involves simple measurements, because no weight is needed. However, a recent study in Spanish Mediterranean population suggested that BAI does not exceed the limitations of BMI[17].

The AVI was developed by Guerrero-Romero et al and is determined from measurements of waist circumference and hip circumference. This index is strongly related to impaired glucose tolerance and type 2 diabetes mellitus[18].

The relationship between obesity and diabetes (DM) is so important that the term 'diabesity' has been coined. The transition from obesity to diabetes is due to a progressive defect of insulin secretion and a progressive increase in insulin resistance. Both situations appear very early in obese patients, and both worsen similarly to diabetes. A general far increase, specially visceral, specifically associated with insulin resistance[19]. Several studies have found a strong and direct association between obesity and DM[20-21].

Currently, diabetes is an uncurable disease, and its prevention has been the main focus of attention. Therefore, developing means to efficiently identify populations at high risk for DM is an important first step towards adopting preventive measures. There are many scales to predict the risk of type 2 diabetes, although the most used in our country it is the FINDRISC questionnaire. This test was initially developed for Finnish population[22] but has now been validated in many countries[23-24].

The close relationship between diabetes and obesity along with the need to advance in the prevention of DM makes us consider this study, whose primary objective is to determine what relationship exists between different indices related to obesity, such as BMI, BAI, AVI, WC, hip circumference, WHR and WtHR) and FINDRISC scale, a test that measures the risk of DM.

Materials and Methods

Subjects and Study Protocol

A cross-sectional study with Caucasians adult workers (ages, 18-69 years) was performed. All subjects were from different regions of Spain and belonged to different productive sectors. Participants in the study

were selected systematically during their work health periodic examination between January and December 2019. Everyday each worker was assigned a number and half of the examined workers were randomly selected using a random number table. Thus, from a total population of 130.487 workers, 65.200 of them were invited to participate in the study. 4.402 (6.8%) refused to participate, 10.676 were eliminated by not having hip circumference measurements (16.4%) and 1.756 (2.7%) they are excluded to be diabetic and not being able to perform the FINDRISC test, being the final number of participants 48.366 (74.2%), with 19.263 women (39.8%) and 29.103 men (60.2%). Mean age of participants in the study was 39.56 years (SD±10.27). All participants were informed of the purpose of this study before they provided written informed consent to participate. Following the current legislation, members of the Health and Safety Committees were informed as well. The study protocol was in accordance with the Declaration of Helsinki and was approved by Balearic Islands Health Area Clinical Research Ethics Committee (institutional review board approval number: IB 4383/20). After acceptance, a complete medical history, including family and personal history and FINDRISC questionnaire, was recorded. The following inclusion criteria were considered: age between 18 and 69 (working age population), no diabetic, agreement to participate in the study and to be gainfully employed. Subjects who did not meet any of the inclusion criteria and those who refused to participate were excluded from the study.

Measurements and Calculations

All anthropometric measurements were made in the morning, after an overnight fast, at the same time (9 a.m.), and according to the recommendations of the International Standards for Anthropometric Assessment (ISAK)[25]. Furthermore, all measurements were performed by well trained technicians or researchers to minimize coefficients of variation. Each measurement was made three times and the average value was calculated. Weight and height were determined according to recommended techniques mentioned above. Body weight was measured to the nearest 0.1 kg using an electronic scale (Seca 700 scale, Secagmbh, Hamburg). Height was measured to the nearest 0.5 cm using a stadiometer (Seca 220 (CM) Telescopic Height Rod for Column Scales, Seca gmbh, Hamburg). BMI was calculated as weight (kg) divided by height (m) squared (kg/m^2). Criteria to define overweight were the ones of the World Health Organization (WHO)[26] which considers obesity when BMI ≥ 30 kg/m^2. Abdominal waist and hip circumferences were measured using a flexible steel tape (Lufkin Executive Thinline W 606). The plane of the tape was perpendicular to the long axis of the body and parallel to the floor. Waist circumference was measured at the level of the umbilicus and the superior iliac crest. The measurement was made at the end of a normal expiration while the subject stood upright, with feet together and arms hanging freely to the sides. Hip circumference was measured over non-restrictive underwear or light-weight shorts at the level of the maximum extension of the buttocks posteriorly in a horizontal plane, without compressing the skin. Waist circumference (WC) and hip circumference (HC) were measured using a tapeline at the level midway between the lateral lower rib margin and iliac crest as well as at the levels of trochanters. WHR was calculated as WC divided by HC. WHtR was calculated by dividing WC by height in cm.

BAI was calculated using the equation ((hip circumference)/((height)1.5)-18), which refers to Bergman et al5. Values obtained were classified in low, normal, high and very high according to criteria established by Gallagher et al for white population[27].

AVI was calculated using the equation AVI = [2 cm (waist)^2 + 0.7 cm (waist-hip)^2]/1,000

Venous blood samples were taken from the antecubital vein with suitable vacutainers without anticoagulant to obtain serum. Blood samples were taken following a 12 h overnight fast. Participants were seated at rest for at least 15 minutes before blood samples were taken. Serum was obtained after centrifugation (15 min, 1,000 g, 4°C) of blood samples. Serum was stored at -20°C and analyses were performed within 3 days. Concentrations of glucose, cholesterol and triglycerides were measured in serum by standard procedures used in clinical biochemistry laboratory using a clinical system Beckman Coulter SYNCHRON CX®9 PRO (Beckman Coulter, Brea, CA, USA).

Blood pressure was determined after a resting period of 10 minutes in the supine position using an automatic and calibrated sphygmomanometer OMRON M3 (OMRON Healthcare Europe, Spain). As indicated for the anthropometrical measures, blood pressure was measured three times with a one-minute gap between each measurement and an average value was calculated.

FINDRISC questionnaire[28] values 8 items: age, BMI, waist circumference, physical activity, dietary consumption of fruits, vegetables, and berries, Use of antihypertensive medication, previously measured high blood glucose and family history of diabetes. The maximum achievable score is 26. Less than 7 points is considered low risk, 7-11 point slightly elevated risk, 11-14 points moderate risk, and 15-26 points high or very high risk.

Statistical Analyses

All data were tested for their normal distribution (Kolmogorov–Smirnov test). Results are expressed as means and standard deviations (SD) and, when required, in percentages. Student t test for unpaired data was used to evaluate differences in anthropometric and biochemical characteristics between genders. Chi-square test was used for the difference of proportions. The existence

of significant bivariate correlations between parameters such as BAI, AVI, WC, HC, WtHR, WHR and FINDRISC questionnaire was ascertained by determining Pearson or Spearman correlation coefficients. The statistical method of ROC curves (Receiver operating characteristic) curves were used to determine AVI discriminatory capacity of obesity). Cutoff values were derived mathematically from the ROC curves. Statistical analysis was carried out using IBM SPSS Statistics 27.0 software. Significance was accepted at $p<0.05$.

Results

Age and anthropometrical and clinical characteristics of the participants in the study as a whole and categorized by gender are shown in **table I**. Significant differences between men and women were found in all parameters analyzed with higher values of age, anthropometric characteristics (height, weight, BMI, WC, HC, WHR and WtHR), systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol and triglycerides in men and low-density lipoprotein cholesterol in women.

Mean values of anthropometrical indices according the FINDRISC test values by gender are shown in **table II**. Significant differences between men and women were found in all parameters analyzed with higher values of AVI, BMI, WC, HC, WtHR and WHR in men and higher values of BAI in women. All parameters examined, in men and women, are increasing in parallel with the values of FINDRISC test.

Table III shows the coefficients of bivariate correlations between anthropometric measures and FINDRISC test values. FINDRISC test showed the highest correlation with BMI, in men and women, and the lowest correlation with WtHR, in men and women also. In women the correlations were higher than men in BAI, HC and WHR, while the men were higher in AVI, BMI, HC and WtHR.

Figure 1 show the ROC curve in men for AVI respect to the presence of obesity determined using the BMI criteria. In men the area under the curve was 0.846 (95% CI 0.841-0.851). The best cut off point for AVI to determine obesity in men was 16.4 liters and, considering this cut off point, the sensibility was 76.3% (95% CI 75.8%-76.8%) and the specificity was 75.9% (95% CI 75.4%-76.4%)

Figure 2 show the ROC curve in women for AVI respect to the presence of obesity determined using the BMI

Table I: Anthropometric, clinical and analytical characteristics of participants in the study.

Characteristics[1]	Women (n=19.263)	Men (n=29.103)	Total (n=48.366)	p value[1]
Age (years)	39.24 ± 10.16	39.77 ± 10.33	39.56 ± 10.27	<0.0001
Weight (kg)	65.34 ± 13.21	81.10 ± 13.88	74.82 ± 15.65	<0.0001
Height (cm)	161.20 ± 6.58	173.94 ± 7.05	168.87 ± 9.28	<0.0001
BMI (kg/m²)	25.16 ± 4.93	26.79 ± 4.19	26.14 ± 4.57	<0.0001
Waist circumference (cm)	73.91 ± 7.90	87.70 ± 9.14	82.21 ± 10.99	<0.0001
Hip circumference (cm)	97.24 ± 8.95	100.05 ± 8.45	98.93 ± 8.76	<0.0001
WHR	0.76 ± 0.07	0.88 ± 0.08	0.83 ± 0.10	<0.0001
WHtR	0.46 ± 0.05	0.51 ± 0.05	0.49 ± 0.06	<0.0001
Systolic BP (mmHg)	114.38 ± 14.79	124.36 ± 15.07	120.39 ± 15.74	<0.0001
Diastolic BP (mmHg)	69.66 ± 10.28	75.39 ± 10.63	73.11 ± 10.86	<0.0001
Cholesterol (mg/dl)	193.58 ± 36.45	195.92 ± 38.87	194.99 ± 37.94	<0.0001
HDL-C (mg/dl)	53.74 ± 7.63	50.99 ± 7.03	52.09 ± 7.40	<0.0001
LDL-C (mg/dl)	122.25 ± 37.01	120.45 ± 37.59	121.17 ±37.37	<0.0001
Triglycerides (mg/dl)	88.07 ± 46.20	123.75 ± 88.03	109.54 ± 76.28	<0.0001

BMI, Body mass index. WHR, waist- to- hip ratio. WHtR, waist-to-height-ratio. Systolic BP, Systolic blood pressure. Diastolic BP, Diastolic blood pressure. HDL-C, high-density lipoprotein cholesterol. LDL-C, low-density lipoprotein cholesterol.
[1] data are expressed as means ± standard deviation.
[2] Statistical significance was estimated by independent t-test

Table II: Values of anthropometrical indices according the FINDRISC test values.

			BAI	AVI	BMI	WC	HC	WtHR	WHR
	FINDRISC	n	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Women	Low	14938	28.43 ± 4.15	10.69 ± 1.52	23.42 ± 3.23	71.39 ± 5.60	94.95 ± 7.19	0.44 ± 0.04	0.75 ± 0.07
	Slightly raised	3073	33.19 ± 4.97	13.93 ± 2.65	30.60 ± 4.89	81.86 ± 7.89	104.25 ± 9.61	0.51 ± 0.04	0.79 ± 0.07
	Moderate	772	34.25 ± 5.39	14.27 ± 3.05	31.59 ± 5.15	82.75 ± 8.83	105.67 ± 9.75	0.52 ± 0.05	0.79 ± 0.07
	High-very high	480	36.68 ± 5.68	15.84 ± 3.64	34.11 ± 5.09	87.16 ± 10.22	109.83 ± 10.51	0.55 ± 0.06	0.80 ± 0.09
Men	Low	19920	24.57 ± 3.33	14.30 ± 1.95	25.07 ± 2.98	83.82 ± 5.97	97.71 ± 7.20	0.48 ± 0.04	0.86 ± 0.07
	Slightly raised	6759	27.63 ± 3.67	18.32 ± 3.36	29.89 ± 3.84	94.97 ± 8.89	104.47 ± 8.49	0.55 ± 0.05	0.91 ± 0.09
	Moderate	1463	29.07 ± 3.90	19.66 ± 3.51	31.85 ± 3.86	98.47 ± 9.02	106.58 ± 8.74	0.57 ± 0.05	0.93 ± 0.09
	High-very high	961	29.85 ± 4.04	20.48 ± 3.76	32.76 ± 4.26	100.48 ± 9.50	107.75 ± 9.23	0.59 ± 0.05	0.94 ± 0.09
	p-value[1]		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

BAI, body adiposity index. AVI, abdominal volume index, BMI, Body mass index. WC, waist circumference. HC, hip circumference. WHtR, waist-to-height-ratio. WHR, waist- to- hip ratio.
[1] Statistical significance was estimated by independent t-test.

Table III: Correlations between anthropometric measures and FINDRISC test values.

FINDRISC	Women	Men	Total
Body adiposity index	0.535*	0.512*	0.424*
Abdominal volumen index	0.641*	0.650*	0.586*
Body mass index	0.749*	0.768*	0.729*
Waist circumference	0.626*	0.643*	0.566*
Hip circumference	0.524*	0.456*	0.491*
Hip- to-waist ratio	0.192*	0.302*	0.275*
Waist-to-height ratio	0.577*	0.542*	0.648*

The level of significance was p*<0.01. Pearson or Spearman correlation coefficient

Figure 1: ROC curve analysis for AVI respect to obesity in men (BMI criteria).

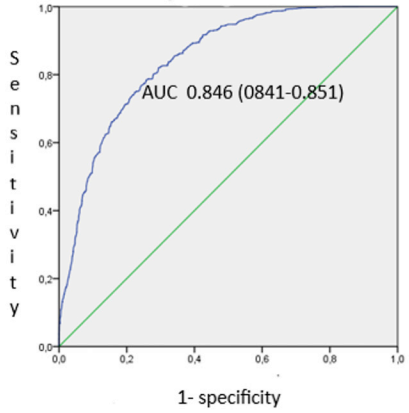
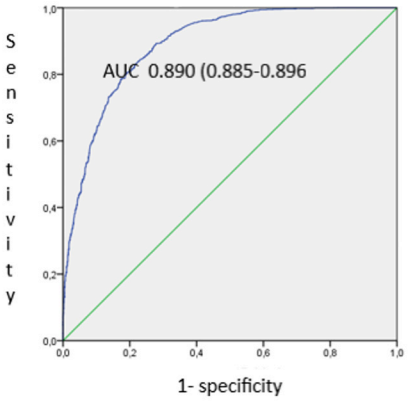


Figure 2: ROC curve analysis for AVI respect to obesity in women (BMI criteria).



criteria. In women the area under the curve was 0.890 (95% CI 0.885-0.896). The best cut off point for AVI to determine obesity in women was 12.3 liters and, considering this cut off point, the sensibility was 80.7% (95% CI 79.8%-81.6%) and the specificity was 80.7% (95% CI 79.8%-81.7%).

Table IV shows the prevalence of normal and high values of different anthropometric indices according FINDRISC test values. In men all of indices analyzed were increasing parallel to the increase of FINDRISC values. In women, BAI, AVI, BMI, WC and WtHR also increased parallel to increase of FINDRISC test values, WHR also increase with FINDRISC test but not parallelly. In general the prevalence of abnormal values of all anthropometric indices was higher in men.

Discussion

The most striking result of this study is that all the scales that assess overweight and obesity analyzed show an increase in prevalence as the values of the Findrisc questionnaire increase. This situation is observed in both sexes, although the prevalence is higher in men.

We have found several articles that agree with us on the increase in BMI values as Findrisc values increase, thus Salinero-Fort in a study carried out in primary care[29] in a population older than ours found that people with FINDRISC values of 15 and above had higher BMI and waist circumference values. Another study conducted by our group in a Spanish Mediterranean population also found this association[30]. We have not found any article that relates other scales of overweight and obesity such as BAI and AVI with the values of the FINDRISC test, so we cannot compare our results with those obtained by other authors. The strengths of the study include the large sample size, more than 48,000 people, and the

Table IV: Prevalence of normal and high values of different anthropometric indices according FINDRISC test values.

	Women					Men				
FINDRISC	Low	Slightly raised	Moderate	High -very high	p-value	Low	Slightly raised	Moderate	High -very high	p-value
BAI low weight	3.8	0.3	0.3	0.0	<0.0001	0.0	0.0	0.0	0.0	<0.0001
BAI normal weight	85.8	64.1	59.7	45.4		8.7	3.4	2.1	1.6	
BAI over weight	9.7	25.8	27.2	28.8		58.1	35.5	27.9	24.7	
BAI obese	0.6	9.8	12.8	25.8		33.3	61.1	70.1	73.8	
AVI normal	85.2	25.6	23.8	10.4	<0.0001	84.3	28.6	17.3	13.8	<0.0001
AVI high	14.8	74.4	76.2	89.6		15.7	71.4	82.7	86.2	
BMI low weight	3.2	0.2	0.1	0.0	<0.0001	0.8	0.0	0.1	0.0	<0.0001
BMI normal weight	68.3	8.1	5.4	1.7		49.4	5.5	1.6	0.8	
BMI over weight	25.1	41.2	33.4	16.0		45.0	51.0	25.1	23.4	
BMI obese	3.4	50.5	61.0	82.3		4.8	43.5	73.2	75.8	
WC normal	95.7	43.7	44.0	30.4	<0.0001	97.3	44.7	29.5	25.8	<0.0001
WC high	4.3	56.3	56.0	69.6		2.7	55.3	70.5	74.2	
WtHR normal	95.9	45.8	40.2	23.5	<0.0001	69.9	16.4	7.7	5.5	<0.0001
WtHR high	4.1	54.2	59.8	76.5		30.1	83.6	92.3	94.5	
WHR normal	92.2	81.4	83.7	74.6	<0.0001	72.9	49.4	41.1	38.8	<0.0001
WHR high	7.8	18.6	16.3	25.4		27.1	50.6	58.9	61.2	

BAI, body adiposity index. AVI, abdominal volume index, BMI, Body mass index. WC, waist circumference. WHtR, waist-to-height-ratio. WHR, waist- to- hip ratio.

variety of overweight and obesity scales analyzed. As limitations we would highlight that it has been carried out in a specific country and in a working population (ages between 18 and 69 years) which could prevent extrapolating the results to other geographical areas and to the general population.

Conclusion

All the overweight and obesity scales analyzed in this study increase in value as the values of the Findrisc scale increase

Interests conflict

The authors declare no conflict of interest.

References

1. Hetherington MM, Cecil JE. Gene-environment interactions in obesity. Forum Nutr. 2010; 63: 195-203.

2. Prevalencia de sobrepeso y obesidad en España en el informe "The heavy burden of obesity" (OCDE 2019) y en otras fuentes de datos. Available at: https://www.bing.com/search?q=prevalencia+obesidad+espa%c3%b1a&qs=UT&pq=prevalencia+obes&sk=UT1&sc=416&cvid=595C87827BDF4420BB235A57DA842940&FORM=QBRE&sp=2#:~:text=www.aesan.gob.es/AECOSAN/docs/documentos/nutricion/observatorio/Resume

3. Must A, Spadano J, Coakley EH, Field AE, Colditz G, et al. The disease burden associated with overweight and obesity. JAMA.1999; 282: 1523-9.

4. Ross R, Berentzen T, Bradshaw AJ, Janssen I, Kahn HS, et al. Does the relationship between waist circumference, morbidity and mortality depend on measurement protocol for waist circumference? Obes Rev. 2008; 9: 312-25.

5. Bergman RN, Stefanovski D, Buchanan TA, Sumner AE, Reynolds JC, et al. A better index of body adiposity. Obesity (Silver Spring).2011; 19: 1083-9.

6. Katzmarzyk PT, Gagnon J, Leon AS, Skinner JS, Wilmore JH, et al. Fitness, fatness, and estimated coronary heart disease risk: the HERITAGE Family Study. Med Sci Sports Exerc.2001; 33: 585-90.

7. Tanaka H, Clevenger CM, Jones PP, Seals DR, DeSouza CA. Influence of body fatness on the coronary risk profile of physically active postmenopausal women. Metabolism.1998; 47: 1112-20.

8. Kannel WB, Dawber TR, Kagan A, Revotskie N, Stokes J. Factors of risk in the development of coronary heart disease–six year follow-up experience. The Framingham Study. Ann Intern Med. 1961;55: 33-50.

9. Eckel RH, Alberti KG, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet.2010; 375: 181-3.

10. Mathieu P, Poirier P, Pibarot P, Lemieux I, Despres JP. Visceral obesity: the link among inflammation, hypertension, and cardiovascular disease. Hypertension.2009; 53: 577-84.

11. Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet.2009;373: 1083-96.

12. Marrugat J, Solanas P, D'Agostino R, Sullivan L, Ordovas J, et al. Coronary risk estimation in Spain using a calibrated Framingham function. Rev Esp Cardio.2003; 56: 253-61.

13. Marrugat J, Subirana I, Comin E, Cabezas C, Vila J, et al.Validity of an adaptation of the Framingham cardiovascular risk function: the VERIFICA Study. J Epidemiol Community Health.2007; 61: 40-7.

14. Heber D. An integrative view of obesity. Am J Clin Nutr.2010; 91 (1): 280S-3S.

15. Low S, Chin MC, Deurenberg-Yap M. Review on Epidemic of Obesity. Ann Acad Med Singapore 2009; 38 (1): 57-9.

16. Bouchard C. BMI, fat mass, abdominal adiposity and visceral fat: where is the 'beef'? Int J Obes (Lond).2007; 31: 1552-3.

17. Lopez AA, Cespedes ML, Vicente T, Tomas M, Bennasar-Veny M, et al. Body adiposity index utilization in a Spanish Mediterranean population: comparison with the body mass index. PLoS One.2012; 7: e35281.

18. Guerrero-Romero F, Rodríguez-Morán M. Abdominal volume index. An anthropometry-based index for estimation of obesity is strongly related to impaired glucose tolerance and type 2 diabetes mellitus. Arch Med Res. 2003;34(5):428-32.

19. Golay A, Ybarra J. Link between obesity and type 2 diabetes. Best Pract Res Clin Endocrinol Metab. 2005;19(4):649-63.

20. Zalesin KC, Franklin BA, Miller WM, Peterson ED, McCullough PA. Impact of obesity on cardiovascular disease. Med Clin North Am. 2011;95:919-37.

21. Reaven GM. Insulin resistance: the link between obesity and cardiovascular disease. Med Clin North Am. 2011;95(5):875-92.

22. Lindström J, Tuomilehto J. The diabetes risk score: a practical tool to predict type 2 diabetes risk. Diabetes Care. 2003;26(3):725-31

23. Soriguer F, Valdés S, Tapia MJ, Esteva I, Ruiz de Adana MS, Almaraz MC, et al. Validation of the FINDRISC (FINnish Diabetes RIsk SCore) for prediction of the risk of type 2 diabetes in a population of southern Spain. Pizarra Study. Med Clin (Barc). 2012;138(9):371-6.

24. Bergmann A, Li J, Wang L, Schulze J, Bornstein SR, Schwarz PE. A simplified Finnish diabetes risk score to predict type 2 diabetes risk and disease evolution in a German population. Horm Metab Res. 2007;39(9):677-82.

25. Bioelectrical impedance analysis in body composition measurement: National Institutes of Health Technology Assessment Conference Statement. Am J Clin Nutr. 1996;64:524S-532S.

26. Organization WH. Obesity: preventing and managing the global epidemic. Report of a WHO Consultation. 2000. Ginebra:WHO

27. Gallagher D, Heymsfield SB, Heo M, Jebb SA, Murgatroyd PR, et al. (2000) Healthy percentage body fat ranges: an approach for developing guidelines based on body mass index. Am J Clin Nutr 72: 694-701.

28. Atayoglu AT, Inanc N, Başmisirli E, Çapar AG. Evaluation of the Finnish Diabetes Risk Score (FINDRISC) for diabetes screening in Kayseri, Turkey. Prim Care Diabetes. 2020 Oct;14(5):488-93.

29. Salinero-Fort MA, Carrillo-de Santa Pau E, Abána-des-Herranz JC, Dujovne-Kohan I, Cárdenas-Valla-dolid J; en nombre del grupo MADIABETES. Riesgo basal de Diabetes Mellitus en Atención Primaria según cuestionario FINDRISC, factores asociados y evolución clínica tras 18 meses de seguimiento. Rev Clin Esp. 2010;210(9):448-53.

30. López-González ÁA, García-Agudo S, Tomás-Salvá M, Vicente-Herrero MT, Queimadelos-Carmona M, Campos-González I. FINDRISC Test: Relationship between cardiovascular risk parameters and scales in Spanish Mediterranean population. Rev Med Inst Mex Seguro Soc. 2017 May-Jun;55(3):309-16. Spanish.

eISSN 2255-0569

ORIGINAL

Assessment of drug utilization patterns of proton pump inhibitors in a tertiary care hospital: a prospective observational study in a south indian tertiary care hospital, India

Evaluación de los patrones de utilización de medicamentos de los inhibidores de la bomba de protones en un hospital de atención terciaria: un estudio observacional prospectivo en un hospital de atención terciaria del sur de la India

Arezoo Roozegar, Balakeshwa Ramaiah

Doctors of Pharmacy, Department of Pharmacy Practice, Karnataka College of Pharmacy, Bengaluru, India

Corresponding author
Arezoo Roozegar
Department of Pharmacy Practice,
Karnataka College of Pharmacy, Bengaluru, India
E-mail: arezoo.roozegar@yahoo.com

Received: 1 - X - 2021
Accepted: 5 - XII - 2021

doi: 10.3306/AJHS.2022.37.01.77

Abstract

Objective: The present study is aimed to assess the drug use patterns of proton pump inhibitors in a south Indian tertiary care hospital.
Methodology: A prospective observational study in 6 months that was conducted in the inpatient department at a tertiary care hospital, treatment chart of inpatients will be review for prescribed patterns of proton pump inhibitors, relevant information will be noted in a predefined data collection form. All of the detail will be used to calculate the result of the study.
Result: 124 patients under randomized, prospective, and observational study are collected in this study .therefore from this sample 73 patients (59%) were male and 51(41%) patients were female, four groups of ages 18 to 30 years old (10.48%), 31 to 50 years old (25%), age of 51 to 70 years old (42.7%) and ages above than71 (21.7%). gastrointestinal disease 16.93%, respiratory disease 50%, alcoholism 2.41%, heart disease 27.42%, veins & vessel &gland disorders 49.19%, kidney disease 25.8%, nerve and brain damages 22.5%, liver disease7.25%, inflectional disease 34.67%, diabetic Mellitus 24.2%and other rare diseases 11.3% were the diagnosis of patients, 164 proton pump inhibitors are used during treatment, these drugs are as 124 pantoprazole (75.6%), 37 Omeprazole (22.56%), 2 rabeprazole (1.2%), 1 lansoprazole (0.6%).wherefore these shows that the pantoprazole and omeprazole are most favorite drug to be prescribed by the physicians, gastroesophageal reflex disease in 63 (50.8%) patient, gastric ulceration in 2 (1.6%) patient, inflectional disease in 59 (47.58%) patients was the indications of PPIs and they are given in injections (75.6%) and (24.4%) orally.
Conclusion: Based on data collected in this study Proton pumps inhibitors are mostly used in males and they are prescribed for respiratory disease, veins disorders, and diabetic Mellitus diagnoses; pantoprazole and omeprazole are the most PPIs prescribed by the doctors and they are prescribed in intravenous more than others routs. It was found the use of PPIs in a wide range of indications; therefore, PPIs generally are indicated for gastroesophageal reflux disease and inflectional disease in great value in mean indications.

Keywords: Proton pump inhibitors, pantoprazole, drug utilization.

Resumen

Objetivo: El presente estudio tiene como objetivo evaluar los patrones de uso de medicamentos de los inhibidores de la bomba de protones en un hospital de atención terciaria del sur de la India.
Metodología: Se trata de un estudio observacional prospectivo de 6 meses de duración que se realizó en el departamento de hospitalización de un hospital de atención terciaria, en el que se revisarán las historias clínicas de los pacientes internos para determinar los patrones de prescripción de los inhibidores de la bomba de protones y se anotará la información pertinente en un formulario de recogida de datos predefinido. Todos los detalles se utilizarán para calcular el resultado del estudio.
Resultado: En este estudio se recogen 124 pacientes en el marco de un estudio aleatorio, prospectivo y observacional. Por lo tanto, de esta muestra 73 pacientes (59%) eran hombres y 51 (41%) eran mujeres, cuatro grupos de edades de 18 a 30 años (10,48%), de 31 a 50 años (25%), de 51 a 70 años (42. Enfermedades gastrointestinales 16,93%, enfermedades respiratorias 50%, alcoholismo 2,41%, enfermedades cardíacas 27,42%, trastornos de las venas y los vasos sanguíneos 49,19%, enfermedades renales 25,8%, daños nerviosos y cerebrales 22,5%, enfermedades hepáticas 7,25%, enfermedades infecciosas 34,67%, diabetes mellitus 24. El diagnóstico de los pacientes fue de un 2% y de otras enfermedades raras de un 11,3%. Durante el tratamiento se utilizaron 164 inhibidores de la bomba de protones, de los cuales 124 eran pantoprazol (75,6%), 37 omeprazol (22,56%), 2 rabeprazol (1,2%) y 1 lansoprazol (0,6%). Por lo tanto, esto demuestra que el pantoprazol y el omeprazol son los fármacos preferidos por los médicos, la enfermedad de reflejo gastroesofágico en 63 (50,8%) pacientes, la úlcera gástrica en 2 (1,6%) pacientes, la enfermedad infecciosa en 59 (47,58%) pacientes fueron las indicaciones de los IBP y se administran en inyecciones (75,6%) y (24,4%) por vía oral.
Conclusiones: Según los datos recogidos en este estudio, los inhibidores de la bomba de protones se utilizan sobre todo en los hombres y se prescriben para enfermedades respiratorias, trastornos venosos y diagnósticos de diabetes mellitus; el pantoprazol y el omeprazol son los IBP más prescritos por los médicos y se prescriben por vía intravenosa más que por otras vías. Se constató el uso de los IBP en una amplia gama de indicaciones; por lo tanto, los IBP están indicados generalmente para la enfermedad por reflujo gastroesofágico y la enfermedad infecciosa en gran valor en las indicaciones medias.

Palabras clave: Inhibidores de la bomba de protones, pantoprazol, utilización de medicamentos.

Introduction

The World Health Organization (WHO) defines drug utilization research (DUR) as "the marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences"[1]. The ultimate goal of DUR is to evaluate whether the drug treatment is rational or not which may provide insights into the various aspects of prescribing patterns such as frequency, dosage, duration of therapy, indication quality, determinants, and outcome of drug use. DUR is used as a potential tool in the evaluation of the healthcare systems as well as a powerful exploratory tool to explain the role of drugs in society. PPIs are one among the most commonly prescribed class of medications in both outpatient and inpatient treatments. These medications are used for long-lasting suppression of gastric acid by inhibiting the hydrogen-potassium adenosine triphosphatase enzyme system, which makes the stomach acidic, and is found in the cells that line the stomach. Over the past few years, the prescriptions for the Proton Pump Inhibitors (PPIs) have consistently increased in the hospital and ambulatory care settings. Studies have shown that the incidence of irrational use of PPIs ranges from 40- 70%[2].

Proton pump inhibitors (PPIs) were developed in the '80s and their use has continuously grown. They represent the first choice in the treatment of acid-related diseases and are currently the most prescribed drugs in the world. Over the past 10 years, there has been a significant increase in their use throughout the world [3,4]. For the treatment of acid-related diseases, various inhibitors of gastric acid emission and killing specialists have been created. At first, killing medications containing aluminum or magnesium, and anticholinergic specialists were utilized. Nonetheless, the effects of those for acid restraint are restricted and their utilization frequently has adverse effects, including cardiovascular occasions, loose bowels, and constipation[5,6].

Proton pump inhibitors are the most generally prescribed class of meds in the United States, and they represent >$10 billion in yearly medical care costs. PPIs are prescribed by a wide scope of primary and specialty care clinicians for a scope of manifestations related to acid reflux sickness. The far-reaching utilization of PPIs has as of late earned consideration from the American Board of Internal Medicine's "Choosing Wisely" mission to promote appropriate stopping of PPIs when appropriate. PPI prescribing guidelines do not promote one PPI formulation over others, as evidence shows similar symptom relief between different PPI formulations. The active ingredients in generic drugs are the same as in brand name drugs and the FDA requires that generic drug manufacturers must prove the bioequivalence of a generic and brand name formulation cost-effectiveness investigations have discovered that conventional PPIs financially overwhelm treatment methodologies with more expensive PPI formulations[7-10]. PPIs are the most generally utilized drug for gastric acid hindrance on the planet. All the PPIs accessible in India, including omeprazole, esomeprazole, lansoprazole, and rabeprazole, have a benzimidazole core in their molecules alongside different sorts of branch structures. Omeprazole was the first proton pump inhibitor (PPI) found and has been accessible in Europe for acid suppression since 1988. Subsequently, other drugs have been identified and several alternatives are currently available: lansoprazole, pantoprazole, rabeprazole, dexlansoprazole, and esomeprazole[4,7].

In the current setting, the consumption of PPIs is overwhelming; studies have to be carried out to examine the prescribing pattern of the PPIs in hospitalized patients. Hence, the present study aimed to assess and evaluate the utilization patterns of PPIs in the inpatient department of a south Indian tertiary care hospital.

Materials and methods

It is a prospective observational study conducted in the inpatient department at a tertiary care hospital. All of the Prescriptions and treatment charts of inpatients will be review for prescribed patterns of proton pump inhibitors (PPIs). And references projects and books will be used as tools to review the prescription and case chart. The admission register will be reviewed for prescription of any PPIs. When the required data are found, then it is noted in performed data form. All medically relevant information will be noted in a predefined data collection form. Alternatively, the demographic data and the detailed history of the patient regarding past, present, family, personal, and drug history were taken. The other details like the present diagnosis, reason for the present admission will be also noted during 6 months. Patients of both genders who are admitted into the inpatient wards in the Hospital, between the age group of 18-87 years were included in the study. The detailed information such as dosage, frequency, route, indication, and any other relevant information will be retrieved and entered into the data collection form. and at the end of collection data, all of the detail will be used to calculate the result of the study[8-10].

Result and discussion

Despite advances occurred in medical sciences[11-15], diverse diseases have been threated the human health[16-19]. In this regard, drug utilization is the best way to treat and control the patterns of diseases, globally. Drug utilization is so important in medical facilities[20,21].

Totally 124 patients under randomized, prospective, and observational studies are collected in this study.

therefore, from this sample 73 patients (59%) were male and 51 (41%) patients were female. Patients are divided into four groups of ages as 18 to 30 years old (no: 13 (10.48%)), 31 to 50 years old (no: 31 (25%)), age of 51 to70 years old (no: 53 (42.7%)) and ages above than 71 (no: 27 (21.7%)) (**Table I**).

Table I: demogeraphy of patients.

Categorized age of patients		
Patient demography	*No of participants*	*Percentage*
age of 18_30	13	10.48%
age of 31_50	31	25%
age of 51_70	53	42.70%
age Above 71	27	21.70%
Categorized of the gender of patients		
Male	73	59%
Female	51	41%
Total Patients	124	100%

Most of the patients are presented and collected from medicine ward (male 33 numbers (26.6%)-female 26 numbers (20.96%)) and intensive care unit (ICU) (male 13 numbers (10.48%)- female 14 numbers (11.29%)) and High intensive care unit(HICU) (male 27 numbers (21.77%) – female 11 numbers (8.87%)).Within all samples (124 patients) of study for proton pumps inhibitors there was no allergy report after use of PPIs during study procedure, diagnosed with gastrointestinal disease 16.93%, respiratory disease 50%, alcoholism 2.41%, heart disease 27.42%, veins & vessel &gland disorders 49.19%, kidney disease 25.8%, nerve and brain damages 22.5%, liver disease7.25%, inflectional disease 34.67%, diabetic Mellitus 24.2%and other rare diseases 11.3% (**Table II**).

Table II: Categorized of ward presented of PPIs.

Ward presented	No of participants		Percentage	
	Male	Female	Male	Female
Highly intensive care unit (HICU)	27	11	21.77%	8.87%
Intensive care unit (ICU)	13	14	10.48%	11.29%
Medicine	33	26	26.60%	20.96%
Total	73	51	59%	41%

164 proton pump inhibitors are used during treatment, these drugs are 124 pantoprazole (75.6%), 37 Omeprazole (22.56%), 2 rabeprazole (1.2%), 1 lansoprazole (0.6%). wherefore there are shows that pantoprazole and omeprazole are the most favorite drug to be prescribed by the physicians in the hospital. proto pumps are prescribed in different diseases by the physicians, it was found the use of PPIs in a wide range of indications, generally, we made classifications on basic use of PPIs, therefore they can be as a gastroesophageal reflex disease in 63 (50.8%) patient, gastric ulceration in 2 (1.6%) patient, inflectional disease in 59 (47.58%) patients (**Table III**).

Table III: Categorized patient diagnosis.

Patient diagnosed	No of participants	Percentage
gastrointestinal disease	21	16.93%
respiratory disease	62	50%
alcoholism	3	2.41%
heart disease	34	27.42%
veins & vessel &gland disor	61	49.19%
kidney disease	32	25.80%
nerve and brain damages	28	22.50%
liver disease	9	7.25%
infectional disease	43	34.67%
diabetic Mellitus	30	24.20%
other rare diseases	14	11.30%

For a totally of 124 patients 164 proton pump inhibitors are used during treatment, these drugs are 124 pantoprazole (75.6%), 37 Omeprazole (22.56%), 2 rabeprazole (1.2%), 1 lansoprazole (0.6%).wherefore these shows that the pantoprazole and omeprazole are most favorite drug to be prescribed by the physicians in the hospital, which is presented in **table IV**.

Table IV: Categorized of PPIs used.

Drug name	No of PPIs	Percentage
pantoprazole	124	75.60%
omeprazole	37	22.56%
rabeprazole	2	1.20%
lansoprazole	1	0.60%
Total drugs	164	100%

Within this study proto pumps are prescribed in different diseases by physicians and it was found the use of PPIs in a wide range of indications, generally, we made classifications on basic use of PPIs, therefore they can be as a gastroesophageal reflex disease in 63 (50.8%) patient, gastric ulceration in 2 (1.6%) patient, inflectional disease in 59 (47.58%) patients, these are presented in **table V**.

Most of the frequency of PPIs was given to 110 patients once a day (67.07%) which was more than twice (32.92%) (59 patients) in a day. They are given in injections (75.6%) and (24.4%) orally. These drugs are given most likely in

Table V: Categorized of PPIs indication use.

Drug indications	No of participants	%	No of participants		Percentage	
			Male	Female	Male	Female
gastroesophageal reflex disease	63	0.508	36	27	29.03	21.77
gastric ulceration	2	0.016	1	1	0.8	0.8
inflectional disease	59	0.4758	36	23	29.3	18.54

injections by the physician. Tablets, intravenous, and capsules are given as PPIs dosage forms, this results that most of PPLs are used in the intravenous dosage form (**Table VI**).

Table VI: Categorized of ward presented of PPIs.

Categorized of the frequency for PPIs		
Frequency	**no of drug**	**percentage%**
Once in a day	110	67.07%
Twice a day	54	32.92%
Categorized of the route of PPIs		
Injections	124	75.60%
Orally	40	24.40%
Categorized of the dosage form of PPIs		
Intravenous	124	0.756
Tablet	35	0.2134
Capsule	5	0.0304

The majority of drug-drug interactions were caused by atorvastatin + pantoprazole 25 (23.4%), followed by propranolol + pantoprazole 19 (17.8%). The frequency and outcomes of the potential drug-drug interactions involving PPIs are summarized in **table VII**.

According to the severity classification of drug-drug interactions, the study showed 87% moderate, 10% minor, and 3% major interactions. The results were compared with those observed in the Airee et al., (2016) study. Major interactions were caused by rabeprazole + clopidogrel, which increased the risk of thrombosis, and pantoprazole + cilostazol, which increased the cilostazol exposure[22].

Conclusion

The present study showed the usage pattern of PPIs in a wide range of indications. Based on data collected in this study Proton pumps inhibitors are mostly used in males and they are prescribed for respiratory disease, veins disorders, and diabetic Mellitus diagnoses; pantoprazole and omeprazole are the most PPIs prescribed by the doctors and they are prescribed in intravenous more than others routs. Generally, PPIs are indicated for gastroesophageal reflux disease and inflectional disease in great value in mean indications. Various efforts should be made to reduce the unnecessary use of PPIs to minimize drug interactions, related risks, and health care.

Interests conflict

The authors declare no conflict of interest.

Table VII: Frequency and outcomes of potential drug-drug interactions.

PDDIs involving PPIs	Outcomes of interaction	Number	Percentage
Atorvastatin+ Pantoprazole	Increased blood levels of atorvastatin	25	23.4
Propranolol +Pantoprazole	Increased propranolol exposure	19	17.8
Torsemide +Pantoprazole	Hypomagnesemia	16	15.0
Torsemide +Rabeprazole	Hypomagnesemia	3	2.8
Furosemide +Pantoprazole	Hypomagensemia	14	13.1
Glimepiride +Esomeprazole	-	1	0.9
Fluconazole +Pantoprazole	Increased plasma concentration of cyp2c19	2	1.9
Clopidogrel + Pantoprazole	Increased effectiveness of clopidogrel	9	8.4
Clopidogrel +Rabeprazole	Increased risk of thrombosis	2	1.9
Fluconazole +Rabeprazole	Increased plasma concentration of cyp2cl9	1	0.9
Cefpodoxime +Pantoprazole	Increased blood levels of cefpodoxime	3	2.8
Rifampin +Pantoprazole	Increased blood levels of rifampin	7	6.5
Cyanocobalamin +Pantoprazole	-	4	3.7
Amikacin +Pantoprazole	Hypomagensemia	1	0.9

References

1. World Health Organization. WHO International Working Group for Drug Statistics Methodology, WHO Collaborating Centre for Drug Statistics Methodology, WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services: Introduction to drug utilization research. Introduction to drug utilization research. Geneva: World Health Organization 2003.

2. Tadvi NA, Shareef SM. Use of proton pump inhibitors in general practice: Is it rationale. International Journal of Medical Research & Health Sciences 2014; 3(1):37-42.

3. Ntaios G, Chatzinikolaou A, Kaiafa G, Savopoulos C, Hatzitolios A, Karamitsos D. Evaluation of use of proton pump inhibitors in Greece. European journal of internal Medicine 2009; 20(2):171-3.

4. Bollavaram C, Bhukya K, Komuravelli S, Valupadas C, Bandaru SB, Eggadi V. Drug Utilization Evaluation of Pantoprazole in Inpatients of Tertiary Care Hospital. Indian Journal of Pharmacy Practice 2021; 14(1):41.

5. Madi L, Ahmed Elhada AH, Alrawashdeh H, Ahmed A. Prescribing Pattern of Proton Pump Inhibitors in Qatar Rehabilitation Institute: A Retrospective Study. J Res Pharm Pract. 2019 Apr-Jun;8(2):101-4.

6. Elnaem MH, Mohamed MHN, bin Nazar AH, binti Ibrahim RNK. Evaluation of proton pump inhibitors prescribing among non-critically ill hospitalized patients in a Malaysian tertiary hospital. Journal of Applied Pharmaceutical Science 2017; 7(12):077-083.

7. van Vliet EP, Otten HJ, Rudolphus A, Knoester PD, Hoogsteden HC, Kuipers EJ, et al. Inappropriate prescription of proton pump inhibitors on two pulmonary medicine wards. Eur J Gastroenterol Hepatol. 2008 Jul;20(7):608-12.

8. Lodato F, Poluzzi E, Raschi E, Piccinni C, Koci A, Olivelli V, et al. Appropriateness of Proton Pump Inhibitor (PPI) prescription in patients admitted to hospital: Attitudes of general practitioners and hospital physicians in Italy. Eur J Intern Med. 2016 May;30:31-6.

9. Gamelas V, Salvado V, Dias L. Prescription Pattern of Proton Pump Inhibitors at Hospital Admission and Discharge. GE Port J Gastroenterol. 2019 Mar;26(2):114-120.

10. Basyal B, Marasine NR, Sankhi S, Lamichhane R, Uprety B N. Prescribing pattern of proton pump inhibitors among patients visiting the outpatient general medicine clinic in a tertiary care teaching hospital in Nepal. Journal of Health Research 2021 (in press).

11. Rahimi E, Yazdanpour S, Dehkordi FS. Detection of Toxoplasma gondii antibodies in various poultry meat samples using enzyme linked immuno sorbent assay and its confirmation by polymerase chain reaction. J Pure Appl Microbiol. 2014;8(1):421-7.

12. Dehkordi FS, Saberian S, Momtaz H. Detection and segregation of Brucella abortus and Brucella melitensis in Aborted Bovine, Ovine, Caprine, Buffaloes and Camelid Fetuses by application of conventional and real-time polymerase chain reaction. The Thai Journal of Veterinary Medicine. 2012 Mar 1;42(1):13.

13. Ranjbar R, Seif A, Dehkordi FS. Prevalence of antibiotic resistance and distribution of virulence factors in the shiga toxigenic Escherichia coli recovered from hospital food. Jundishapur Journal of Microbiology. 2019;12(5):8.

14. Nejat S, Momtaz H, Yadegari M, Nejat S, Safarpour Dehkordi F, Khamesipour F. Seasonal, geographical, age and breed distributions of equine viral arteritis in Iran. Kafkas Univ Vet Fak Derg. 2015 Jan 1;21(1):111-6.

15. Rahi A, Kazemeini H, Jafariaskari S, Seif A, Hosseini S, Dehkordi FS. Genotypic and phenotypic-based assessment of antibiotic resistance and profile of staphylococcal cassette chromosome mec in the methicillin-resistant Staphylococcus aureus recovered from raw milk. Infection and drug resistance. 2020;13:273.

16. Sheikhshahrokh A, Ranjbar R, Saeidi E, Dehkordi FS, Heiat M, Ghasemi-Dehkordi P, Goodarzi H. Frontier therapeutics and vaccine strategies for sars-cov-2 (COVID-19): A review. Iranian Journal of Public Health. 2020 Jul 11.

17. Ranjbar R, Mahmoodzadeh Hosseini H, Safarpoor Dehkordi F. A review on biochemical and immunological biomarkers used for laboratory diagnosis of SARS-CoV-2 (COVID-19). The Open Microbiology Journal. 2020 Dec 15;14(1).

18. Mirzaie A, Halaji M, Dehkordi FS, Ranjbar R, Noorbazargan H. A narrative literature review on traditional medicine options for treatment of corona virus disease 2019 (COVID-19). Complementary therapies in clinical practice. 2020 Aug 1;40:101214.

19. Halaji M, Farahani A, Ranjbar R, Heiat M, Dehkordi FS. Emerging coronaviruses: first SARS, second MERS and third SARS-CoV-2: epidemiological updates of COVID-19. Infez Med. 2020;28(suppl):6-17.
20. Madi L, Elhada AH, Alrawashdeh H, Ahmed A. Prescribing pattern of proton pump inhibitors in Qatar rehabilitation institute: a retrospective study. Journal of research in pharmacy practice. 2019 Apr;8(2):101.

21. D'Souza AM, Shastry CS, Mateti UV, Kabekkodu S, Chand S. Drug Utilization and Evaluation of Proton Pump Inhibitors in General Medicine Ward of a Tertiary Care Hospital. Journal of Pharmaceutical Sciences and Research. 2019 Jun 1;11(6):2174-9.

22. Airee, R.S., Rawal, A., John, N.N., Binu, K.M., (2016). Drug use evaluation of proton pump inhibitors in a private tertiary care teaching hospital. WJPPS. 5(1), 922-30.

eISSN 2255-0569

ORIGINAL

Drug use evaluation of oral hypoglycemics in diabetic patients in a tertiary care hospital, India

Evaluación del uso de hipoglucemiantes orales en pacientes diabéticos en un hospital de atención terciaria, India

Seyedsahand Gheybi, Peter Kandel

Doctors of Pharmacy, Department of Pharmacy Practice, R R College of Pharmacy, Bengaluru, India

Corresponding author
Seyedsahand Gheybi
Department of Pharmacy Practice,
R R College of Pharmacy, Bengaluru, India
E-mail: gheybi.sahand@gmail.com

Received: 4 - XI - 2021
Accepted: 7 - XII - 2021

doi: 10.3306/AJHS.2022.37.01.82

Abstract

Objective: To evaluate drug use of oral hypoglycemic in hospitalized diabetic patients in a tertiary care hospital.
Methodology: A retrospective study of 6 months duration was undertaken during 2017-2018. A total number of 110 patients case sheets were utilized for study from diabetics patients, department of Sapthagiri Institute of Medical Sciences & Research Centre (SIMSRC). Patients were included in study with any age with diagnosis of diabetes mellitus. Randomization was done by selecting alternative case sheets. The data's were collected in proforma, which includes name, age, gender, diagnosis, number of drugs prescribed, with dose and routes of drug administration and also condition of patient on discharge were recorded. blood transfusion and nutritional preparations were not included in the study. Source of data was collected from patient's case sheets obtained from record section. Ethical clearance was taken from institutional ethical committee. Drugs data on the utilization of oral hypoglycemics and patient's data were computed using MS Excel and statistical analysis was done by using SPSS (Statistical package for the social sciences).
Results: Out of 110 patients enrolled in the study from inpatient department, Majority of patients 34.5% belonged to age group of 51-60 years. the number of Female patients were high by 10.9%. 55.4% patients were females and 44.5% patients were males. In Diabetes mellitus patients the most common co-morbid conditions are Hypertension (47.4%), Ischemic Heart Disease (11.4%), Coronary Artery Disease (8%), Unstable Angina (6.8%), Asthma (4%), Chronic Kidney Disease (4%), Anemia (3.4%), Myocardial Infarction (3.4%), Liver Dysfunction (2.2%), Congestive Cardiac Failure (1.7%), COPD (1.7%), ESRD (1.1%) and hyperlipidemia, Infection (1.1%). Among these 15 co-morbid conditions Hypertension and Ischemic Heart Disease are comparatively high. Out of 110 prescriptions, the total number of drugs prescribed were 816. Number of appropriate prescriptions were 95.4% and Number of inappropriate prescriptions were 4.5%. Anti-diabetics were the commonest class of drugs prescribed accounting for 20.7% of the total drugs. Glimepiride + metformin was used most widely 54.2% as a combination therapy. Out of 173 Oral Hypoglycemic prescribed 69.9% were given as Twice a day, followed by 21.9% were given as Three times a day and Once daily in 5.2%.
Conclusion: This study gives an overview of the Evaluation Of Oral Hypoglycemics in the study area. The study showed that patients between the ages of 51 and 60 years were admitted more frequently than other age groups. The most common illness for which patients were hospitalized involves Type 2 DM, Hypertension, Ischemic Heart Disease, Coronary Artery Disease and Unstable Angina. In Diabetes mellitus patients the most common co-morbid condition is Hypertension. In this study Anti-diabetics were the commonest class of drugs prescribe. In monotherapy, Biguanides (Metformin) utilization was high and in combination therapy, Glimepiride + metformin was used most widely. The most frequency of treatment observed were given twice a day.

Keywords: Oral hypoglycemics, Diabetes mellitus, Metformin, Biguanides, Glimepiride, Hypertension, Evaluation.

Resumen

Objetivo: Evaluar el uso de fármacos hipoglucemiantes orales en pacientes diabéticos hospitalizados en un hospital de tercer nivel.
Metodología: Se realizó un estudio retrospectivo de 6 meses de duración durante 2017-2018. Se utilizaron para el estudio un total de 110 hojas de casos de pacientes diabéticos, departamento del Sapthagiri Institute of Medical Sciences & Research Centre (SIMSRC). Se incluyeron en el estudio pacientes de cualquier edad con diagnóstico de diabetes mellitus. La aleatorización se realizó mediante la selección de hojas de casos alternativos. Los datos se recogieron en un formulario que incluía el nombre, la edad, el sexo, el diagnóstico, el número de fármacos prescritos, la dosis y las vías de administración de los mismos, así como el estado del paciente al ser dado de alta. La fuente de datos se recogió de las hojas de los casos de los pacientes obtenidas de la sección de registros. Se obtuvo la autorización ética del comité ético institucional. Los datos de los fármacos sobre la utilización de hipoglucemiantes orales y los datos de los pacientes se calcularon con MS Excel y el análisis estadístico se realizó con SPSS (Statistical package for the social sciences).
Resultados: De los 110 pacientes inscritos en el estudio desde el departamento de hospitalización, la mayoría de los pacientes, el 34,5%, pertenecían al grupo de edad de 51-60 años. El 55,4% de los pacientes eran mujeres y el 44,5% eran hombres. En los pacientes con diabetes mellitus, las enfermedades comórbidas más comunes son la hipertensión (47,4%), la cardiopatía isquémica (11,4%), arteriopatía coronaria (8%), angina inestable (6,8%), asma (4%), enfermedad renal crónica (4%), anemia (3,4%), infarto de miocardio (3,4%), disfunción hepática (2,2%), insuficiencia cardiaca congestiva (1,7%), EPOC (1,7%), enfermedad renal terminal (1,1%) e hiperlipidemia e infecciones (1,1%). Entre estas 15 enfermedades comórbidas, la hipertensión y la cardiopatía son comparativamente altas. De las 110 prescripciones, el número total de medicamentos prescritos fue de 816. El número de prescripciones apropiadas fue del 95,4% y el número de prescripciones inapropiadas fue del 4,5%. Los antidiabéticos fueron la clase de fármacos más recetados, con un 20,7% del total de fármacos. La combinación de glimepirida y metformina fue la más utilizada (54,2%). De los 173 hipoglucemiantes orales prescritos, el 69,9% se administró dos veces al día, seguido del 21,9% que se administró tres veces al día y del 5,2% que se administró una vez al día.
Conclusión: Este estudio ofrece una visión general de la evaluación de los hipoglucemiantes orales en el área de estudio. El estudio demostró que los pacientes de entre 51 y 60 años fueron ingresados con mayor frecuencia que otros grupos de edad. Las enfermedades más comunes por las que fueron hospitalizados los pacientes son la DM tipo 2, la hipertensión, la cardiopatía isquémica, la arteriopatía coronaria y la angina inestable. En los pacientes con diabetes mellitus, la enfermedad comórbida más común es la hipertensión. En este estudio, los antidiabéticos fueron la clase de fármacos más prescritos. En monoterapia, la utilización de biguanidas (metformina) fue elevada y en terapia combinada, Glimepirida + metformina fue la más utilizada. La mayor frecuencia de tratamiento observada se administró dos veces al día.

Palabras clave: Hipoglucemiantes orales, Diabetes mellitus, Metformina, Biguanidas, Glimepirida, Hipertensión, Evaluación.

Introduction

Diabetes mellitus (DM) is one of the oldest diseases known to man, which was the first reported in Egyptian literature about 3000 years ago[1]. The name diabetes was first given by the Greek Physician Aretaeus (30 - 90CE). Avicenna, is the famous Arabian physician who first described the complications and progression of the disease[2]. People living with type 2 DM are more vulnerable to various forms of both short and long-term complications, which often lead to their premature death. The world health organization (WHO) defines diabetes mellitus as "A metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in the insulin secretion, insulin action, or both."[3,4] India has the largest population of diabetes in the world. The international diabetes federation (IDF) estimates the number of people with diabetes in India will reach 80million by the year 2025 [5]. The world health organization (WHO) has projected that the global prevalence of type-2 diabetes mellitus will more than double from 5 million in 1995 to 300 million by 2025. Between 1995 and 2025, there will be a 35% increase in worldwide prevalence of diabetes mellitus, from 4 to 5.4%[6].

Diabetes prevalence is continuously growing all over the world. Type 2 diabetes constitute about 85% to 95% of the diabetic population in the developed countries and even higher in the developing countries. In 2003, 194 million people having age between 20 to 79 years are diabetic and a quarter of them belong to developing countries. There is a rapid increase in the prevalence of diabetes in Asian countries[7]. Various classes of anti-diabetic drugs including insulin and oral hypoglycemic agents (OHA) are currently used in the treatment of diabetes, which acts by different mechanisms to reduce the blood glucose levels to maintain optimal glycemic control [8]. There are several classes of oral drugs used to control blood glucose levels, including: Sulfonylureas, such as glipizide and glimepiride, are considered hypoglycemic agents because they stimulate the release of insulin from beta cells in the pancreas, thus reducing blood glucose levels[9].Glipizide 2.5 to 10mg PO before breakfast and evening meal, start with low dose.45 glimepiride 1 to 2 mg orally once a day[10].

Diabetes mellitus requires ongoing medical care as well as patient and family education both to prevent acute illness and to reduce the risk of long term complications. Evaluation of drug use has become an integral part of the pharmacotherapy. Participation in drug utilization study programmes can directly improve the quality of patients' care, by preventing the use of unnecessary or irrational drug therapy and by preventing adverse drug reactions[11]. Drug utilization studies provide physicians with feedback on their performance and assist the design of educational programmes that may improve prescribing and drug use performance[12]. Considering the fact that, India carries a huge diabetic population which is swelling further, medicine utilization studies might be one of the strategies to rationalize the medicine use in diabetics and to manage disease better in the community. Hence a medicine utilization study of oral hypoglycemic was carried out at the Medicine Outpatient Department (OPD) in tertiary care hospital. There were two aims of the study to assess the prescribing pattern of oral hypoglycemic drugs by using ADA guideline, and to correlate association of diabetes with demographic details of patients.

Materials and methods

This study was conducted for a period of 6 months, the study included 110 patients from IP department of Sapthagiri Institute of Medical Science, a tertiary care hospital in Bangalore.

The purpose and other details of the study were discussed with the patients. An oral consent was taken from all the participating patients, prior inclusion in the study. diabetes mellitus patients, irrespective of age and sex, who were prescribed at least one oral hypoglycemic were included in the present study. Diagnosed diabetic patients who do not receive pharmacological therapy, unable to reply verbal questions as well as mentally retarded and unconscious patients were excluded from the study. This is a retrospective and prospective observational study. The patients who satisfied the inclusion criteria was enrolled into the study with the help of patient consent form. The clinical pharmacist reviewed the patient case notes, medication chart, laboratory data and other relevant data. A structured data collection form was used to record all the necessary data including patient demographic details, patient medication history, co morbid conditions and reason for admission, medication details and lab investigation. The pattern of drug dosing was also recorded.

Result and discussion

This study was carried out with an aim to assess the Oral Hypoglycemics used in hospitalized patients of tertiary care hospital in Sapthagiri Institute of Medical Science And Research Centre, Bangalore. The duration of study was six months.

The patient were divided in six age group such as 30-40, 41-50, 51-60, 61-70, 71-80 and >80.

The majority of patients, 34 % were on age group 51-60 years, this may be due to fact that age is a risk factor for developing diabetes mellitus supported by Mandana Moradi et.al.[13] (**Table I**).

Table I: Age Distribution Of Patients Observed (n=110).

AGE DISTRIBUTION (IN YEARS)	TOTAL NO. OF PATIENTS	IN PERCENTAGE
30-40	11	10%
41-50	13	11.80%
51-60	38	34.50%
61-70	25	22.70%
71-80	17	15.40%
>80	6	5.40%

Out of 110 patients, 49 (44.5%) patients were males and 61 (55.4%) patients were females. the number of female patients were high by 10.9%.The study shows that female patients are more than male patients, however in earlier study female predominance were seen which is in agreement with our result supported by Syed Muhammad Ashar et.al[14]. The reason for having diabetes more in fmales than in males could be because of lifestyle.

In Diabetes mellitus patients the most common co-morbid conditions are Hypertension, Ischemic Heart Disease, Coronary Artery Disease, Unstable Angina, Asthma, Chronic Kidney Disease, Anemia, Myocardial Infarction, Liver Dysfunction, Congestive Cardiac Failure, COPD, ESRD and hyperlipidemia, Infection. Among these 15 co-morbid conditions Hypertension and Ischemic Heart Disease are comparatively high (**Table II**).

Table II: Co-Morbid Conditions Of Patients (n=175).

Co-morbid conditions	No. of Patients	In Percentage
Hypertension	83	47.40%
IHD	20	11.40%
CAD	14	8%
Unstable angina	12	6.80%
Asthma	7	4%
CKD	7	4%
Anemia	6	3.40%
MI	6	3.40%
Liver dysfunction	4	2.20%
CCF	3	1.70%
Acute kidney injury	3	1.70%
COPD	3	1.70%
Infection	3	1.70%
ESRD	2	1.10%
Hyperlipidemia	2	1.10%

The total number of drugs prescribed were 816. Average number of drugs per prescription were 7.41. The risk of drug interaction may increase with increase innumber of drugs per prescription which ultimately lead to prescribing errors and in hazardous to the health of patient. Anti-diabetic drugs were the most common drugs prescribed which accounts for 169 (20.7%) of total drugs (**Table III**).

Table III: Number Of Medications Prescribed In Study Population.

Total no of prescriptions	110
Total no of drugs prescribed	816
Average no of drugs per prescription	7.41
No. of appropriate prescriptions	105 (95.4%)
No. of inappropriate prescriptions	5 (4.5%)

In the present study 47.4% patient reported hypertension along with diabetes mellitus, these results were supported by Dashputra AV et al[15] .This study indicates that hypertension is the commonest co-morbidity seen with diabetes mellitus. Anti-platelet were the second commonest drug prescribed which accounts for 69 (9.3%) antibiotics 53 (6.4%), Analgesic 45 (5.2%), Diuretics 37 (4.5%), Hypolipidemic 35 (4.2%), Anti-angina 31 (3.7%), Respiratory agent 14 (1.7%), Calcium channel blocker 12 (1.4%), Benzodiazepines 8 (0.9%), Antihistamine 8 (0.9%), Antihypertensive drugs 8 (0.9%), and others (PPIs, IV fluids, Corticosteroids, Antacid, Anti-emetic, Antifungal, Vitamins) 328 (40.1%) were prescribed (**Table IV**).

Table IV: Distribution Of Different Types Drugs Prescribed (n=816).

Drugs prescribed	Total No. of drugs	In Percentage
Anti-diabetic	169	20.70%
Anti-platelet	69	9.30%
Antibiotics	53	6.40%
Analgesic	45	5.20%
Diuretics	37	4.50%
Hypolipidemic	35	4.20%
Anti-angina	31	3.70%
Respiratory agent	14	1.70%
Calcium channel blocker	12	1.40%
Benzodiazepines	8	0.90%
Antihistamine	8	0.90%
Antihypertensive drugs	7	0.80%
Others*	328	40.10%

* PPIs, IV fluids, Corticosteroids, Antacid, Anti-emetic, Antifungal, Vitamins

Anti-diabetic drugs commonly prescribed as monotherapy were metformin (49.2%), Glimepiride (25.36%), Sitagliptin (15.21%), Glyburide (10.1%) and as combination therapy Glimepiride/metformin (54.2%), Glimepiride/metformin/voglibose (25.7%), Sitagliptin/metformin(20%). Biguanides (metformin) (49.2%) utilization was high as monotherapy in prescription, this may be due to its high advantages of no weight gain these results were supported by Ramachandran G et al[16]. In combination therapy Glimepiride/metformin combination was most widely used (54.2%) (**Table V**).

Table V: Evaluation Of Single Prescribed Oral Hypoglycemics (n=138).

Monotherapy	Number Of Prescription	In Percentage
Metformin	68	49.20%
Glimepiride	35	25.36%
Sitagliptin	21	15.21%
Glyburide	14	10.10%
Total	138	100.00%

Anti-platelet were the second commonest drug prescribed which accounts for 69 (9.3%) antibiotics 53 (6.4%), Analgesic 45 (5.2%), Diuretics 37 (4.5%), Hypolipidemic 35 (4.2%), Anti-angina 31 (3.7%), Respiratory agent 14 (1.7%), Calcium channel blocker 12 (1.4%), Benzodiazepines 8 (0.9%), Antihistamine 8 (0.9%), Antihypertensive drugs 8 (0.9%), and others (PPIs, IV fluids, Corticosteroids, Antacid, Anti-emetic, Antifungal, Vitamins) 328 (40.1%) were prescribed (**Table VI**).

Table VI: Evaluation Of Combination Therapy Of Oral Hypoglycemics (n=35).

Combination therapy	No of Prescription	In Percentage
Glimepiride/metformin	19	54.20%
Glimepiride/metformin/voglibose	9	25.70%
Sitagliptin/metformin	7	20%
Total	35	100

Out of 173 Oral Hypoglycemic prescribed 69.9% were given as Twice a day, followed by 21.9% were given as Three times a day and Once daily in 5.2%. This is based on the choice and course of drugs for the therapy (**Table VII**).

Table VII: Distribution of frequency of treatment observed (n=173).

FREQUENCY OF OF	NUMBER PATIENTS PRESCRIBED WITH ANTIBIOTICS	TREATMENT IN PERCENTAGE
Once Daily	9	5.20%
Twice a day	121	69.90%
Three times a day	38	21.90%
Four times a day	5	2.80%

Conclusion

This observational study of evaluation of oral Hypoglycemics shows metformin was the most commonly prescribed anti-diabetic drug in Monotherapy followed by Glimepiride. Among Fixed drug combination therapy Glimepiride/metformin was the most commonly prescribed antidiabetic drug. The study showed that Majority of patients belonged to age group of 51-60 years. Hypertension was most common associated co-morbidity in diabetic patients. Incidence of diabetes has been found higher in female as compared to male and majority of the patients develop diabetes in the most productive years of their life. In this study, males were found to be more affected by type 2 diabetes mellitus than females. Most of the patients were prescribed two Oral Hypoglycemic. Average number of drugs per prescription was found to be 7.1. The most commonly drugs prescribed apart from antidiabetic were Anti-platelet drugs followed by Analgesics. It was observed that most prescribed Oral Hypoglycemic was Metformin, Glimepiride and Sitagliptin.

Interests conflict

The authors declare no conflict of interest.

References

1. Ahmed AM. History of diabetes mellitus. Saudi medical journal. 2002 Apr 1;23(4):373-8.

2. Olokoba AB, Obateru OA, Olokoba LB. Type 2 diabetes mellitus: a review of current trends. Oman medical journal. 2012 Jul;27(4):269.

3. Monteiro C, Silvestre S, Duarte AP, Alves G. Assessment of suspected adverse drug reactions in elderly patients with diabetes mellitus based on a Portuguese spontaneous reporting database: analysis of reporting from 2008 to 2018. Expert Opinion on Drug Safety. 2021 Jun 1:1-9.

4. Acharya KG, Shah KN, Solanki ND, Rana DA. Evaluation of antidiabetic prescriptions, cost and adherence to treatment guidelines: A prospective, cross-sectional study at a tertiary care teaching hospital. Journal of basic and clinical pharmacy. 2013 Sep;4(4):82.

5. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. Diabetes care. 1998 Sep 1;21(9):1414-31.

6. Sierra GN. The global pandemic of diabetes. African Journal of Diabetes Medicine. 2009;17(11):4-8.

7. Ashar SM, Hanif A, Jadoon A, ur Rehman M. Assessment of Drug Use Pattern Using WHO Prescribing Indicators in the Medication Therapy of Indoor Diabetic Patients. International Journal of Basic Medical Sciences and Pharmacy (IJBMSP). 2016 Jul 3;6(1).

8. Agarwal AA, Jadhav PR, Deshmukh YA. Prescribing pattern and efficacy of anti-diabetic drugs in maintaining optimal glycemic levels in diabetic patients. Journal of basic and clinical pharmacy. 2014 Jun;5(3):79.

9. Mukhtar Y, Galalain A, Yunusa U. A modern overview on diabetes mellitus: a chronic endocrine disorder. European Journal of Biology. 2020 Nov 23;5(2):1-4.

10. Kumar A, Sharma AK, Dutt R. Reverse-Phase High-Performance Liquid Chromatography Method Development and Validation for Estimation of Glimepiride in Bulk and Tablet Dosage Form. International Journal of Pharmaceutical Quality Assurance. 2020 Jun 25;11(02):296-302.

11. Baksaas I, Lunde PK. National drug policies: the need for drug utilization studies. Trends in pharmacological sciences. 1986 Jan 1;7:331-4.

12. Parthasarathi G, Nyfort-Hansen K, Nahata MC, editors. A text book of clinical pharmacy practice: essential concepts and skills. Orient Blackswan; 2004.

13. Moradi M, Mousavi S. Drug use evaluation of diabetes mellitus in nonhospitalized patients. Int J Pharm Pharm Sci. 2016; 8(8), 337-41.

14. Ashar SM, Hanif A, Jadoon A, ur Rehman M. Assessment of Drug Use Pattern Using WHO Prescribing Indicators in the Medication Therapy of Indoor Diabetic Patients. International Journal of Basic Medical Sciences and Pharmacy (IJBMSP). 2016 Jul 3;6(1).

15. Dashputra AV, Badwaik RT, Borkar AS, Date AP, Kalnawat NR. Pattern of antidiabetic drugs used in outpatient and hospitalized patients in a tertiary health institute of central India. Hypertension. 2014;89(59.3):68.

16. Ramachandran G, Rohith V, Topno I. Evaluation of prescribing pattern of anti-diabetic drugs using WHO prescribing indicators in a tertiary care hospital in Puducherry: A cross-sectional study. The Pharma Innovation. 2015 Jul 1;4(5, Part B):76.

eISSN 2255-0569

ORIGINAL

Use of the geographical information system integrated in smartphone to reduce transportation time for general medical care in Ibiza, Spain

Uso del sistema de información geográfica integrado en el teléfono inteligente para reducir el tiempo de transporte para la atención médica general en Ibiza, España

Hans A. Eguía[1], Franco Vinciarelli[2], Walter Curioso[3], Francisco Javier Sanz García-Donato[4], César Oliver Sotelo García[5], Carlos Sánchez Bocanegra[6]

1. MD Lægehuset Rudkøbing. Danmark. UOC researcher 2. Engineer - Master en telemedicina Senior Full Stack Developer. Italy 3. PhD Bioinformatics Vice-rector for Research - Continental University. Perú 4. MD Primary care physician - Conselleria de Sanitat Valenciana 5. MD Primary care physician - SESPA Asturias 6. PhD Head of the IT Department of the Malaga Department of Agriculture

Corresponding author
Hans A. Eguía
UOC / lægehuset Rudkøbing
Endraget 7, 5900 Rudkøbing. Danmark
E-mail: hello@hanseguia.doctor

Received: 6 - X - 2021
Accepted: 9 - XII - 2021

doi: 10.3306/AJHS.2022.37.01.86

Abstract

Introduction: Allocated time for GP out-of-hours service is scarce. Reducing transportation time is one way to increase GP-patient consultations during out-of-hours service. Geographical information systems (GIS) used to reduce response time may be a promising way to address this issue. This study aimed to compare response time between GP vehicles using GIS (from WhatsApp®) and GP vehicles using telephone-assisted driver guidance for non-acute patients who contacted a GP out-of-hours service with an unknown address.
Material & Methods: This study was a prospective observational controlled study using two groups. For each group, vehicles were dispatched simultaneously from the out-of-hours office. One group had vehicles with GIS and the other one had vehicles with telephone-assisted guidance to locate the patient. The main outcome was the response time from two different approaches.
Results: In 515 GP out-of-Hours services 63 patients did not know their location. A total of 61 non-acute patients agreed to participate. Patient age varied from 25 to 78 years with a mean of 56.6 (SD 12,86). Women comprised 28 of the patients (45,9%). The main tentative diagnoses were sore throat, otitis and superficial wound treatment. The vehicles with GIS were significantly faster ($p < 0.0001$) to reach the patient destination (mean 20 minutes) compared to vehicles using phone guidance (mean 28 minutes).
Discussion: In this feasibility study, GIS guidance seems to help reduce the transportation time of GP vehicles to patients with unknown address compared to telephone guidance.

Keywords: Out-of-hours medical care, physician, needs and demand, health services, application, tourists.

Resumen

Introducción: el tiempo asignado para visitas domiciliarias el servicio fuera de horario de atención normal de centros de salud es escaso. Reducir el tiempo de transporte es una forma de aumentar las consultas de pacientes durante el servicio fuera del horario de atención. Los sistemas de información geográfica (SIG) utilizados para reducir el tiempo de respuesta pueden ser una forma prometedora de abordar este problema. El objetivo de este estudio fue comparar el tiempo de respuesta entre los vehículos de médicos de Atención Primaria (MAP) que usan SIG (de la aplicación WhatsApp®) y los vehículos de MAP que usan la guía asistida por teléfono del paciente para llegar a su ubicación. En ambos casos sólo se valoraron pacientes no agudos que se comunicaron con nuestra clínica fuera de horario de atención normal con una dirección desconocida.

Materiales y métodos: se realizó un estudio prospectivo observacional controlado que utilizó dos grupos. Para cada grupo, los vehículos fueron despachados simultáneamente desde el centro de salud en horas fuera de horario habitual. Un grupo conducía un vehículo con SIG y el otro conducía un vehículo con la pauta dada por el paciente para llegar a su ubicación. El resultado principal fue el tiempo de respuesta con dos enfoques diferentes.

Resultados: Durante la realización del estudio 515 pacientes fueron registrados, de los cuales 63 desconocían su ubicación. Un total de 61 pacientes no agudos aceptaron participar. La edad del paciente varió de 25 a 78 años con una mediana de 56,6 (DE 12,86). Las mujeres comprendían 28 de los pacientes (45,9%). Los principales diagnósticos tentativos fueron dolor de garganta, otitis y tratamiento de heridas superficiales. Los vehículos con SIG fueron significativamente más rápidos ($p <0,0001$) para llegar al destino del paciente (promedio de 20 minutos) en comparación con los vehículos que utilizan la guía telefónica (promedio de 28 minutos).

Discusión: En este estudio de factibilidad, la guía SIG parece ayudar a reducir el tiempo de transporte de MAP hacia pacientes con dirección desconocida en comparación con la guía del paciente usando el teléfono.

Palabras clave: Atención médica fuera de horario; médico; Necesidades y Demanda, Servicios de Salud; solicitud; turistas.

Introduction

In many countries, general practitioners (GP) are responsible for out-of-hours primary care services (OOH). The OOH is a very important service[1], in particular, patients waiting time related to suboptimal use of OOH is a problem and should be reduced[2]. A central determinant that contributes to suboptimal use is patients calling OOH without knowing their address or position.

Visitors from foreign countries relatively often use OOH and in many cases due to language barriers can experience difficulties in the accessibility to their OOH[3]. These difficulties could be aggravated if the GP has to come to the patient's location. In a similar way, tourists can face difficulties, when they fell ill in foreign countries, especially if they do not speak the local language[4]. This difficulty would be worsened if the patient cannot be quickly located because they do not know which is their current address or where they are in the moment of medical need.

In Germany, it is estimated that as many as 10% of all emergency calls do not include info about the position of the patients -i.e. the OOH does not know the position of a central part of their patients[5]. Furthermore, a UK study showed that common reasons for communication difficulties comprise problems related to the missing information to the ambulance service call receiver[6], which also included the actual position of the patient. In the EU considerable time is lost by emergency services during their intervention for approximately 3,5 million calls, due to the fact that the location information provided by the caller is later found to be inaccurate[7].

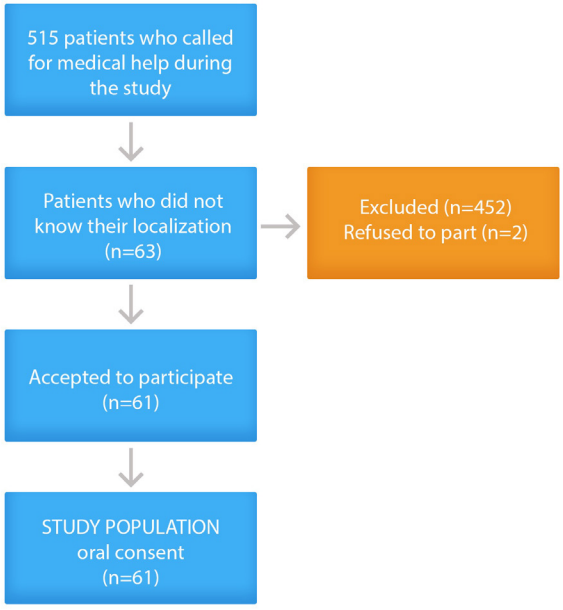
Delays in all kinds of medical care are more common in rural or semi-rural areas[8]. But in case of medical emergencies, reducing the arrival time (AT) of medical care in rural or semi-rural areas play an even more important role. In cardiac arrest, reducing ambulance AT has been shown to increase the survival rate[9] even if the appearance of operational problems can delay more of the 40% of ambulance dispatches[10]. We hypothesize that smartphone technology can help reducing ambulance AT[11]. This is the reason why would be important to measure the effect of geographic information systems (GIS) by monitoring the arrival time of vehicles sent to patients who do not know their address (tourists) and also with simple pathologies, this to avoid risks for patients but obtaining data that could be extrapolated in more acute situations.

Material and methods

The present study was conducted during the summer of 2019 in a private GP clinic in Ibiza to patients (among whom were tourists) who can call for a home medical consultation. In order to be able to start with the study, an ethics committee was formed and accepted the study realization, and it was decided that to accomplish the General Data Protection Regulation (GDPR) Regulation (EU) 2016/679 on the protection of natural persons concerning the processing of personal data[12]; only the age, gender, localization, country of origin and pathology would be used in the study avoiding any way to identifying the patient with the data recorded.

A strict selection of the cases was done, no critically ill patients were selected (chest pain, breathlessness, dizziness, etc) while stable patients over 18 years old (sore throat, cold, otitis, conjunctivitis, etc) were included. Patients who knew their location, who were lodged in a hotel, were Spanish, or patients who did not use the WhatsApp application were also excluded. A total of 515 patients were eligible; if they knew their location, they were excluded (**Figure 1**).

Figure 1: Trial Flow.



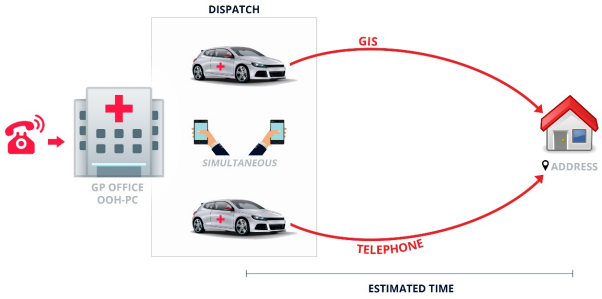
They were then asked to participate and gave oral consent. All included patients were asked to send us their location using GIS and also the directions to arrive at the place where they were. With the information obtained, two vehicles were simultaneously dispatched to the patient: "vehicle A" used the GIS data and "vehicle B" used the directions given by the patient, each vehicle was driven by a different GP, they both had the same working time on the island.

To avoid bias, both of the vehicles were parked in the same garage (one on the side of the other), both of the same brand (Nissan Micra) and date of production (2014). The mileage of each of the vehicles was written down every time before the car was dispatched and time began to be measured after the two GPs (working both

in the same clinic and they were also the drivers for the study) were seated in the cars ready to go, and a helper activated the mobile´s timing at the same time and gave it to both drivers.

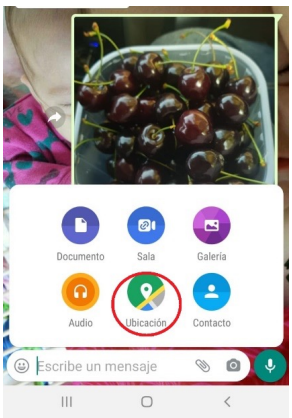
Both of the drivers were instructed on the way of driving (normal, without exceeding speed limits, or in a hurry to save time), as well as, that they had to stop the chronometer when arriving at the address (not when parking or when entering the patients' house) and write it down in a special blanket given (**Figure 2**).

Figure 2: Project process.



The WhatsApp application was selected among many other applications because it is widely used in all of Europe[13]. The app is simple to use and has an end-to-end encryption protocol that prevents any external party from having access to the messages, furthermore, only the location was sent via this application (WhatsApp), no other patient data was sent through this system. The rest of the data were obtained during the consultation with the patient. The only person to have access to the messages is the receiver as only the recipient and the sender have the special key needed to unlock and read the message[14]. Its usage is very easy, clicking over the "paperclip" icon and then selecting "my ubication" (see **figure 3**). The usage of this app is even able to reduce the response time in new communication and its efficiency in its use during the consultation, relaying quick information during clinical communication[15].

Figure 3: How to send your ubication using WhatsApp®.



Statistical analyses

This study was a prospective observational control study using two vehicles. The main outcome was to measure the response time from two different approaches.

The difference between the two groups of vehicles (A and B) was described via descriptive statistics and a graph of mean and confidence intervals. Student´s T for paired data was used for the primary outcome. We used free statistical software R 3.4.0 and WinBUGS 1.4 for the inference.

Results

The average age of all the 515 patients was 30 years old, with a mean of 56,6 years and a mode of 43. A total of 463 patients came from Europe and 52 (10%) came from countries out of the EU (Morocco, South Africa, Argentina, Russia, US, India, Ukraine, Saudi Arabia and Canada). Out of the 63 patients not knowing their location Table 01 shows that 28 patients were women (0,46) and 33 men (0,54), their age varied from 25 years to 78 years old with an age mean of 56,6 (SD: 12,86). The patients who did not know their location did not differ with regard to the home country. Overall, 80,3% came from Europe and everybody spoke English at an intermediate level.

AT range of vehicle A was between 4 and 40 minutes with a mean of 19,98 (SD: 8,1) and the range of vehicle B was between 3 and 49 minutes with a mean of 27,98 (SD: 10,21). AT of vehicle B was 8,02 minutes longer than vehicle A (see table 02).

This 8-minute difference between both of the vehicles and considering the SD of 8 minutes would result in a 95% confidence interval of around 16 minutes. We have to take into consideration that this may be due to long journeys to rural areas, the lack of knowledge of the patients of the area in which they are located or the road to reach their respective homes, and finally the reduced sample size.

Discussion

According to our knowledge, this is the first study to look into the impact of GIS on arrival time in OOH. There are data available in relation to urgent calls in the Ibiza area - average waiting time (061 – IBSalut)[16], with an arrival time of around 9 minutes which is considered adequate; However, the intention of this study is to assess whether it is feasible to reduce the arrival time for patient care (especially tourists with little command of the local language or English) and that it can be extrapolated to other geographical areas.

Our results show a significant reduction in arrival time of GPs in OOH using GIS, with a mean of 8 minutes and that many of the patients who participated were people over 25 years old (mean of 57 years old) resulting interesting that these older patients have also access to the internet and a smartphone but probably are no so trained on its use[17,18].

These results can present a pleasing alternative to the suboptimal use of OOH-GP[2] reducing both the driving time as well as the waiting time of the patient. Can also avoid the misunderstanding of an address due to the lack of language proficiency (tourists and migrants). That is the reason why our study was conducted between May and October for being the season (summer) with the highest influx of tourists in Ibiza, many renting Villas or apartments without knowing the precise address once living there.

Several limitations must be mentioned. Our study had some selection biases at baseline, which may decrease the total population generalization. Only patients who called to our clinic were included (mostly only tourists) also patients without a smartphone or internet access mobile were excluded. Another limitation was that the development of the project took place during the summer period (due to the extra influx of tourists). Patients with an acute problem or emergency were also ruled out and maybe the inclusion of them could show a different result. The use of 61 patients to develop the study could be a not significant number of patients, but we consider it as a pilot to future research. The usage of WhatsApp as GIS could be not the most accurate but it is also the most universal and could serve as a starting point for a more complete assessment (using another application or location system).

We can precise that the use of WhatsApp (or other instant messaging application with the possibility of GIS) could be very useful for medical teams' coordination because it can show actual patients localization letting the medical team arrive as fast as possible with the fastest route available. Moreover, using e-Copernicus data[7] the impact of economic resources savings in the EU could be around 467 000 hours with its equivalent in money provisions.

Table I: Description of patient's characteristics.

	min	mean	max
Age	25 years (youngest)	56,6 years (SD 12,86)	78 years (oldest)
Gender:			
Male	33 (54,1%)		
Female	28 (45,9%)		
Nationality:	Percentages		
United Kingdom	16 (26,2%)		
Germany	7 (11,5%)		
France	6 (9,8%)		
Argentina, Russia, Holland (each)	4 (6,6%) per country: 12 (19,8%)		
Italy, Belgium (each)	3 (4,9%) per country: 6 (9,8%)		
South Africa, Poland, Sweden, Norway (each)	2 (3,3%) per country: 8 (13,2%)		
Ukraine, Morocco, Austria, Wales, United States, Ireland (each)	1 (1,6%) per country: 6 (9,8%)		
Patient complaints			
Nausea	16 (26,2%)		
Cough	14 (23,0%)		
Otitis	7 (11,5%)		
Pharyngitis	7 (11,5%)		
Skin related	7 (11,5%)		
Muscle contracture	3 (4,9%)		
Viremia	3 (4,9%)		
Conjunctivitis	1 (1,6%)		
Vaginitis	1 (1,6%)		
Advice	1 (1,6%)		
Prescriptions	1 (1,6%)		

Table II: Descriptive vehicles and patient characteristics.

	Mean	Coefficient of variation	Percentile 5 (p5)	Percentile 50 (p50)	Percentile 95 (p95)
Patients age	56,6	0,23	37	55	77
Vehicle A (seconds)	19,98	0,41	5	21	30
Vehicle B (seconds)	27,98	0,36	7	28	42
Difference (seconds)	8	0,45	2	8	14

Conclusion

Our results show that it would be interesting to develop a strategy to reduce the time interval between the medical call and the arrival of help. This would contribute to the consequent saving of resources (money and time), as well as, with the greater satisfaction of the patient. In addition, it must be considered that the delays could be dangerous especially to critically ill patients.

Reducing the AT will offer the possibility of fast in-field-treatment, as well as, the prearrival notification of the medical problem to the hospital or clinic which will save more time to prepare, even with the mean arrival time avoiding the triage barrier that personal from the ambulance can sometimes become[19]. Further studies are warranted to survey GIS in the GP out-of-hours service.

Interests conflict

The authors declare no conflict of interest.

References

1. Keizer E, Maassen I, Smits M, Wensing M, Giesen P. Reducing the use of out-of-hours primary care services: A survey among Dutch general practitioners. European Journal of General Practice. 2016 Jul 2;22(3):189–95.

2. Nørøxe KB, Huibers L, Moth G, Vedsted P. Medical appropriateness of adult calls to Danish out-of-hours primary care: A questionnaire-based survey. BMC Family Practice. 2017 Mar 14;18(1):34.

3. Keizer E, Bakker P, Giesen P, Wensing M, Atsma F, Smits M, et al. Migrants' motives and expectations for contacting out-of-hours primary care: a survey study. BMC family practice. 2017 Nov 21;18(1):92.

4. Dick L. American family physician. American Family Physician. 1998 Aug 1;58(2):383.

5. Weinlich M, Kurz P, Blau MB, Walcher F, Piatek S. Significant acceleration of emergency response using smartphone geolocation data and a worldwide emergency call support system. Kou YR, editor. PLOS ONE. 2018 May 23;13(5):e0196336.

6. Higgins J, Wilson S, Bridge P, Cooke MW. Communication difficulties during 999 ambulance calls: Observational study. British Medical Journal. 2001 Oct 6;323(7316):781-2.

7. EENA Operations Document-Caller Location in Support of Emergency Services EENA asbl info@eena.org-www.eena.org is a non-for-profit association 1 EENA Operations Document Caller Location in Support of Emergency Services Title: Caller Location in Support of Emergency Services Version: 2.0 Code: 2.2.2.v2.0.Final Revision. 2014 [cited 2021 Oct 26]; Available from: www.eena.org

8. Takei Y, Inaba H, Yachida T, Enami M, Goto Y, Ohta K. Analysis of reasons for emergency call delays in Japan in relation to location: High incidence of correctable causes and the impact of delays on patient outcomes. Resuscitation. 2010 Nov 1;81(11):1492-8.

9. Pell JP, Sirel JM, Marsden AK, Ford I, Cobbe SM. Effect of reducing ambulance response times on deaths from out of hospital cardiac arrest: cohort study. BMJ (Clinical research ed). 2001 Jun 9;322(7299):1385-8.

10. Spaite DW, Valenzuela TD, Meislin HW, Criss EA, Hinsberg P. Prospective validation of a new model for evaluating emergency medical services systems by in-field observation of specific time intervals in prehospital care. Annals of Emergency Medicine. 1993 Apr 1;22(4):638-45.

11. Jaldell H, Lebnak P, Amornpetchsathaporn A. Time Is Money, but How Much? the Monetary Value of Response Time for Thai Ambulance Emergency Services. Value in Health. 2014 Jul 1;17(5):555-60.

12. EUR-Lex - 02016R0679-20160504 - EN - EUR-Lex [Internet]. [cited 2020 Jun 4]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1532348683434&uri=CELEX:02016R0679-20160504

13. Giordano V, Koch H, Godoy-Santos A, Dias Belangero W, Esteves Santos Pires R, Labronici P. WhatsApp Messenger as an Adjunctive Tool for Telemedicine: An Overview. Interactive Journal of Medical Research. 2017 Jul 21;6(2):e11.

14. Miller R, Beaumont O, McGrath S. Is it now safe to use WhatsApp for clinical messaging? The American Journal of Surgery. 2016 Nov 1;212(5):1032-3.

15. Ganasegeran K, Renganathan P, Rashid A, Al-Dubai SAR. The m-Health revolution: Exploring perceived benefits of WhatsApp use in clinical practice. International Journal of Medical Informatics. 2017 Jan 1;97:145-51.

16. Memoria 2018 RESUMEN GENERAL MEMORIA 2018.

17. Xavier AJ, D'orsi E, De Oliveira CM, Orrell M, Demakakos P, Biddulph JP, et al. English longitudinal study of aging: Can internet/e-mail use reduce cognitive decline? Journals of Gerontology - Series A Biological Sciences and Medical Sciences. 2014;69(9):1117-21.

18. Barbosa Neves B, Fonseca JRS, Amaro F, Pasqualotti A. Social capital and Internet use in an age-comparative perspective with a focus on later life. Lozano S, editor. PLOS ONE. 2018 Feb 26;13(2):e0192119.

19. Richards ME, Hubble MW, Crandall C. Influence of Ambulance Arrival on Emergency Department Time to Be Seen. Prehospital Emergency Care. 2006 Jan 2;10(4):440-6.

eISSN 2255-0569

ORIGINAL

The effect Phenthymol (Thyme, Anethum graveolens, Ajwain and Honey) in the Treatment of Corona Virus Disease (Covid 19)

El efecto Phenthymol (Thyme, Anethum graveolens, Ajwain y Honey) en el tratamiento de la enfermedad por virus corona (Covid 19)

Mahdi Mazinani[1], Samira Sangi[2], Sareh Sangy[1], Hamzeh Safavi Hammami[1], Pegah Farshidfar[2]

1. Department of Traditional medicine clinic, ponak salamatkadeh, Iran university of medical sciences, Tehran, Iran
2. Family Social Group, Applied Science Center, Kahrizak Charity Hospital for the Elderly and the Disabled, Tehran, Iran

Corresponding author
Sareh sangy
Department of Traditional medicine clinic, ponak salamatkadeh,
Iran university of medical sciences, Tehran, Iran
E-mail: sareh.sangy@gmail.com

Received: 11 - X - 2021
Accepted: 13 - XII - 2021

doi: 10.3306/AJHS.2022.37.01.91

Abstract

Introduction: Coronavirus is one of the main pathogens and since common coronary therapies such as hydroxychloroquine are often symptomatic, the use of traditional medicine herbs is one of the ways to obtain new drugs. The aim of this study was to evaluate the effect of Thyme, Anethum graveolens, Ajwain and Honey in the treatment of corona virus disease (Covid 19)

Methods: Double-blind randomized clinical trial, with a control group with a sample size of 60 people in patients with a diagnosis of Quid-19 referred to the Tehran Punak Health Center from the beginning of January 2016, patients in the placebo group received treatment in addition to standard treatment (5 g every 6 hours). The results were assessed using SPSS software.

Findings: There was no significant difference in the baseline data of sex, age, height, weight, past medical history, initial symptoms, disease diagnosis, and medication between the patients diagnosed with and suspected to have COVID-19 among the three treatment groups (P>0.05). Fever, diarrhea, shortness of breath and body aches and fatigue in people who used the herbal composition (Thyme, Anethum graveolens, Ajwain and Honey) had a significant reduction on 14th day.

Conclusion: Since the nature of the herbal composition used is hot and dry, is combined with honey and it can be effective in reducing the cold of cold organs. Also, Thyme, Anethum graveolens, Ajwain and honey have antioxidant and anti-inflammatory, analgesic and effective effects. They are used to treat infections. It is evident in patients with coronavirus because of the high levels of white blood cells and chemokines.

Keywords: Thyme, anethum graveolens, ajwain, honey, covid19.

Resumen

Introducción: El coronavirus es uno de los principales patógenos y dado que las terapias coronarias comunes, como la hidroxicloroquina, a menudo son sintomáticas, el uso de hierbas medicinales tradicionales es una de las formas de obtener nuevos medicamentos. El objetivo de este estudio fue evaluar el efecto de Thyme, Anethum graveolens, Ajwain y Honey en el tratamiento de la enfermedad por coronavirus (Covid 19)

Métodos: Ensayo clínico aleatorizado doble ciego, con un grupo control con un tamaño de muestra de 60 personas en pacientes con diagnóstico de Quid-19 remitidos al Centro de Salud de Teherán Punak desde principios de enero de 2016, los pacientes del grupo placebo recibieron tratamiento además del tratamiento estándar (5 g cada 6 horas). Los resultados se evaluaron mediante el software SPSS.

Hallazgos: No hubo diferencias significativas en los datos iniciales de sexo, edad, altura, peso, historial médico anterior, síntomas iniciales, diagnóstico de la enfermedad y medicación entre los pacientes diagnosticados y con sospecha de tener COVID-19 entre los tres grupos de tratamiento (P> 0,05). La fiebre, la diarrea, la dificultad para respirar y los dolores corporales y la fatiga en las personas que usaron la composición a base de hierbas (tomillo, Anethum graveolens, Ajwain y miel) tuvieron una reducción significativa el día 14.

Conclusión: Dado que la naturaleza de la composición herbal utilizada es caliente y seca, se combina con miel y puede ser eficaz para reducir el frío de los órganos fríos. Además, el tomillo, el Anethum graveolens, el ajwain y la miel tienen efectos antioxidantes y antiinflamatorios, analgésicos y eficaces. Se utilizan para tratar infecciones. Es evidente en pacientes con coronavirus debido a los altos niveles de glóbulos blancos y quimiocinas.

Palabras clave: Tomillo, anethum graveolens, ajwain, miel, covid19.

Introduction

Corona is a single-stranded RNA virus found in other animals including pigs in 2014 which has caused diarrhea, dehydration and even death in animals. Subsequently, the latest and most recent coronavirus appeared on January 30 in Wuhan, China, which the World Health Organization called Covid 19 (Cronavirus 2019). The Covid virus can be transmitted from animal to human and from human to human through mucous secretions (sneezing and coughing) or physical contact. Common symptoms of this virus are cough, sore throat, fever and chills, and sometimes gastrointestinal symptoms and loss of sense of smell and taste, diarrhea and acute respiratory symptoms. In addition, coronaviruses also cause shingles infection[1]. Common therapies, including hydroxychloroquine, chloroquine, and amiodarone, are often used to treat symptoms. On the other hand, diseases that have occurred throughout history have much in common (such as cholera), which reminds people of their experiences so that they do not fall prey to the repetition of history.

Cholera has killed humans for many years about a century while fighting and controlling cholera with the simple principles of which society was unaware at the time. The weather is found. It is caused by Vibrio Cholera, which is the worst epidemic[2]. The disease has become a pandemic over and over again in the past, and it took years for humans to control cholera. After cholera, human life changed dramatically[3]. This could be the starting point for changing the eating behaviors of East Asians and even Be the people of the world[4&5]. The outbreak of this disease caused a lot of research in different countries. In this regard, medicinal plants have also been considered by researchers.

Using traditional medicine herbs is one of the ways to get new medicines. But systematic search for the active ingredients of these plants on all diseases is very long. Therefore, relying on indigenous teachings is one of the most accepted strategies in the world in the discovery, application and research of medicinal plants. Traditional Iranian medicine is one of the ancient foundations of medicine and contains valuable information in the use of plants in treatment. Among these medicinal plants, we can mention Thyme, Anethum graveolens, Ajwain and honey.

Thyme

Thyme belongs to the Labiatae family and is widely distributed in Iran, Afghanistan and Pakistan. Thyme is useful and invigorating for strengthening the nerves, treating depression, fatigue and insomnia. This plant has antimicrobial, antibacterial, antifungal and anti-parasitic properties and has anti-diarrheal properties. Also, the drug is used in traditional medicine as a mucus in bronchitis and other diseases of the respiratory system is used and in terms of scientific anti-inflammatory properties, antioxidant, analgesic, anti-rheumatic, anti-worm, anti-oxidant, anti-spasmodic properties antidiarrheal and Anticonvulsants[6]. On the other hand, thymol, which is the active ingredient of thyme, due to its antiseptic effect can appear in intestinal diseases or its disinfection in spontaneous poisoning due to intestinal infection, dysentery and cholera with a beneficial effect[7].

Ammi Trachyspermum (Ajwain)

The scientific name of this plant is Ammi Trachyspermum from the genus Parsley (Umbelliferae). It is an herbaceous, annual, hairless plant with a height of 30 to 90 cm that goes by car in the eastern regions of India, Iran and Egypt. They have been used in traditional Iranian medicine for thousands of years. The fruits are small, oval and yellow in color and have a smell similar to the smell of thymol which is the medicinal part of this plant. Antiemetic, expectorant and topically used in the treatment of rheumatic pain[8]. Broncho dialysis and analgesic effects for copticum C was shown. Therapeutic effects of this plant in gastrointestinal disorders such as reflux, cough, abdominal tumors, abdominal pain and bloating and Helicobacter pylori have been seen and also has a therapeutic effect on skin, neurological and urinary diseases of the genitals, diuretics, anti-flatulence and anti-worm has been proven[9&10].

It is also an invigorating, tonic, stimulant and windbreaker[11]. Ammi Trachyspermum also has antimicrobial activity on standard strains of infection and food poisoning in vitro. It is because of components such as Thymol, Cymene, Pinene-ῑ, γ-Trepinene and Sabinene[11]. Pandi and etal have shown effect of Antibacterial of Ammi Trachyspermum extract on bacteria such as Streptococcus Staphylococcus 'haemolyticus' Corynebacterium diphtheria 'aureus Escherichia, Proteus vulgaris 'Klebsiella coli[12].

Anethum graveolens

It is a Mediterranean plant that grows as a vegetable in all parts of the world. Anethum graveolens has long been used as a medicinal plant to treat headaches, vascular diseases. D-Caron and D-Flandron are the most important chemical compounds in the vegetative body and Karun and Limonen are the most important chemical compounds in the seeds of this plant. Karun and limonene have analgesic, anti-inflammatory and antioxidant properties that stabilize liver cell membranes and reduce the release of enzymes into the blood. Anethum graveolens seed extract has a protective effect on gastric mucosa due to its flavonoid compounds. Anethum graveolens essence also has an antimicrobial

effect which is due to the presence of Karun substance. This plant increases breast milk and the resulting milk has anti-colic properties in infants. It is not recommended for hot-tempered people and pregnant women. Seed extract has a protective effect on gastric mucosa due to its flavonoid compounds. Anethum graveolens essence also has an antimicrobial effect which is due to the presence of Karun substance. This plant increases breast milk and the resulting milk has anti-colic properties in infants. It is not recommended for hot-tempered people and pregnant women[13].

Honey

Honey is the main and most widespread product of bees which is prepared from the digestive processing of nectar flowered and stored in honeycomb cells. In general, honey is marketed because it is nutritious. In ancient times it was used as a topical treatment, while in recent years it has been introduced as an adjunct and clinical medicine[14].

Due to pollen grains and ascorbic acid, Vitamin B is present in small amounts in honey[15]. On the other hand, honey has anti-inflammatory activity (flavonoid content, etc.) inhibits the release of pro-inflammatory agents and has activity. It is an antioxidant that phenols are the most important antioxidant elements of honey and the composition of phenols is very different based on plant origin. Honey is expected to show a wide range of antioxidant power[16].

Laboratory evaluations also show that a wide range of pathogenic microorganisms effective in wound infection are inhibited by honey[17]. Causes of antibacterial activity of honey are: Its weight is water. 2. Acidity: The pH of honey varies between 3.2 to 4.5 which is a deterrent to many animal pathogens. 3. Hydrogen peroxide: An enzyme called glucose oxidase enters the nectar from the pharyngeal glands of bees, which by acting on glucose leads to the production of glucuronic acid and hydrogen peroxide[18].

One of the important reasons for selecting these plants in this study is their frequency due to their naiveness and easy access to these plant resources and the fact that no study has been done on the composition of these plants to improve coronary symptoms[19]. Their medicinal properties are mentioned Jorjani medical book.

Methods

Double-blind randomized clinical trial with a control group with a sample size of 60 patients in patients with a diagnosis of Quid-19 referred to the Tehran Punak Health Center from the beginning of January 2016 were assessed. Witnesses were divided. To prepare the target drug, 500 g of thyme powder with 500 g of Ajwain powder, 500 g of Anethum graveolens powder and 4.5 kg of honey were combined and the ingredients were carefully mixed and gently stirred to create a uniform composition and the product The final is an oral concoction that was stored in suitable 150 g cans and packaged as medicine. To prepare the placebo, 3000 grams of starch powder with 3000 grams of sugar syrup were mixed well and with natural and authorized color, it was completely similar to the main medicine and then it was packed in 150-gram packages. In addition to standard treatment, patients in the case group received 5 g of the target drug every 6 hours, and the control group received standard treatments with placebo (5 g every 6 hours). The diagnostic test was evaluated on the first and last day of the study, and the following symptoms were evaluated: fever, diarrhea, nausea, body aches, fatigue, loss of appetite, shortness of breath, cough, ESR, CRP leukopenia, respiratory rate, CT Chest scan. The results were assessed using SPSS software.

Findings

There was no significant difference in the baseline data of sex, age, height, weight, past medical history, initial symptoms, disease diagnosis, and medication between the patients diagnosed with and suspected to have COVID-19 among two groups ($P > 0.05$).

The following were reported by examining the clinical symptoms in patients: fever ($p < 0.292$), diarrhea ($p < 0.035$), nausea ($p < 0.592$), body aches ($p < 0.284$), fatigue ($p < 0.118$), loss of appetite ($p < 0.754$), shortness of breath ($p < 0.037$), cough ($p < 0.602$), high ESR ($p < 0.787$), CRP positive ($p < 0.069$), leukopenia ($p < 0.774$), number of breaths per minute ($p < 0.292$) , Abnormal CT ($p < 0.598$).

Conclusion

In conclusion, the effect of Thyme, Anethum graveolens, Ajwain and Honey in the treatment of coronavirus (Covid 19) referred to Punak Health Center in Tehran has been investigated. Fever, diarrhea, shortness of breath and body aches and fatigue in people who used the herbal composition (Thyme, Anethum graveolens, Ajwain and Honey) had a significant reduction on day 14. Also, from the perspective of traditional medicine, people in old age (from the age of 60 to the end of life) when the main heat and humidity in this period has reached its minimum due to analysis during the previous period of life (2) their temperament is colder and due to poor digestion, Abnormal and unnaturally deadly moisture is produced

between the body parts of this group of people (3) and the temperament in one of the four age periods of those who have equal warmth and cold in them and have high humidity, i.e. hot and cold temperament, moisture prevails, such people are often early. They also become infected[20]. Such people are more likely to develop infectious fevers in the first place[21]. Statistics also show that the incidence of coronary heart disease is higher in people with a cold temper, so that in Italy, until May 21, in the age range of 60-89 years, men died 63.9% of the total cases. Since the nature of the herbal composition used is hot and dry, combined with honey can be effective in reducing the cold of cold organs. On the other hand, the results of a study conducted by Shahabi et al. Show that the tendency of cytokine pattern in cold temperament is less towards Th2 than in hot temperament, which is consistent with the warm and dry nature of the studied plant composition .[22]

Clinical signs	Group	Day 14	P-value
Fever	Placebo	14 16	0.292
	Medicine	10 20	
Diarrhea	Placebo	16 14	0.035
	Medicine	8 22	
Nausea	Placebo	18 12	0.592
	Medicine	20 10	
Body pain	Placebo	13 17	0.284
	Medicine	9 21	
Fatigue	Placebo	16 14	0.118
	Medicine	10 20	
Loss of appetite	Placebo	24 6	0.754
	Medicine	23 7	
Shortness of breath	Placebo	17 13	0.037
	Medicine	9 21	
Cough	Placebo	18 12	0.602
	Medicine	16 14	
ESR high	Placebo	19 11	0.787
	Medicine	20 10	
CRP positive	Placebo	17 13	0.069
	Medicine	10 20	
Leukopenia	Placebo	8 22	0.774
	Medicine	9 21	
Number of breaths per minute	Placebo	14 16	0.292
	Medicine	10 20	
CT abnormal	Placebo	19 11	0.598
	Medicine	17 13	

On the other hand, Thyme, Anethum graveolens, Ajwain and Honey have antioxidant and anti-inflammatory effects, analgesics and are effective in treating infections[23]. Involvement of cells is due to the activity of the innate immune system and is acquired (the virus is evident in patients with coronavirus, so the reduction in fever and diarrhea in patients undergoing treatment can probably be attributed to this. On the other hand, in a study, a significant inhibitory effect of thyme on herpes simplex virus type one (HSV-1) was reported (60) which is consistent with the present study. Ajwain is also known as thymol (42-41%), gamma-terpene and paracetamol for the treatment of infections, bloating, headache and wound healing fungal infections, bacterial infections and as an antihistamine[24]. Two polyphenolic compounds called Rosmarinus and caffeic acid have been identified as potent antioxidants for Ajwain[25]. H et al. demonstrated the antibacterial effect of Ajwain essence on Staphylococcus aureus, Escherichia coli, Streptococcus hemovaliticus, Corynebacterium diphtheria, Proteus vulgaris and Klebsiella by agar and halo propagation. The results of in vitro studies showed that the extract extracted from the medicinal plant Xenia has antimicrobial activity against Staphylococcus aureus, Bacillus cereus and Escherichia coli which can be used as a suitable alternative in the production of new herbal medicines with minimal side effects due to non-chemical and to be used against the above bacteria[26].

The analgesic, anti-inflammatory, antimicrobial and antioxidant properties that stabilize liver cell membranes and reduce the release of enzymes into the blood have also been attributed to the most important chemical compounds in Anethum graveolens seeds, Karun and Limonin. On the other hand, phenols in honey which are the most important antioxidant elements of honey (flavonoid content, etc.) play a role in anti-inflammatory activity and inhibit the release of pro-inflammatory agents. On the other hand, laboratory evaluations show that a wide range of Pathogenic microorganisms are effective in inhibiting wound infection by honey[27]. It varies from 3.5 to 4.5 which is inhibitory for many animal pathogens.

On the other hand, thymol in women due to its antiseptic effect, can appear in intestinal diseases or its disinfection in spontaneous poisoning due to intestinal infection, dysentery and cholera with a beneficial effect. Cholera is consistent with this issue. Anethum graveolens seed extract also has a protective effect on the gastric mucosa due to its flavonoid compounds which may have been effective in improving the diarrhea of a person with coronary heart disease. In one study, when thyme oil was fed to a rabbit or injected into its muscles, it lowered blood pressure in the arteries while accelerating regular heart contraction, and at higher doses increased respiration rate. When 5% salt solution was injected into the cat's veins as an emulsion, thyme oil increased respiration volume and decreased blood pressure[28].

In the present study, improvement of dyspnea was reported in patients consuming the plant composition which can be attributed to the effect of thyme on bronchitis, pertussis and inflammation of the mucous membrane secreted from the upper respiratory tract and can be attributed to the presence of thymol in the plant. In 2012, Taherian et al. stated that the effect of hanging pain relief is due to the presence of phenolic monoterpenes of thymol and carvacrol in the plant.

The thyme includes carvacrol, tannins, Flonoeid, saponins and bitter substances is also an integral part of these flavonoids inhibitor of cyclooxygenase inhibiting the production of prostaglandins in the body and causing pain and mediators in the body[29]. Ajwain also contains several compounds such as monoterpenes, tranoidohalophalanoids which phalloidins inhibit phospholipase, lipoxins and cyclooxygenase which directly affect the synthesis of prostaglandins and have analgesic effects. The reduction of coronary muscle pain due to corona can be attributed to these compounds. Anethum graveolens is also an enhancer of breast milk due to (its chemical composition of Karun and D-Flanderon is a vegetative body) and thyme is appetizing. It is present in small amounts in honey which may be due to the reduction of fatigue in patients consuming the plant composition. Todays, due to the effects of chemical abuse and antibiotic resistance due to improper use of antibiotics, replacement of these substances with natural substances such as essences and plant extracts including plants studied in this study to control and prevent Corona is recommended.

Interests conflict

The authors declare no conflict of interest.

References

1. Ketabchi S, Papari Moghadamfard M. [Medicinal Plants Effective in the Prevention and Control of Coronaviruses (Persian)]. Complementary Medicine Journal. 2021; 10(4):296-307. https://doi.org/10.32598/cmja.10.4.1014.1

2. Lu H. Drug treatment options for the 2019-new coronavirus (2019-nCoV). Biosci Trends. 2020; 14(1):69-71. [DOI:10.5582/bst.2020.01020] [PMID]

3. Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal. 2020 March. [DOI: 10.1016/j.jpha.2020.03.001] [PMID]

4. Gholampour A, Ghorbanzadeh H, Jafari Nejad M. Application of NaCl in Traditional Medicine Sources, First International Congress of Complementary and Alternative Medicine, 2015, 189

5. Biranvand A, Salari Lak Sh, Nowruzzadeh J, Azizi F, Rostami R. Prevalence of iodine deficiency in pregnant women covered by health centers in Urmia, 2010, Volume 5, Special Issue of the 6th Iranian Epidemiological Congress; page 49

6. Nickbakhsh S, Ho A, Marques DFP, McMenamin J, Gunson RN, Murcia PR. Epidemiology of seasonal coronaviruses: Establishing the context for the emergence of coronavirus disease 2019. J Infect Dis. 2020; jiaa185. [DOI:10.1093/infdis/jiaa185]

7. Alizadeh Behbahani, B. Shahidi, F Evaluation of the antimicrobial effect of Carum copticumessential oil on some standard microbial strains, indices of infection and food poisoning: an in vitro study Iranian Journal of Food Science and Technology, JFST No. 111, Vol. 18, May 2021

8. Mohammadi manesh Z, Heidarieh N, Moghadami rad M. "Effect of Hydroalcholic Extract Of Trachyspermum Copticum on Anxiety in Male Rats". Applied Biology, 7, 28, 2018, 21-29.

9. Samini M, Dehpour AR, Babazadeh Khameneh E. Study of the effect of melatonin on water immersion stress-induced gastric lesions. Tehran, J Facul Med 2003; 60(3): 178-181. [In Persian]

10. Komeili GH, Sargazi M, Soluki S, Maaleki SH, Saeidy-Neek F. Effect of Hydroalcholic Extract of Carum Copticum Seed on the Treatment of Peptic Ulcer Induced by Ibuprofen in Rats, Ofogh-e-Danesh. GMUHS Journal. 2012; Vol. 18, No.2

11. Amiri A, Jomehpour N. Evaluation the Effect of Anti-bacterial of Ferula assa-foetida L, Carum copticum, Mentha piperita L Hydroalcoholic Extract on Standard Sensitive and MethicillinResistant Staphylococcus aureus, Escherichia coli O157H7 and Salmonella typhimurium, Scientific Journal of Ilam University of Medical Sciences,

12. Haghiroalsadat BF, Vahidi AR, Azimzadeh M, Kalantar SM, Bernard F, Hokmollahi F. Chemical Assessment of Active Ingredients and Anti-oxidant Effects of Trachyspermum Copticum's Seeds harvested In Yazd Province. J Rafsanjan Univ Med Scie 2012; 11(3): 197-206. [Farsi

13. Zarshenas MM, Moein M, Samani SM, Petramfar PJJonr. An overview on ajwain (Trachyspermum ammi) pharmacological effects; modern and traditional. 2013;14(1):98-105

14. Jafari-Sales A, Rasi-Bonab F, Sayyahi J. The Survey on Antimicrobial Effects of Methanolic Extract of Carum Copticum L. on Staphylococcus Aureus, Bacillus Cereus, Escherichia Coli and Pseudomonas Aeruginosa in Laboratory Conditions, Paramedical Sciences and Military Health, Volume 13, Number 4, Winter 2019

15. Leung AY, Foster S. Encyclopedia of common natural ingredients: used in food, drugs, and cosmetics. A Wiley Interscience Publication - John Wiley & Sons, Inc. 1996; p. 649.

16. Momeni T, Shahrokhi N. Plant essential oils and their therapeutic effects. University of Tehran Press. 1370

17. Nadiad HA, Makizadeh Tafti M. Review of Thyme leaf (L. vulgaris Thymus), -64 Quarterly Journal of Medicinal Plants, No. 7, Summer 2003.

18. Najibzade T, Yadegari MH, Naghdibadi H. [Evaluation antifungal effects of essential oils Satureja khuzestanica and Myrtus communis]. MSc Thesis Tarbiat Modares Uni Tehran. 2009

19. Arbabikalati F, Shirzai M, Pourzamani M, Dabiri S. [The effect of plant extracts of thyme cloves and cinnamon with Nystatin on the inhibition of Candida albicans in vitro] . J Research Dental Sci 2011;8:175-9. (Persian)

20. Akbari S. [Antifungal activity of Thymus valgaris L and Origanum vulgare L Against fluconazole resistant and susceptible Candida albicans isolates]. J Med Plants 2007; 6: 53-62. (Persian)

21. Zia MA, Bayat M, Khalkhali H, Saffari S. [Effect of Thymus vulgaris, Myrtus communis and nystatin on Candida albicans.] J Gorgan Uni Med Sci2014; 15: 59-65. (Persian)

22.Haghighi F, Roudbar Mohammadi SH, Soleimani N, Satarie M. [Valuate the antifungal activity of essential oils of thyme parsley cumin black Wazire on Candida albicans compared with fluconazole]. J Med Sci Modares 2011; 14:29-35. (Persian)

23. Dadashpoor M, Rasouli I , Sorourizanjanian R, Sefidkon F, Taghizadeh M. [Antimicrobial activity cytotoxicity free radical scavenging of nitric oxide and thyme oil daenensis]. J Med Sci Modares 2011;14:37-47. (Persian)

24. Mohammadi S, Ebrahimi H, Sayehmiri K. Comparison of the Effect of Garlic and Thyme Plants on Candida albicans: A Systematic Review and Meta-analysis, Scientific Journal of Ilam University of Medical Sciences

25. Keramati K, Asghari baghkheirati A, Abdollahi M, Rezaei F. [The Interferential Effect of Extracts of Thymus vulgaris and Matricaria Chamomilla on visceral pain in mice: Experimental study (Persian). J Anesth Pain 2017;7(4):84-91.

26. Afsharpour F, Hashemipour S, Khadem-Haghighian H, Koush-an Y. Effects of Iranian propolis on glucose metabolic changes, inflammatory factors, liver enzymes levels in type 2 diabetic patients: A randomized, double-blind, placebo-controlled, clinical trial. J Nut Sci Diet. 2017; 3(2):1-6

27. Hesami S, Khadem Haghighian H. The Therapeutic Effects of Bioactive Compounds in Honeybee Products. The Journal of Qazvin University of Medical Sciences. 2019; 22(6):190-203. https://doi.org/10.32598/JQUMS.22.6.

28. Seyedeh Faezeh Miryousefiata, Fatemeh Alsadat Miryousefi Ata. The effect of Familact probiotic supplement in patients with diabetes (Evaluation of Blood Glucose Parameters, Lipid Profile). ACADEMIC JOURNAL OF HEALTH SCIENCES. 2021; 36 (3): 52-63. doi: 10.3306/AJHS.2021.36.03.52 www.medicinabalear.org

29. Sangy S, Miryousefiata F, Miryousefiata F.Study of Thymus and T-cell Development and Tumor Immunology Budapest International Research in Exact Sciences. 2021; 3,(3) :162-170 DOI: https://doi.org/10.33258/birex.v3i3.2081

eISSN 2255-0569

ORIGINAL

Caries experience and caries risk of pre-school children

Experiencia de caries y riesgo de caries de los niños en edad preescolar

Maria Lourdes E. Cantor, Siavash Samadi Khasraghi, Zahra Shirazi

1. School of Dentistry, University of Baguio, Baguio, Philippine.

Corresponding author
Maria Lourdes E. Cantor
School of Dentistry, University of Baguio, Baguio, Philippine
E-mail: marialourdescantor@yahoo.com

Received: 14 - X - 2021
Accepted: 16 - XII - 2021

doi: 10.3306/AJHS.2022.37.01.97

Abstract

Introduction: Oral health is an important aspect of a child's overall health. Children who have high levels of caries experience in their primary teeth are more prone to developing caries in their permanent teeth. Many surveys around the world show moderate to high caries experience among preschool children. One main factor in caries development is sugar consumption. Although some previous studies have shown low correlation between caries experience and consumption of sweets, most studies have shown that there is a significant correlation between these variables.
Objectives: This study aimed to determine the level of caries experience and level of caries risk from sugar consumption among preschool children. The relationship between caries experience and caries risk was also determined.
Methods: The "dmf" index and the 24 hour diet recall for scoring sweets were used in gathering data.
Results: A very high percentage of the children examined (96.77%) had dental caries. Only two children (3.23 %) were caries free. The overall mean dmf score of the children is 8.98 which means that on the average, 45% or each child's primary teeth had caries experience. This is further interpreted as moderate caries experience among the preschool children examined. The mean sweet score of the children is 6.43 which is interpreted as moderate caries risk. Based on the responses in the 24 hour recall, most parents give or allow their children to eat snack foods with refined sugar.
Conclusions: There is a moderate positive correlation between caries experience and caries risk from sugar intake. At an early age, these children already experienced dental caries. If their teeth with dental caries are left untreated, this could lead to the early loss of their primary teeth. The children frequently consume sweets within a day. This practice contributes to the risk of caries development among the children. Children with a higher risk from sugar or sweet intake have higher occurrence of dental caries.

Keywords: Dental caries, dental caries susceptibility, caries check.

Resumen

Introducción: La salud bucodental es un aspecto importante de la salud general del niño. Los niños que tienen altos niveles de experiencia de caries en sus dientes primarios son más propensos a desarrollar caries en sus dientes permanentes. Muchos estudios realizados en todo el mundo muestran una experiencia de caries de moderada a alta entre los niños en edad preescolar. Un factor principal en el desarrollo de la caries es el consumo de azúcar. Aunque algunos estudios anteriores han mostrado una baja correlación entre la experiencia de caries y el consumo de dulces, la mayoría de los estudios han demostrado que existe una correlación significativa entre estas variables.
Objetivos: Este estudio tenía como objetivo determinar el nivel de experiencia de caries y el nivel de riesgo de caries por el consumo de azúcar entre los niños preescolares. También se determinó la relación entre la experiencia de caries y el riesgo de caries.
Metodología: Para la recogida de datos se utilizó el índice "dmf" y el recuerdo de la dieta de 24 horas para puntuar los dulces.
Resultados: Un porcentaje muy elevado de los niños examinados (96,77%) tenía caries dental. Sólo dos niños (3,23%) no tenían caries. La puntuación media global del dmf de los niños es de 8,98, lo que significa que, por término medio, el 45% de los dientes primarios de cada niño tenía experiencia de caries. Esto se interpreta como una experiencia de caries moderada entre los niños preescolares examinados. La puntuación media de dulzura de los niños es de 6,43, lo que se interpreta como un riesgo moderado de caries. En base a las respuestas en el recuerdo de 24 horas, la mayoría de los padres dan o permiten a sus hijos comer bocadillos con azúcar refinado.
Conclusiones: Existe una correlación positiva moderada entre la experiencia de caries y el riesgo de caries por la ingesta de azúcar. A una edad temprana, estos niños ya han experimentado la caries dental. Si sus dientes con caries no se tratan, esto podría conducir a la pérdida temprana de sus dientes primarios. Los niños consumen frecuentemente dulces en el día. Esta práctica contribuye al riesgo de desarrollo de caries entre los niños. Los niños con mayor riesgo por la ingesta de azúcar o dulces tienen mayor incidencia de caries dental.

Palabras clave: Caries dental, susceptibilidad caries dental, revision de caries.

Introduction

Based on previous surveys, dental caries is still the most prevalent dental disease. In a global study, it was found that among the oral diseases that affected at least 3.58 billion people around the world, caries of the permanent teeth is the most prevalent. Also, 486 million children have carious primary teeth[1]. In the 2015 national dental epidemiology survey in England, 25% of 5 year old children had experienced tooth decay, having an average of 3 to 4 teeth affected[2]. In a study among preschool children of Western Maharashtra, a high prevalence of caries was noted[3]. Another study also found high caries experience among preschool children[4]. In a province in the Philippines, the children in the selected day care centers manifest severe early childhood caries[5]. Children who have toothache or who need treatment may have to be absent from school and parents may also have to take time off work to take their children to a dentist or to hospital. Oral health is therefore an important aspect of a child's overall health status and of their school readiness. Children who have high levels of disease in primary teeth have an increased risk of disease in their permanent teeth. If treated, these teeth will require long term maintenance throughout life[2].

Oral health is an important part of overall health. Early childhood caries is a health problem throughout the population that poses a significant health burden in specific at-risk communities[6]. Dental caries is a multifactorial disease. One factor that plays a big role in caries development is sugar intake. Sugars in food and drinks play a major role in the development of dental caries. Bacteria within the plaque use the sugar as energy and release acid as a waste product, which gradually dissolves the enamel in the teeth[7]. In a previous study, a significant finding showed that children who had sugar at least three times a day had higher Decayed, Missing, and Filled Teeth (DMFT) scores than those did not[8]. Dietary free sugars are the most important risk factor for dental caries[9]. The impact of fruit, vegetables, and grains on mechanical stimulation of salivary flow helps mitigate the potential risk of the sugars. Sugars other than these intrinsic natural sugars are classified by WHO as free sugars which include all monosaccharides and disaccharides added to foods by manufacturer, cook, or consumer plus those sugars naturally present in honey, syrups, and fruit juices and concentrates. It is the intake of free sugars that should be restricted for health reasons[10].

This study aimed to determine the relationship between caries experience and caries risk from sugar consumption of preschool children. The results of this study can be utilized as basis for planning caries control and oral health education programs for preschool children.

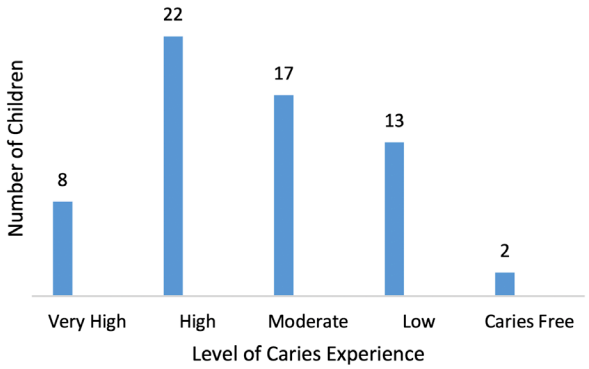
Methodology

A total of 62 preschool children were included in the study. The study was conducted in two daycare centers in two communities in the Philippines during the first quarter of 2018. The authorities in the community approved the conduct of the study. Informed consent was obtained from the parents of the children. Coding was used to protect the identity of the children and their parents. Only the parents who volunteered and the children who willingly underwent examination of their teeth were included. The decayed, missing and filled teeth (dmf) index for primary teeth was used to determine the level of caries experience. The 24-hour recall questionnaire which was answered by the parent was used to determine the level of caries risk from sugar consumption. Mean and percentage was used to describe the caries experience and caries risk while the Pearson product moment correlation was used to determine the strength of the relationship between the two variables in the study.

Results and discussion

The level of caries experience of the preschool children is presented in **figure 1**

Figure 1: Caries Experience of the Preschool Children.

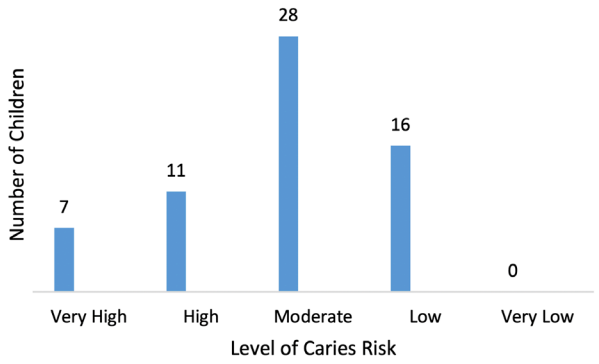


A very high percentage of the children examined (96.77%) had dental caries. Only two children (3.23 %) were caries free. The ranking of the levels is as follows: 35.48% of the children had high caries experience; 27.42% had moderate caries experience; 20.97% had low caries experience; 12.90% had very high caries experience; and 3.23% had no caries experience. The overall mean dmf score of the children is 8.98 which means that on the average, 45% or each child's primary teeth had caries experience. This is further interpreted as moderate overall caries experience among the preschool children examined. This implies that at an early age, these children already experienced dental caries. If their teeth with dental caries are left untreated, this could lead to the early loss of their primary teeth. The caries experience of the children in this study is higher compared to previous studies: 59.3% in Kerala[11]; 47.29% in Eastern India[12]; and 25% of 5-year olds in England[2]. On the other hand, the result of this study is not far from the 87.5% in Western Maharashtra[3]. In a previous study in the Philippines, 94.13% of the children had dental caries[5],

which is very close to the finding of this study which is 96.77%. This proves that there is really a high prevalence of dental caries among preschool children in the country. The mean dmf score of 8.98 in this study is just a little higher than the mean dmf of 8.86 in the study of Atienza, Austria, and Navarro[5].

The level of caries risk of the preschool children is presented in **figure 2**.

Figure 2: Caries Risk of the Preschool Children.



The mean sweet score of the children is 6.43 which is interpreted as moderate caries risk. This means that the children frequently consume sweets within a day. This practice contributes to the risk of caries development among the children. Based on the responses in the 24 hour recall, most parents give or allow their children to eat snack foods with refined sugar. In relation to the findings of this study, Iftikhar, Zafar, and Kalar also found that chocolates as snacks were consumed by 60% of children in their study[13]. In another study, about 85% of children consumed some type of sweetened beverage, dessert, sweet, or salty snack in a day[14].

The Pearson r of 0.44 indicates moderate positive correlation between caries experience and caries risk from sugar intake. Children with a higher risk from sugar or sweet intake have higher occurrence of dental caries. The result of this study is similar with the finding that there was a strong and consistent relation of the snacking habits with the prevalence of dental caries among the preschool children of Karad city[3]. In the study of Viswanath and Sabu, there was a direct association between the frequency of sugar consumption and dental caries[15]. The finding of this study can be further supported by the finding in a previous study that children who had sugar at least three times a day had higher DMFT scores than those did not and was found to be significant[8].

Conclusions

At an early age, these children already experienced dental caries. If their teeth with dental caries are left untreated, this could lead to the early loss of their primary teeth. The children frequently consume sweets within a day. This practice contributes to the risk of caries development among the children. Children with a higher risk from sugar or sweet intake have higher occurrence of dental caries.

Interests conflict

The authors declare no conflict of interest.

References

1. GBD Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1211-59.

2. Public Health England. Health matters: child dental health 2017. Available at:https://www.gov.uk.

3. Jain R, Patil S, Shivakumar KM, Srinivasan SR. Sociodemographic and behavioral factors associated with early childhood caries among preschool children of Western Maharashtra. Indian J Dent Res 2018;29:568-74.

4. Hegde,V. Nanukuttan A. Dental caries experience among preschool children from Anganwadi centers of Mangalore Taluk: A cross-sectional study. J Indian Assoc Public Health Dent 2018;16:133-6.

5. Atienza A, Austria DA, Navarro HM. Prevalence of common oral diseases among children aged 3-5 years in San Juan, Batangas province, Philippines. Philippine Journal of Health Research and Development (PJHRD) 2015;19(2).

6. American Dental Association Science Institute. Prevention and control of early childhood caries 2018. Available at:https://www.ada.org.

7. NHS Choices. "Tooth Decay," 2014. Available at:http://www.nhs.uk/conditions/dental-decay/Pages/Introduction.aspx>.

8. Wilson B, Mallikarjuna S, Narsimha V, Muddaiah S, Suresh L. Dental Caries and Co-Relation with Sugar Intake in 12-Year-Old School Children Coorg, India. Journal of Public Health 2018; 2(2).

9. Moynihan P. Sugars and Dental Caries: Evidence for Setting a Recommended Threshold for Intake. Advances in nutrition (Bethesda, Md.) 2016;7(1), 149-56.

10. World Health Organization 2015. Sugars intake for adults and children. Geneva: WHO.

11. Suchithra MS, Sreedharan S, Thomas V, Nayar B. Dental caries experience in preschool children of Thiruvananthapuram, Kerala: is it related to the sociodemographic factors? Journal of Dental and Medical Sciences 2018;17(7):49-56.

12. Chugh VK, Sahu KK, Chugh, A. Prevalence and risk factors for dental caries among preschool children: A cross-sectional study in Eastern India. Int J Clin Pediatr 2018; 11(3):238-43.

13. Iftikhar A, Zafar M, Kalar M. The relationship between snacking habits and dental cariesin school children. International Journal of Collaborative Research on Internal Medicine & Public Health 2012;4(12).

14. Fox M, Condon E, Briefel R, Reidy K, Deming D. Food consumption patterns of Young Preschoolers: Are They Starting Off on the Right Path? Journal of the Academy on Nutrition and Dietetics 2010;110(12) S52–S59.

15. Viswanath D, Sabu N. Prevalence of dental caries, the effect of sugar intake and tooth brushing practices in children aged 5-11 years in Bangalore North. SRM J Res Dent Sci 2014;5:155-62.

eISSN 2255-0569

ORIGINAL

A systematic review of palm and dorsal hand vein recognition techniques

Una revisión sistemática de las técnicas de reconocimiento de las venas de la palma y la vena dorsal de la mano

Rajendra Kumar[1], **Ram C. Singh**[2], **Rohit Khokher**[3]

1. School of Engineering and Technology, Sharda University, Greater Noida, India
2. School of Basic Sciences and Research, Sharda University, Greater Noida, India.
3. Vidya Prakashan Mandir Pvt. (Ltd.), Meerut, India.

Corresponding author
Rajendra Kumar
School of Engineering and Technology,
Sharda University, Greater Noida, India
E-mail: rajendra.kumar@sharda.ac.in

Received: 15 - X - 2021
Accepted: 17 - XII - 2021

doi: 10.3306/AJHS.2022.37.01.100

Abstract

Introduction: Use of vein patterns for biometric recognition is being seen as an efficient identification method because of hygiene and security reasons.
Methods: Several methods and techniques based on traditional computer vision and deep learning for palm and dorsal hand vein recognition have been developed in last 10 years, however, still, the commercialization of vein recognition is very limited.
Results: The deep learning methods have shown significantly better performance over traditional vein apperception techniques predicated on computer vision.
Conclusion: This paper presents a comparative study of methods and techniques used along with their merits and demerits in last 10 years for palm and dorsal hand vein.

Keywords: Vein biometrics, vein patterns, pattern recognition, computer vision, deep learning, CNN, NIR.

Resumen

Antecedentes: El uso de patrones venosos para el reconocimiento biométrico se considera un método de identificación eficaz por razones de higiene y seguridad.
Material y métodos: En los últimos 10 años se han desarrollado varios métodos y técnicas basados en la visión tradicional por computadora y el aprendizaje profundo para el reconocimiento de las venas de la palma de la mano y dorsal, sin embargo, aún así, la comercialización del reconocimiento de las venas es muy limitada.
Conclusiones: Este artículo presenta un estudio comparativo de los métodos y técnicas utilizados junto con sus méritos y deméritos en los últimos 10 años para la palma y la vena dorsal de la mano.

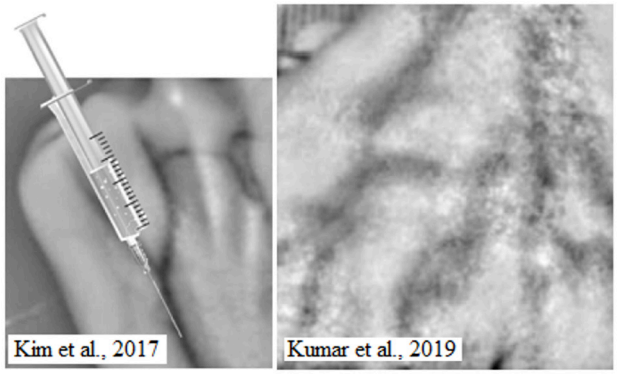
Palabras clave: biometría de venas, patrones de venas, reconocimiento de patrones, visión por computadora, aprendizaje profundo, CNN, NIR.

Introduction

The effectiveness of a vein recognition method depends upon theoretical analysis, security, reliability, etc. the vein recognition in contrast to other physiological traits like a fingerprint, palm-print, face recognition, etc. is much secure as the vein patterns are underneath the skin and it is very difficult to capture them without apprising a person especially a finger and palm veins. However, the dorsal hand vein and face veins can be captured from a distance using a far-infrared sensor as the face and lower part of the hand are open most of the time at public places.

The notion of vein recognition has initiated from medical imaging. Many times, the medical practitioners need Venepuncture as an important diagnosis process for vein locating in infants and obese persons. Also, for coloured skin patients, it is still a difficult task even for skilled practitioners. To deal with such cases, different infrared vein finders have been used and commercially available for vein pattern acquisition for research purposes. Different vein finders have been used in medical institutes and hospitals to detect the veins to inject the drugs[23]. **Figure 1** shows the use of a vein finder in the medical field and a vein images of dorsal hand.

Figure 1: : (a) Venipuncture using Vein Finder (b) Dorsal hand Vein image.



As the time passed, the medical scientist observed that the vein patterns are unique for every person. Later, it was observed that vein patterns are also different even in twins[62]. Several researchers were then encouraged to study vein patterns as biometric recognition. Several methods and techniques based on traditional computer vision[3,13,14,20,21,28,29,34,57] were developed and enhanced over the years.

General Framework for Vein Recognition

This review of palm and dorsal hand vein recognition techniques and methods includes traditional computer vision (conventional system) and deep learning both. The need and size of the dataset decides the method and technology adapted. If it is a vein based attendance system in an office, then a template based matching system is sufficient as it is easy and simple to implement up to few hundreds or thousands persons to monitor. But, if it is a huge system contains lakhs or million persons like AADHAR or a banking system for user authentication using template based vein pattern matching is much inconvenient and the best solution is deep learning.

Conventional or Computer Vision based Vein Recognition

Image classification began with a non-training based system, also known as traditional computer vision or conventional methods that use the traditional way of feature extraction in conjunction with digital image processing to classify objects. Traditional computer vision uses feature descriptors such as minutiae-based matching, scale-invariant feature transform (SIFT)[37], speed up robust features (SURF)[36], binary robust independent elementary features (BRIEF)[21], local binary patterns (LBP)[32], etc. Unlike traditional computer vision, deep learning uses deep neural networks for object detection and classification.

Conventional palm and dorsal hand vein recognition methods are less robust to noise and misalignment-problem than the deep learning approaches. The image pre-processing methods are conventionally applied to make fast the feature extraction process and matching to surmount the verbalized quandaries. However, various traditional vein recognition methods are developed achieving noteworthy development.

The methods for vein recognition, based on traditional computer vision use the concepts of digital image processing for feature extraction and matching. The very common and effective methods under traditional computer vision are SIFT, SURF, LBP, BRIEF, etc. The major drawback of these methods is that it is very difficult for them to handle a large amount of data because the features are extracted manually and one-to-one matching is performed. Therefore, it is a manual and very time consuming manual process. The solution to overcome this problem is to adapt the training based system popularly known as deep learning.

Deep Learning based Vein Recognition

Some deep learning techniques like SVM and CNN, etc. are applied for extracting the feature from vein images and match the biometric features for human identification. These techniques are already verified to be efficient for extraction of features, matching those features, and improving the performance of a vein recognition method. Most of the vein recognition methods, deep learning classifiers are applied as matching step[27]. However, traditional vein recognition approaches apply Euclidian

distance calculation for matching purposes[37].

The training based systems use light[58] and deep convolution neural networks (CNNs) to build models that can predict the classes more accurately[63]. The deep CNNs use filters (also known as kernels) to extract the features from images constituting a class. Once the model is trained with good validation accuracy and minimum losses, it predicts the classes very fast and efficiently. The major drawbacks of deep learning models include (i) too much time-consuming training process (ii) dataset with a sufficient number of vein images in each class[25].

The deep learning models take too much time while trained with central processing unit (CPU) rather than graphics processing unit (GPU) and the programmer often needs to repeat the training process again and again until the desired training accuracy is achieved. Deep learning should not be used just because it is trending. The programmer's experience states that one should go for deep learning training, only when it is highly required (in case a large amount of data to be handled) otherwise a few lines code based on traditional computer vision (template based matching) may work well[25].

The main components and parameters in the design of a CNN model are input layer, activation function[24], filters, pooling layer, stride and padding, dropout probability[49], batch normalization[17], dense or fully connected layer, classifier, and output layer.

The most common activation functions are *tanh, sigmoid*, and *ReLU*. In recent years, *ReLU* has gained much popularity in object detection and classification models. The activation functions create non-linearity in the image.

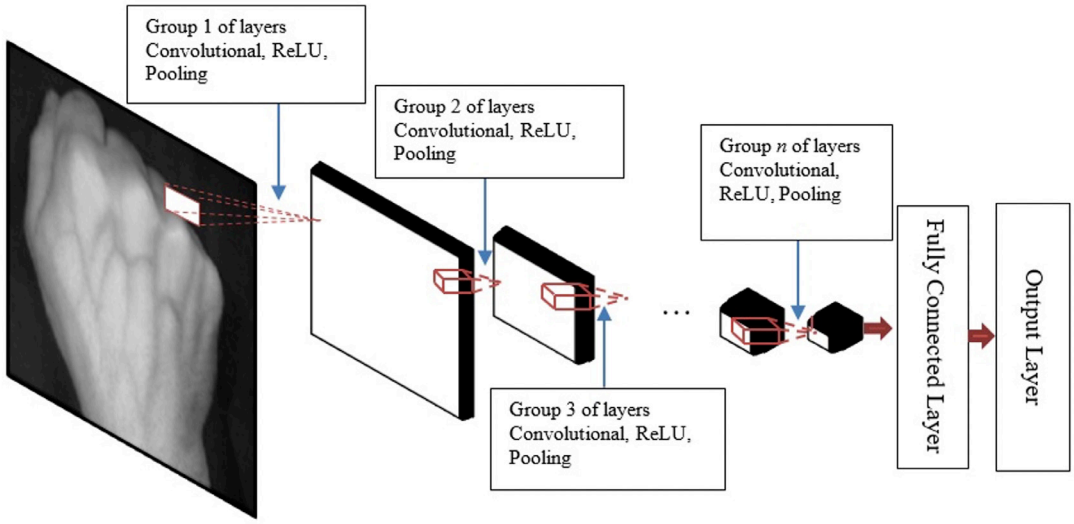
To reduce the training time and occupancy of high memory, a technique called pooling[10] is used in CNN hidden layer. The pooling layer shortens the size of the feature map so that the computational cost is reduced. The common pooling techniques are max-pooling and average-pooling. The most used classifier at the output layer is softmax for image classification. The specific collection of layers between the input and output layer lies in hidden layers. The counting of hidden layers depends upon how minute feature details need to be extracted from images and also it is problem-centric. The vein recognition for human identification is a multiclass classification problem that requires models with 4-5 convolutional layers to VGG Net-16[46] and above. With the development of residual networks, the very deep CNN are very much in practice to produce high performance. Kumar et al. presented a very deep learning model based on residual blocks having 35 convolutional layers for dorsal hand vein recognition using children and adults' datasets[27].

The deep learning models learn from examples therefore, deep models for image classification need many images in the dataset by using those the model trained. The insufficient number and low-quality images produce overfitting during the training and cause to termination of the training process in middle by the programmer. The problem of overfitting may be reduced by adding dropout layer(s) in the CNN.

The CNN Architecture

Figure 2 presents the basic components of a CNN architecture. It consists of an input and output layer along with one or more hidden layers. The hidden layers contain a specific combination of convolutional, ReLU, pooling, dropout layers followed by one or more fully connected layers.

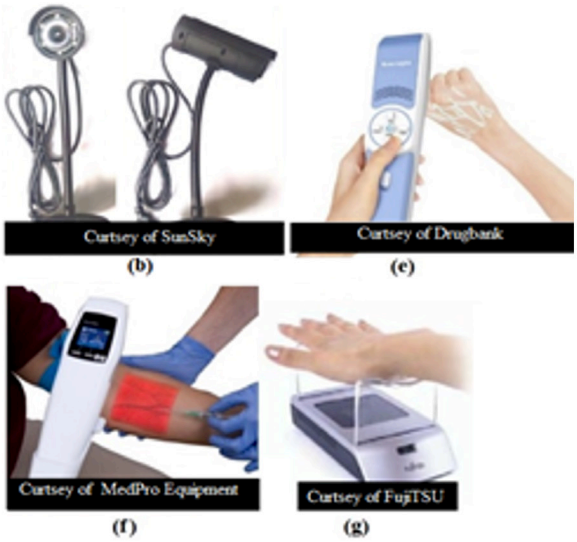
Figure 2: The architecture of CNN.



The NIR Sensors

The infrastructure support required for a vein recognition system includes an NIR sensor equipped with a web camera for the acquisition of vein images. **Figure 3** presents some popular vein finders and NIR sensors for vein image acquisition. The wavelength of near-infrared sensor applicable for this purpose lies between 800 nm and 1000 nm.

Figure 3: Different NIR sensors for vain pattern acquisition[56].



The NIR modules by researchers

The majority of vein acquisition prototypes built by the researcher are contactless. These prototypes consist of NIR LEDs for infrared illumination, a camera to acquire vain images during illuminance, and a power source inside a cabinet. The researchers set up their vein acquisition systems by placing the components as per their plan and requirement.

Kauba et al. 2019, presented a touchless hand vein capturing device (**Figure 4**) comprising an NIR enhanced camera, an NIR pass-through filter, two NIR illuminators, a laser module and an illumination control board inside a wooden cabinet.

A palm vein acquisition prototype developed HES-SO and the [Idiap] comprised of a camera, ICX618 sensor, and infrared LEDs of wavelength 940 nm as shown in **figure 5**.

Figure 5: A prototype for palm vein acquisition[51].

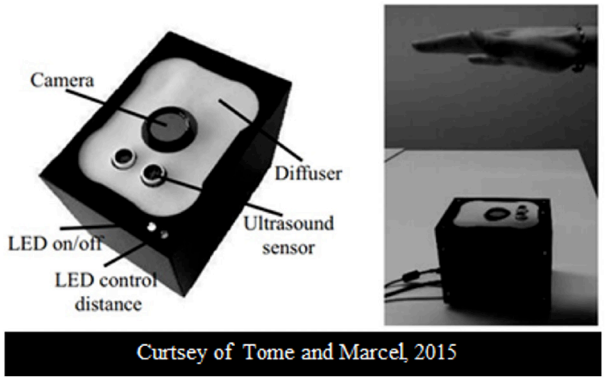


Figure 6 shows the dorsal hand vein and fingerprint acquisition system28. The vein finder VF620 and a fingerprint scanner were connected to laptop through USB port for data acquisition. This acquisition system created SRD dataset of 8000 dorsal hand vein images from 400 volunteers (both hands and 10 images per hand in different environmental conditions).

Figure 6: Dorsal hand vein acquisition using NIR camera VF620[26]

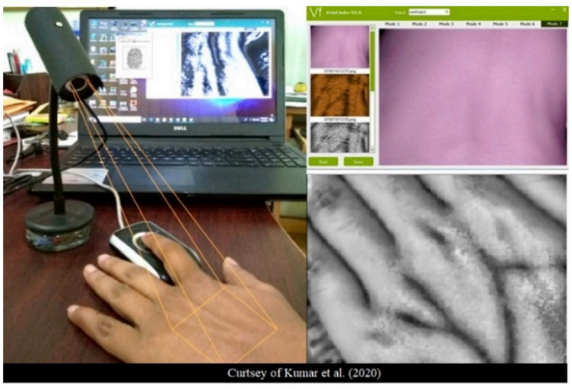
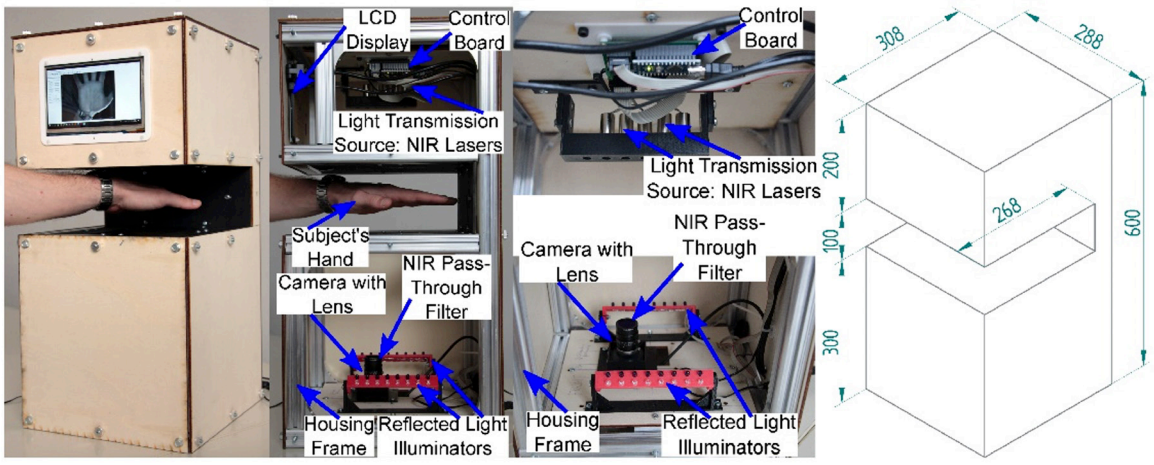


Figure 4: Touchless hand vein capturing device[22].



Different researchers developed low-cost prototypes using NIR sensors. A low-cost system[18] is developed for dorsal hand vein image acquisition. It consists of a modified infrared filter, an image pickup sensor for the camera to pass the light, and a high pass filter to block the visible light to the human eyes and allowing only infrared radiation. **Figure 7** shows this setup. (a) presents the modified camera (b) presents the CMOS sensor. (c) shows inside the housing of the camera lens where the infrared filter is installed and (d) shows the filter that allows the passage of the visible light. Janes and Junior acquired a total of 1240 images from 248 volunteers in self-constructed dataset. The accuracy of recognition they observed is 3.15% in terms of EER using the receiver optical characteristic (ROC) curve[18].

The Vein Datasets

The datasets have a key role in traditional computer vision and machine learning methods for image classification. The datasets are either self-constructed by the researchers or the downloaded datasets which are available for research purpose. As much the images are provided to the deep-learning model for training, the model learns faster and improves the accuracy. Also, the matching and classification accuracy depends upon the quality of input images.

Some Popular Existing Vein Datasets

The deep models are trained over the image datasets. The dataset is split into two parts training set and test set as per the defined split ratio. The popular datasets available for palm and dorsal hand vein recognition research are presented in **table I**, along with details like the number of images in the dataset, number of samples per volunteer, and image format.

Before the launch of commercial products for palm vein recognition, the most complete research followed by patents is conducted by Fujitsu in Japan[55]. The research comprised of a dataset of 150000 palm vein images acquired from 75000 volunteers of different age groups. This dataset was not available for non-Fujitsu researches and therefore no further details are accessible.

Image Augmentation

Artificially generating many images from a given input image using image transformation methods is known as image augmentation. It is highly desirable in deep model training for better accuracy. The Keras function Image data generator is mostly used to generate augmented images. Keras data generator alters images with varying slight rotation, shear, zoom, width and height shift, brightness, etc. This increases the size of training and test datasets. Önsen Toygar et al. increased the training dataset size[35] of Dr. Badawi dataset from 50 to 5000 and

Figure 7: A modified NIR sensor.

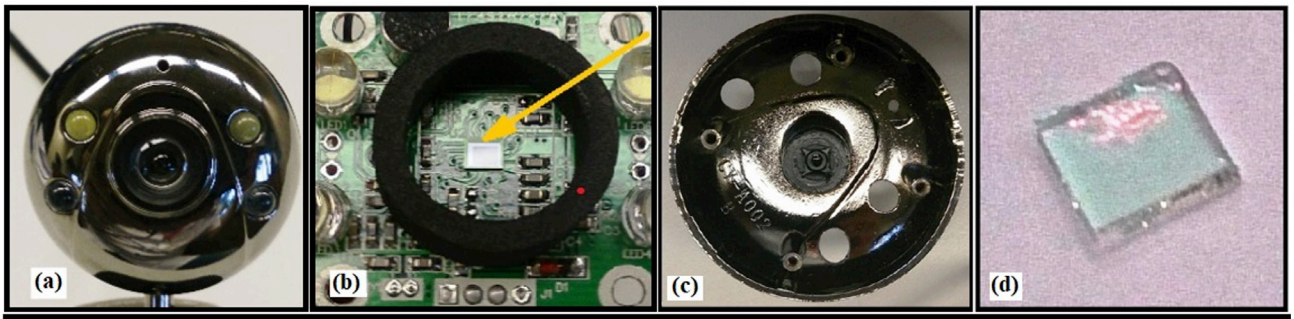


Table I: Major Datasets of palm and dorsal hand vein images.

Dataset Type	Name of Dataset	Number of images	Sampling	Image size and format
Palm Vein	Institute of Automation, Chinese Academy of Sciences (CASIA)[6]	7200	100 volunteers	200×266 (jpeg)
	Idiap Research Institute VERA Palmvein Database [Idiap][16]	2200	110 volunteers (40 women and 70 men)	480×680 (png)
	FYO-PV[35]	1920	160 volunteers (111 males and 49 females)	800×600 (png)
Dorsal Hand Vein	SRD Lab2[6]	8000	400 volunteers (200 males, 150 females, and 50 children 10 images of left hand 10 images of the right hand	640×480 (png)
	BOSPHORUS[5]	1575	100 volunteers with 3 images per hand in 5 conditions and another 75 images in normal condition.	300×240 (bmp)
	Dr. Badawi[45]	500	50 volunteers with 5 image of the left hand and 5 images of the right hand	320×240 (bmp)
	Sakarya University of Applied Sciences (SUAS)[50]	919	155 adults (80 male, 75 female)	256×192 (jpeg)
	FYODV35	640	160 volunteers and 2 images per hand	800×600 (png)

test dataset from 5 to 500; Bosphorus training dataset from 54 to 5400 and test dataset from 6 to 600; VERA Training dataset from 45 to 4950 and test dataset from 5 to 550; and FYO training dataset from 18 to 5760 and test dataset from 2 to 640. To avoid the model from overfitting, the technique used is dropout. Also, the cross-validation is performed by swapping the test set with a section of the training set and repeating the model training for better understanding of accuracy. This repetition may be done many times without repeating the test set.

Palm-Vein Recognition

The palm-vein recognition offers big space for feature extraction to produce better recognition than finger vein. Most of the palm-vein scanners use touch of the palm with scanner. Therefore, it is little bit unhygienic, however it is more secure than dorsal hand vein recognition as the palm-vein patterns are very difficult to capture by cyber criminals without the consent of a person. **Table II** presents some major contributions in palm-vein recognition research.

Table II: Some major palm-vein recognition contributions.

Contribution	Technique	Dataset(s) used	Major contribution	Recognition Accuracy
Palm vein recognition performance based on the geometrical structure				
Lee (2012)[30]	2D Gabor filter, Hamming distance	Self-constructed	Directional coding technique to encode the palm vein features	99.18%
Han and Lee (2012)[13]	Different types of Gabor filters, Hamming distance	Self-constructed	Encoding palm vein features in bit-string representation	Single Gabor 99.30% Multi Gabor 99.45% Adaptive Gabor 99.35%
Palm vein recognition performance based on Statistics data				
Ojala et al. (2002)[34]	Local Binary pattern, Score level fusion	PolyU	Generalized grayscale and rotational invariant operator presentation	99.87%
Mirmohamadsadeghi and Drygajlo (2011)[32]	Local derivative pattern, histogram intersection	CASIA	Local texture patterns	98.30%
Kang and Wu (2014)[19]	Local Binary pattern, Support Vector Machine	CASIA	Improved mutual foreground LBP	100%
Lu et al. (2016)[31]	Multi-scale Local Binary pattern, Local derivative pattern, similarity measure	CASIA	Discretional information derived from LBP	99.99%
Rivera et al. (2015)[43]	Local tetra pattern Local directional texture patterns	PUT	Facial expression and scene recognition	100%
Akbar et al. (2016)[1]	Local directional texture patterns, Chi-square dissimilarity test	CASIA	Local derivative patterns for feature extraction and histogram intersection	95%
Palm Vein recognition performance based on invariant features				
Ladoux et al. (2009)[29]	SURF, Score level fusion, Sum of absolute difference distance measure	PUT and PolyU	Prototype for image acquisition	98.81%
	SIFT, Euclidean distance	Self-constructed		99.86%
Hassan et al. (2012)[14]	SIFT Morphological features	Self-constructed using Fujitsu's PalmSecure™ scanner	Linear Vector Quantization classifier is used with changed parameters	Genuine Accept Rate at learning rate 0.05: 98.06% (SIFT) 95.99% (Morphological features)
Verma and Dubey (2014)[52]	Gaussian and low pass filters for edge detection	Not reported	Review of palm vein in last 10 years	Not applicable
Kang et al. (2014)[20]	SIFT, RootSIFT, Hellinger Kernel	CASIA, Self-constructed	Combining difference of Gaussian and histogram equalization	CASIA 99.006% Self-constructed 96.888%
Sayed (2015)[44]	Coset decomposition to identify encoded palm vein features	Dataset of 50 volunteers (5 images per volunteer with a 1-week interval per image)	Matching algorithm for extracting code word	99.80%
Yan et al. (2015)[61]	Score ORB and SIFT, bidirectional matching	Self-constructed	Score level fusion	99.86%
Palm Vein recognition performance based on the sub-space method				
Zhou and Kumar (2011)[64]	Neighborhood matching Radon Transform, Hessian Phase	CASIA	Orientation preserving features and novel region-based matching	NMRT 99.49% Hessian 98.56%
Perwira (2014)[38]	Principle component analysis, Probabilistic neural network	PolyU CASIA	Competitive hand valley detection	NMRT 99.996% Hessian 99.57% 84%
Zhou et al. (2014)[65]	Gaussian radon transform, principle oriented features	PolyU, CASIA	Algorithm to extract directions to compose for classification of subspace	PolyU 99.91% CASIA 99.33%
Elnasir and Shamsuddin (2015)[12]	Linear Discriminative analysis, Cosine distance	PolyU	Comparison with PCA and Gabor filter method	99.74%
Xu (2015a)[59]	2D Fisher Linear Discriminant, Euclidean distance	Self-constructed	The highly secure and high degree of user acceptance	99.29%
Xu (2015b)[60]	Partial least square, Euclidean distance	Automation research institute of Chinese academy of sciences	image coordinate in subspace for classification and recognition	98.70%
Cho & Kar-Ann (2018)[9]	Gabor filter, Hamming distance	PolyU	RGB palm-vein images	99.13%
Hernández-García et al. (2019)[15]	CLAHE	CASIA Multi-Spectral Palmprint Images	combining DAISY descriptor and the Coarse-to-fine PatchMatch	99.28%
Pititheeraphab et al. (2020)[39]	Geometric affine invariants	Self- constructed	geometry-modality	99.76%

Dorsal Hand Vein Recognition

Dorsal hand veins are much encouraged as the scanners used are contactless totally. Also, in the dorsal hand vein, big space is available so that sufficient features may be obtained resulting in better accuracy than finger vein recognition. **Table III** shows some major contributions in dorsal hand vein recognition using traditional computer vision and deep learning.

Traditional computer vision has its limitation like the features are extracted manually, therefore, such a system cannot handle a large amount of data. To overcome this problem the training-based methods are used generally known as deep learning. The datasets namely used are Bosphorus, SRD, Dr. Badawi, IITK and some those self-constructed.

Performance of Vein Biometric Systems

The reliability and applicability of a biometric system are based on its performance ability. Evaluating the performance is a complex process since many variables affect the system's performance. El-abed et al. stated that the performance of these systems is evaluated based on three broad categories: 1) Quality, 2) Usability, and 3) Security[11].

The performance evaluation of a vein recognition method is a paramount way to judge whether used algorithms are good or lamentable. ROC instinctively presents the steadiness between FAR and FRR. To make a judgment on the matching algorithms, a threshold is applied to fix EER optimally. If the threshold is decremented, the FAR is incremented, and FRR or FNMR is decremented. Similarly, when the threshold is incremented, the FRR is incremented, and FAR is decremented. The EER value can simply be obtained from ROC curve when FAR and FRR are equal. The lower the EER, the better is the system performance. Ideally, the EER should be 0%. Half Total Error Rate (HTER) is another way to measure the performance of a biometric system. It is calculated as an average of FAR and FRR. Genuine Accept Rate (GAR) is defined as the ratio of the number of input samples correctly classified out of the total number of positive input samples.

Additional way to observe the performance of a biometric system is the confusion matrix. The confusion matrix represents the true and false predictions for input samples. Four parameters are used to categorize the predicted results: true-positive (*TP*), true-negative (*TN*), false-positive (*FP*), and false-negative (*FN*).

Table III: Some major contributions in dorsal hand vein recognition.

Contribution	Technique	Dataset(s) used	Major contribution	Recognition Accuracy
Traditional computer vision-based contributions				
Wang (2008a)[53]	Minutiae features extraction	Self-constructed	Novel technique to analyse vein patterns	EER 0%
Wang (2008b)[54]	Wavelet algorithm	TJU dataset	Multi-resolution wavelet algorithm	EER 1.96%
Naidile and Shrividya (2015)[33]	Correlation method	Self-constructed	Applied maximum curvature against temporal fluctuation in vein brightness and width	Accuracy 75%
Raghavendra et al. (2015)[41]	Log-Gabor and Sparse representation classification	Self-constructed	New dorsal hand vein sensor for good quality vein acquisition	EER 0.7%
Belean et al. (2017)[4]	Geometry and pixel intensity distribution	Bosphorus dataset	Image processing pipeline for vein characterization	EER 0.83%
Kumar et al. (2019)[28]	SIFT, SURF, Euclidean distance	Self-constructed dataset	Children dataset Model for patient identification	EER 0.035%
Deep Learning based contributions				
Chin et al. (2020)[7]	Features extraction based on statistical and Gray Level Co-occurrence Matrix, ANN.	Bosphorus. dataset	ROI segmentation on Gray Level Co-occurrence Matrix	99.32%
Chin et al. (2021)[8]	ROI, mean filtering, CLAHE, histogram equalization, LBP, ROI, ANN	Bosphorus dataset	The ANN was then utilized in the MATLAB GUI program for testing 100 images	99.86%
Kumar et al. (2020)[25]	CNN	Self-Constructed and SRD dataset of good, medium, and low-quality images	Fine-tuning VGG Net-16 Difference image	99.60% (Good quality) 98.46% (Medium quality) 97.99% (low quality)
Al-Johania and Elrefai (2019)[2]	CNN	Dr. Badawi and BOSPHORUS	Error-correcting output codes with KNN and SVM	99.25%
Sree et al. (2014)[48]	Linear Hugh transform	Self-constructed	Morphological operations with KNN classifier	96.25%
Premvathi et al. (2018)[40]	Local binary pattern, Local ternary pattern, KNN	North China University of Technology (NCUT) dataset	New minimum distance classification	95.10%
Rajalakshmi et al. (2018)[42]	CNN, random forest, logistic regression	Self-constructed	Ensemble method to improve accuracy	96.77%
Soni et al. (2010)[47]	Traditional computer vision, morphological operations	IITK dataset	New absorption-based approach for data acquisition; Modified connected compound labelling algorithm	Not reported

Discussion

Excellent developments are seen around vein recognition and other related research for image classification using deep learning methods. In recent research, several improvements are observed in terms of activation function for better convolution, normalization for model stability, etc. The use of a graphics processing unit (GPU) has made computation much faster. Deep learning training using GPU involving feature extraction has speeded up many times than a CPU.

This paper presents a review of all the processing steps of vein recognition: image acquisition process, image pre-processing, feature extraction, and matching. We withal discuss different sensors, datasets and the performance of traditional computer vision and deep learning algorithms developed and utilized for vein apperception.

Some of the major palm vein researches are enlisted in **table II**. More than 98% contributions in last 10 years observed recognition accuracies between 98% to 100% using methods like LBP, SIFT, SURF, etc., with Gaussian filtering, low pass filtering, Coset decomposition, CLAHE, histogram intersection, local tetra patterns, etc. The contribution by Perwira[38] applying competitive hand valley detection with PCA and probabilistic neural network observed minimum accuracy of classification as 84% among all enlisted research. The **figure 8** presents accuracy graph of various palm vein recognition work done from 2011 to 2020.

Figure 8: Palm Vein Recognition Accuracy Graph of selected research between 2011-2020.

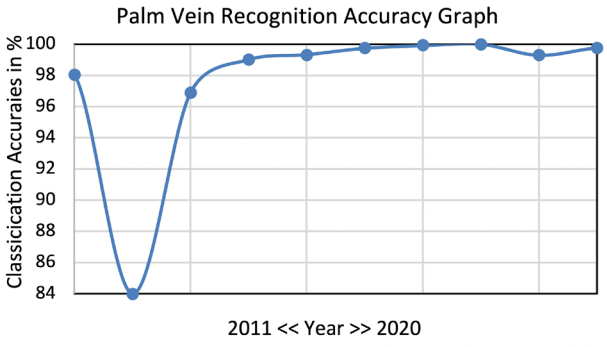
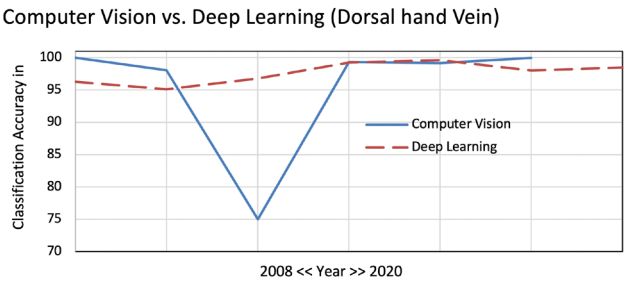


Table III presented some major contributions on dorsal hand vein using traditional computer vision and deep learning. The **figure 9** represent recognition accuracy graph for some researches. Naidile and Shrividya observed recognition accuracy as 75% using correlation method on self-constructed dataset[33]. Except this, other computer vision based researches observed recognition accuracy more than 98%. In deep learning based contributions, all observed recognition accuracy more than 95%, however, Soni et al. did not report recognition accuracy[47]. The **figure 9** presents accuracy graph of various dorsal hand vein recognition work done from 2008 to 2020.

Figure 9: Recognition accuracy graph for computer vision and deep learning methods on dorsal hand vein



Conclusions

This study provides an ample review of traditional computer vision and deep learning-predicated vein recognition approaches. The methods and techniques presented based on major work done are assessed in the key recognition steps of image acquisition, pre-processing, feature extraction, and features matching using various methods and techniques. Additionally, the feature extraction methods are regulated into two groups namely traditional computer vision and deep learning are discussed and compared. The deep learning methods have shown significantly better performance over traditional vein apperception techniques predicated on computer vision.

The study presented in this work, discussed the last 10 years' contributions in area of palm and dorsal hand vein recognition for human identification. Also, it has many challenges that need to be resolved. To get better performance of vein apperception, a good image acquisition system is required to get a good quality of vein images. A sizably voluminous dataset is needed as the deep models to learn from examples. A high apperception spoof detection in vein recognition methods is highly desirable to identify spoof attacks. Furthermore, deep learning approaches play a consequential role in vein recognition. With the prelude of deep learning approaches in vein apperception, the apperception performance is potentially enhanced in a broad sense. In conclusion, this review of vein recognition can be utilized as a platform for emerging approaches, and a commonplace for a wide range of benefits and challenges in biometrics.

Interests conflict

The authors declare no conflict of interest.

References

1. Akbar AF, Wirayudha TAB, Sulistiyo, MD. Palm Vein Biometric Identification System Using Local Derivative Pattern. Proceedings of 4th Int. Conf. Inf. Communication Technology. 2016;4:1-6.

2. Al-Johania NA, Elrefaei, LA. Dorsal Hand Vein Recognition by Convolutional Neural Networks: Feature Learning and Transfer Learning Approaches. Int. J. Intell. Eng. Syst. 2019;12(3):178-91.

3. Alhaija HA, Mustikovela, SK, Mescheder L, Geiger A, Rother C. Augmented Reality Meets Computer Vision: Efficient Data Generation for Urban Driving Scenes. International Journal of Computer Vision. 2018; 126 (9):961-72

4. Belean B, Streza M, Crisian S, Emerich, S. Dorsal Hand Vein Pattern Analysis and Neural Networks for Biometric Authentication. Studies in Informatics and Control 2017;26(3):305-14.

5. Bosphorus dataset available at http://bosphorus.ee.boun.edu.tr/hand

6. CASIA-MS-PalmprintV1 dataset, http://www.cbsr.ia.ac.cn/MS_Palmprint Database.asp

7. Chin SW, Tay KG, Huong A, Chew CC. Dorsal Hand Vein Pattern Recognition Using Statistical Features and Artificial Neural Networks. IEEE Student Conference on Research and Development (SCOReD), 2020;217-221.

8. Chin SW, Tay KG, Chew CC, Huong A, Rahim RA. Dorsal hand vein authentication system using artificial neural network, Indonesian Journal of Electrical Engineering and Computer Science. 2021;21(3):1837-46

9. Cho S, Kar-Ann T. Palm-Vein Recognition Using RGB Images. Proceedings of the 3rd International Conference on Biomedical Signal and Image Processing. 2018;47-52

10. Dominik S, Müller A, Behnke S. Evaluation of Pooling Operations in Convolutional Architectures for Object Recognition. In Proceedings of the 20th International Conference on Artificial Neural Network. 2010;92–101.

11. El-Abed M, Charrier C, Rosenberger C. Evaluation of Biometric Systems, New Trends and Developments in Biometrics, Jucheng Yang, Shan Juan Xie, IntechOpen, 2012. doi:10.5772/52084. Available from: https://www.intechopen.com/books/new-trends-and-developments-in-biometrics/evaluation-of-biometric-systems.

12. Elnasir S, Shamsuddin SM. Proposed Scheme for Palm Vein Recognition Based on Linear Discrimination Analysis and Nearest Neighbour Classifier. In Proceedings of International Symposium on Biometrics and Security Technology. 2015;67-72.

13. Han WY, Lee JC. Palm Vein Recognition Using Adaptive Gabor Filter. Expert Systems with Applications. 2012;39:13225-34.

14. Hassan S, Abdelnasser SM, Ahmed A. Feature Level Fusion of Palm Veins and Signature Biometrics. International Journal of Video & Image Processing and Network Security. 2012;12(1):28-39.

15. Hernández-García R, Barrientos RJ, Rojas C, Mora M. Individuals Identification Based on Palm Vein Matching under a Parallel Environment, Applied Sciences. 2019;9(2805):1-25.

16. IDIAP Palm Vein Dataset, https://www.idiap.ch/dataset/vera-palmvein

17. Ioffe S, Szegedy C. Batch Normalization: Accelerating Deep Network Training by Reducing Internal Covariate Shift. In Proceedings of 32nd International Conference on Machine Learning, Lille, France. 2015;37:1-9.

18. Janes R, Junior AFB. A Low Cost System for Dorsal Hand Vein acquisition. First International Conference on Systems Informatics. Modelling and Simulation. 2014: 37-42.

19. Kang W, Wu Q. Contactless Palm Vein Recognition Using a Mutual Foreground-Based Local Binary Pattern. IEEE Transaction on Information Forensics and Security. 2014; 9:1974-85.

20. Kang W, Liu Y, Wu Q, Yue X. Contact-free Palm-Vein Recognition Based on Local Invariant Features. Plos ONE. 2014;9(5) 1-12.

21. Karami E, Prasad S, Shehata M. Image Matching Using SIFT, SURF, BRIEF and ORB: Performance Comparison for Distorted Images. In Proceedings of the 2015 Newfoundland Electrical and Computer Engineering Conference, St. johns, Canada. 2015:1-5.

22. Kauba C, Prommegger B, Uhl A. Combined Fully Contactless Finger and Hand Vein Capturing Device with a Corresponding Dataset. Sensors. 2019;19(22):1-25.

23. Kim D, Kim Y, Yoon, S, Lee D. Preliminary Study for Designing a Novel Vein-Visualizing Device. Sensors. 2017;17(2):304.

24. Krizhevsky A, Sutskever I, Hinton GE. ImageNet classification with Deep Convolutional Neural Networks. Communications of the ACM. 2012;6(6):1097-105.

25. Kumar R, Singh RC, Kant S. Dorsal Hand Vein-Biometric Recognition Using Convolution Neural Network. Advances in Intelligent Systems and Computing, Springer, Singapore, 2020;1165:1087-107.

26. Kumar R, Singh RC. SRD dataset of Dorsal Hand Veins (2017) available at https://www.socrd.org/srd-research-lab/

27. Kumar R, Singh RC, Kant S. Dorsal Hand Vein Recognition Using Very Deep Learning. Macromolecular Symposia. 2021:397:1-13

28. Kumar R, Singh RC, Sahoo AK. SIFT based Dorsal Vein Recognition System for Cashless Treatment through Medical Insurance. International Journal of Innovative Technology and Exploring Engineering, 2019;8(10S):444-51.

29. Ladoux PO, Rosenberger C, Dorizzi B. Palm Vein Verification System Based on SIFT Matching. In International Conference on Biometrics, Springer. 2009:1290-98.

30. Lee JC. A Novel Biometric System Based on Palm Vein Image. Pattern Recognition Letter. 2012;33:1520-28.

31. Lu W, Li M, Zhang L. Palm Vein Recognition Using Directional Features Derived from Local Binary Patterns. International Journal of Signal Processing, Image Processing and Pattern Recognition. 2016;9(5):87-98.

32. Mirmohamadsadeghi L, Drygajlo A. Palm vein recognition with Local Binary Patterns and Local Derivative Patterns. International Joint Conference on Biometrics (IJCB), Washington, DC. 2011:1-6.

33. Naidile S, Shrividya G. Personal Recognition Based on Dorsal Hand Vein Pattern. International Journal of Innovative Research in Science, Engineering and Technology. 2015;4(5):3189-96.

34. Ojala T, Pietikainen M, Maenpaa, T. Multiresolution Gray-Scale and Rotation Invariant Texture Classification with Local Binary Patterns.

IEEE Transactions on Pattern Analysis and Machine Intelligence. 2002;24(7):971-87.

35. Önsen T, Felix OB, Yiltan B. FYO: A Novel Multimodal Vein Database with Palmar, Dorsal & Wrist Biometrics. IEEE Access. 2020;8:82461-70.

36. Panchal PM, Panchal SR, Shah SK. A Comparison of SIFT and SURF. International Journal of Innovative Research in Computer and Communication Engineering. 2013;1(2):323-7.

37. Peng J, Wang N, Abd El-Latif AA, Li Q, Niu X. Finger-Vein Verification Using Gabor Filter and SIFT Feature Matching. In Proc. of the 8th Int. Conf. on Inte. Info. Hiding and Mul. Sig. Proc. 2012:45-8.

38. Perwira DY. Personal Palm Vein Identification Using Principal Component Analysis and Probabilistic Neural Network. In Proceedings of International Conference on Information Technology Systems and Innovation. 2014:99-104.

39. Pititheeraphab Y, Thongpance N, Aoyama H, Pintavirooj C. Vein Pattern Verification and Identification Based on Local Geometric Invariants Constructed from Minutia Points and Augmented with Barcoded Local Feature, Applied Sciences. 2020;10(3192):1-27.

40. Premavathi C, Thangaraj P. Efficient Hand-dorsa Vein Pattern Recognition Using KNN Classification with Completed Histogram CB in TP Feature Descriptor. Int. J. Rec. Tech. Eng. 2018;7(4S):50-5.

41. Raghavendra R, Surbiryala J, Busch C. Hand Dorsal Vein Recognition: Sensor, Algorithms and Evaluation. In Proceedings of IEEE International Conference Imaging System and Techniques. 2015:1-6.
42. Rajalakshmi M, Rengaraj R, Bharadwaj M, Kumar A, Raju NN, Haris M. An Ensemble Based Hand Vein. Pattern Authentication System, CMES. 2018;114(2):209-20.

43. Rivera AR, Castillo JR, Chae O. Local Directional Texture Pattern Image Descriptor. Pattern Recognition Letter. 2015;51:94-100.

44. Sayed M. Palm Vein Authentication Based on the Coset Decomposition Method. Journal of Information Security. 2015;6:197-205.

45. Shahin M, Badawi A, Rasmy M. Multimodal Biometric System Based on Near-Infra-Red Dorsal Hand Geometry and Fingerprints for Single and Whole Hands. World Academy of Science, Engineering and Technology. 2010;4(4);268-83.

46. Simonyan K, Zisserman A. Very Deep Convolutional Networks for Large-Scale Image Recognition. In Proceedings of International Conference Learning Representations. 2015:1-14.

47. Soni M, Gupta S, Rao MS, Gupta P. A New Vein Pattern-based Verification System." IJSCIS International Journal of Computer Science and Information Security, 2010;8(1):58-63.

48. Sree V, Krishna, Rao PS. Dorsal Hand Vein Pattern Authentication by Hough Peaks. International Journal of Research in Engineering and Technology. 2014;3:16-22.

49. Srivastava N, Hinton G, Krizhevsky A, Sutskever I, Salakhutdinov R. Dropout: A Simple Way to Prevent Neural Networks from Overfitting. Journal of Machine Learning Research. 2014;15(56):1929-58.

50. SUAS (Sakarya University of Applied Sciences) Dorsal Hand Vein dataset, https://www.kaggle.com/oboyraz/suas-dorsal-hand-vein-database.

51. Tome P, Marcel S. Palm Vein Database and Experimental Framework for Reproducible Research. Idiap. 2015:1-7.

52. Verma D, Dubey S. A Survey on Biometric Authentication Techniques Using Palm Vein Features, JGRCS. 2014;5(8):5-8.

53. Wang LG, Leedham, Cho DS. Minutiae Feature Analysis for Infrared Hand Vein Pattern Biometrics. Pattern Recognition. 2008a;41: 920-9

54. Wang YT, Liu J. A Multi-Resolution Wavelet Algorithm for Hand Vein Pattern Recognition. Chinese Optics Letter. 2008b;6: 657-60.

55. Watanabe M. Palm Vein Authentication. Advances in Biometrics, Springer London. 2008:75-88.

56. White paper by Fujitsu, Palm Vein Pattern Authentication Technology, available at https://www.fujitsu.com/ downloads/COMP/ffna/palm-vein/palmsecure_wp.pdf

57. Wu J, Peng B, Huang Z, Xie J. Research on Computer Vision-Based Object Detection and Classification. IFIP Advances in Information and Communication Technology, Springer, Berlin, Heidelberg. 2013:392.

58. Xiang W, Ran H, Zhenan S, Tieniu T. A Light CNN for Deep Face Representation with Noisy Labels. Journal of Latex Class Files, 2017;14(8):1-13.

59. Xu J. An Online Biometric Identification System Based on Two Dimensional Fisher Linear Discriminant. In Proceedings of 8th International Congress on Image and Signal Processing. 2015a:774-8.

60. Xu J. Palm Vein Identification Based on Partial Least Square. In Proceedings of 8th International Congress on Image and Signal Processing, Shenyang. 2015b:670-4.

61. Yan X, Deng F, Kang W. Palm Vein Recognition Based on Multi Algorithm and Score-Level Fusion. In Proceedings of 7th International Symposium on Computational Intelligence. 2015;1:441-4.

62. Zhang H, Tang C, Li X, Kong AWK. A Study of Similarity between Genetically Identical Body Vein Patterns. IEEE Symposium on Computational Intelligence in Biometrics and Identity Management, Orlando, FL. 2014:151-9.

63. Zheng HH, Zu YX. A Normalized Light CNN for Face Recognition. Journal of Latex Class Files. 2018;14(8);1-13.

64. Zhou Y, Kumar A. Human Identification Using Palm-Vein Images. IEEE Transaction on Inf. Forensics Security. 2011;6:1259-74.

65. Zhou Y, Liu Y, Feng Q, Yang F, Huang J, Nie Y. Palm-Vein Classification Based on Principal Orientation Features. PLoS ONE, 2014;9(11):1-12.

eISSN 2255-0569

ORIGINAL

A prospective study on impact of clinical pharmacist interventions in management of patients with cardiovascular diseases in a tertiary care hospital, India

Un estudio prospectivo sobre el impacto de las intervenciones de los farmacéuticos clínicos en la gestión de pacientes con enfermedades cardiovasculares en un hospital de atención terciaria, India

Shahin Mojra, Mekkanti Manasa Rekha

Doctors of Pharmacy, Department of pharmacy practice, Gautham College of Pharmacy, Bengaluru, India.

Corresponding author
Shahin Mojra
Department of pharmacy practice,
Gautham College of Pharmacy, Bengaluru, India
E-mail: mojra4133@gmail.com

Received: 17 - X - 2021
Accepted: 15 - XII - 2021

doi: 10.3306/AJHS.2022.37.01.110

Abstract

Objective: To evaluate the impact of clinical pharmacist interventions in the management of patients with cardiovascular diseases in a tertiary care hospital.
Methodology: The Present Study was a Prospective Interventional study conducted over a minimum period of 6 months from October 2019 to March 2020 in Cardiology and General Medicine Departments In a Tertiary Care Hospital, India. 220 prescription was evaluated out of which 140 prescription had pDDIs. The patient demographics and all medically relevant information were noted in a predefined data collection form. Alternatively, these case charts were reviewed for potential drug interactions, drugs involved in interactions, laboratory investigations, followed up for assessing observed adverse drug interaction, and pharmacist's intervention.
Result: Out of 220 prescriptions analyzed, 140 prescriptions comprised of potential drug interactions and it was found that 234 drug interactions were present. The incidence of potential drug interaction was 63.64%, A total of 28 adverse drug reactions were recorded among 234 pDDI.
Conclusion: This study attempted to assess the potential drug-drug interaction in the prescription of cardiac patients in the inpatient hospital setting. This study also examined patient, drug characteristics, causality, and severity of pDDIs. This study shows that DDIs are frequent among hospitalized cardiac patients. About 234 drug interactions were reported during the study period with a median number of 1.67 pDDIs in the cardiac patients. This study emphasizes the need to consider pDDIs during therapeutic planning, protect patients from the consequence of drug interactions. In addition, providing DDI-related information to the prescribers and drug interaction alert software to the dispensing pharmacist can play a vital role in minimizing the incidence rate of DDI.

Keywords: Cardiovascular, Potential drug-drug interaction, Drug interaction.

Resumen

Objetivo: Evaluar el impacto de las intervenciones del farmacéutico clínico en el manejo de pacientes con enfermedades cardiovasculares en un hospital de tercer nivel.
Metodología: El presente estudio fue un estudio prospectivo de intervención realizado durante un período mínimo de 6 meses desde octubre de 2019 hasta marzo de 2020 en los departamentos de cardiología y medicina general en un hospital de atención terciaria, India. Se evaluaron 220 prescripciones de las cuales 140 tenían pDDIs. Los datos demográficos del paciente y toda la información médicamente relevante se anotaron en un formulario de recogida de datos predefinido. Además, se revisaron las historias clínicas para determinar las posibles interacciones farmacológicas, los fármacos implicados en las interacciones, las investigaciones de laboratorio, el seguimiento para evaluar la interacción farmacológica adversa observada y la intervención del farmacéutico.
Resultado: De las 220 prescripciones analizadas, 140 incluían posibles interacciones farmacológicas y se descubrió que había 234 interacciones farmacológicas. La incidencia de interacciones farmacológicas potenciales fue del 63,64%, y se registraron un total de 28 reacciones farmacológicas adversas entre las 234 pDDI.
Conclusión: Este estudio trató de evaluar la potencial interacción farmacológica en la prescripción de pacientes cardíacos en el ámbito hospitalario. Este estudio también examinó las características del paciente, del fármaco, la causalidad y la gravedad de las pDDI. Este estudio muestra que las IDP son frecuentes entre los pacientes cardíacos hospitalizados. Se notificaron unas 234 interacciones farmacológicas durante el periodo de estudio, con una mediana de 1,67 IDP en los pacientes cardíacos. Este estudio enfatiza la necesidad de considerar las pDDIs durante la planificación terapéutica, para proteger a los pacientes de las consecuencias de las interacciones farmacológicas. Además, el suministro de información relacionada con las IDP a los prescriptores y el software de alerta de interacciones farmacológicas al farmacéutico dispensador pueden desempeñar un papel vital para minimizar la tasa de incidencia de las IDP.

Palabras clave: Cardiovascular, posible interacción medicamentosa, interacción medicamentosa.

Introduction

By causing an estimated 17.9 million passing's every year, cardiovascular diseases (CVDs) are the main deadly diseases all around the world, making 31% of all-cause mortality[1]. As a result of various etiologies and simultaneous comorbidities, CVD patients are treated with a mind-boggling therapeutic routine containing numerous various drugs. For instance, in the United States of America, the elderly CVD patients (age > 65 years) had eight simultaneous comorbidities and took 13 drugs on normal[2]. In like manner, prescription of countless various drugs (range 2-24 drugs) to CVD patients have been accounted for by studies directed somewhere else.[3,4,5,6]

Cardiovascular diseases (CVDs) remain the biggest cause of death worldwide. A WHO report (2012) estimated that 17.5 million people die of CVDs each year representing 31% of all deaths. Of these, about 7.4 million are due to coronary heart disease and 6.7 million dues to stroke. By 2030, an estimated 23.6 million people will kick the bucket from CVDs basically from coronary illness and stroke. These are projected to stay the single driving reason for death[7].

Even though pharmacotherapy in cardiovascular diseases can further develop prosperity, its benefit can be undermined by drug-related problems (DRPs). A drug-related problem is any occasion or situation including drug therapy that meddles with the patient accomplishing an ideal result of clinical consideration[8-11]. They act as a huge danger, prompting huge morbidity and mortality. In a survey of worldwide examinations, it was tracked down that about 28% of all crisis division visits were related to DRPs and 24% of them brought about medical clinic confirmation. In a review directed by Zaredar, N[9] et al in 2017, it was seen that about 87% of hospitalized patients have drug-related problems. In one more review directed by Nascimento[10] et al in 2009, the incidence of DRPs was accounted for as 91.7. An Indian review announced that the incidence of DRPs was observed to be more noteworthy than cited in created nations. The high incidence of unseemly measurement and ill-advised drug choice saw in the review was ascribed to the absence of standard therapy conventions and the varying therapy designs between the clinical wards in every Indian medical clinic.[11] Cardiovascular drugs are one of the drug classifications frequently engaged with drug-related problems. A concentrate by Andreazza[8] et al in 2011 reported cardiovascular drugs to account for the majority of all DRPs. Detection and prevention of DRPs can save lives along with enhancing patients' quality of life and optimizing healthcare costs. Among DRPs potential drug-drug interaction is the most important part of cardiovascular pharmacotherapy.

The role of drug-drug interaction during medicinal therapy can be considered a bivalent outcome that can be either beneficial or profoundly unintended and distressful. The identification of such unintended interaction is the primary goal of this research. As it has been already identified by the Committee for Human Medicinal Product (CHMP) of the European Medicines Agency that drug-drug interaction is a common problem during drug treatment and is the major reason behind numerous hospitalizations as a result of adverse drug reactions, sometimes serious or even fatal adverse events[12-16]. Drug-drug interaction may also result in a decrease or completely inhibit treatment efficacy. Many studies have proven the significance of pharmacists in identifying and resolving potential drug-drug interactions through timely interventions. Gattis et al[14] observed that including a drug specialist as an individual from a multidisciplinary heart failure (HF) group altogether diminished mortality and HF occasions. Studies evaluating the pervasiveness of potential drug-drug cooperation's in hospitalized cardiovascular patients and the meaning of drug specialist mediation in such cases are lacking in India. The potential for drug collaboration is higher with cardiovascular drugs[15,16,17] and there is gives an account of expected DDIs in the cardiology division from India.[18,19] No examinations are detailing the real incidence of DDIs in the Indian setting. Henceforth, the current review was intended to evaluate the incidence and example of DDIs in hospitalized heart patients in a tertiary consideration emergency clinic, with the appraisal of a planned report on the effect of clinical drug specialist intercessions in the management of patients with cardiovascular diseases.

Materials and methods

Prospective Interventional Study was conducted in Cardiology and General Medicine Departments. 220 prescription was evaluated out of which 140 prescription had pDDIs. The patient demographics and all medically relevant information were noted in a predefined data collection form. On the other hand, these case outlines were reviewed for potential drug interactions, drugs associated with interactions (route, indication frequency, dose, therapy duration), lab examinations, followed readily for evaluating drug connection and drug specialist's intercession. The progressions and the everyday notes in the case sheets were followed until the patient was released or moved to different wards. The Micromedex, Medscape, and references books were utilized as instruments to audit the prescription and case diagrams. drug interactions were sorted as minor, moderate, or significant which shows the potential dangers of the event of the potential drug interactions which can happen in patients, however not the real seriousness of drug interactions. The information acquired was utilized to classify interactions dependent on the instrument as pharmacokinetic or pharmacodynamics. The pharmacokinetic drug interactions were additionally sorted into interactions dependent on ingestion, conveyance, digestion, and end. The severities of the

interactions were evaluated and classified as major (can cause permanent harm or life hazard), moderate (can cause mischief and treatment are required) or minor (can cause little or no clinical impact, with no treatment required). The information was put away privately and exposed to additional examination utilizing appropriate programming.

Result and discussion

The present study identified the pattern of pDDIs among patients admitted to the cardiac unit of the general medicine ward. The data of 220 patients admitted to the inpatient ward during the period October 2019 and March 2020 were analyzed for assessment of potential drug interaction. Among them, 140 patients had at least one potential drug interaction. The mean age of the study population was 64.43 (±14.58) years which is in agreement with the study conducted in Nepal[20]. However, another study conducted in the cardiology ward of South Indian hospital reported lower mean age of 57.27±14.0 years. In the group of 140 cardiac patients, 67.85% were males that are in line with the fact that men are more prone to heart disease compared to women of similar age[17]. A study conducted in Bangladesh showed higher (72%) men's dominance in cardiac patients[16]. The majority of the study subjects were in a group of geriatric (75.71%), which is related to more incidence of heart disease in the older population. In general, elderly patients are at higher risk for DDIs because they are likely to have multiple diseases and polypharmacy that usually occur with an increased duration of disease conditions and altered physiology. In many of the reported studies, age more than 60 was reported as an independent risk factor for DDIs.[21]

It was observed that 83 (59.28%) had diabetes mellitus type 2 as a major co-morbidity which is similar to a study conducted in Tamil Nadu53. Comorbidity increases the total burden of the illness in a patient and also contributes to clinical outcomes as well as to economic outcomes. Hypertension (65%) was the most common diagnosis followed by CHF (28.67%) and MI (19.28%). A similar result was reported by other studies conducted on cardiac patients. [20] Most of the patients had a hospital stay of five to ten days. The median hospital stay was 7 days. A study conducted in Pakistan showed a median hospital stay of 6 days[22] (**Table I**).

Among 140 study population, most of the patients had hypertension (65%) as a major diagnosis. Another main diagnosis was CHF (28.67%) and MI (19.28%). The pattern of primary cardiovascular disorder is shown in **table II**.

Out of 220 prescriptions analyzed, 140 prescriptions comprised of potential drug interactions and it was found

Table I: Study patient's demographic details.

Parameter	Gender				Total	
	Male		Female			
	n	%	N	%	n	%
	Patient age (Years)					
20-30	2	1.42	1	0.71	3	2.14
31-40	5	3.57	1	0.71	6	4.28
41-50	14	10	6	4.28	20	14.28
51-60	11	7.85	4	2.85	15	10.71
61-70	28	20	15	10.71	43	30.71
71-80	27	19.28	13	9.28	40	28.57
81-90	8	5.71	5	3.57	13	9.28
Sub total	95	67.85	45	32.14	140	100
	Special population					
Geriatric	70	50	36	25.71	106	75.71
Renal impairment	5	3.57	2	1.42	7	5
Hepatic impairment	3	2.14	0	0	3	2.14
	Co-morbidities					
Diabetes Mellitus	50	35.71	33	23.57	83	59.28
CKD	2	1.42	2	1.42	4	2.857
Pulmonary Disorder	9	6.42	3	2.14	12	8.57
Seizure Disorder	3	2.14	2	1.42	5	3.57
Other	67	47.85	41	29.28	108	77.14

Table II: Primary cardiovascular diagnosis in study patients.

Main Diagnosis	Male		Female		Total	
	N	%	n	%	n	%
Hypertension	58	41.42	33	23.57	91	65
MI	22	15.71	5	3.57	27	19.28
CHF	26	18.57	14	10	40	28.57
Atrial fibrillation	2	1.42	1	0.71	3	2.14
ACS	4	2.85	4	2.85	8	5.71
CVA	6	4.28	2	1.42	8	5.71

that 234 drug interactions were present. The incidence of potential drug interaction was 63.64%. Among 234 drug interactions, 90 types of interaction combinations were identified. The studied prescription comprised 58.11% moderate interaction, 40.59% major drug interactions, and 1.28 minor drug interactions. Among them, 57.26% were pharmacodynamic drug interactions followed by 36.75% of pharmacokinetic interaction and 5.98% of unknown mechanism interactions. The summary of potential drug-drug interactions is listed in **table III**.

Table III: Summary of potential drug-drug interaction.

Parameters		Total	
		N	%
Severity	Major	95	40.59
	Moderate	136	58.11
	Minor	3	1.28
Pharmacodynamic Interaction		134	57.26
Pharmacokinetic Interaction		86	36.75
Unknown Mechanism		14	5.98
Management	Monitoring	173	73.93
	Dose adjustment	32	13.67

Among 234 drug interactions, 90 types of interaction combinations were identified. However, another study of South Indian teaching hospital identified 388 pDDIs in 249 patients involving 51 different drugs with a total of 74 different drug combinations. Cardiac patients have previously been found to have a higher chance of having drug interactions compared to other groups of patients.[23]

In most patients, the cases of one potential drug interaction were identified with a median of 1.67 potential drug-drug interactions. Among them, 30% of prescriptions had two potential drug-drug interactions. The frequency of pDDIs is shown in **table IV**.

Out of 234 drug interactions, aspirin/clopidogrel and clopidogrel/atorvastatin were the most common drug interaction pairs observed among prescribed medications. The clinical important and most common potential drug interaction pair is summarized in **table V**.

Most interactions were documented as good (44.44%) followed by fair (41.45%) and excellent (14.10%). The documentation of pDDIs is shown in **table VI**.

Most interactions were classified as not specified, accounting for 60.25%. Whereas 31.19% were of delayed-type. The onset of pDDI is listed in **table VII**.

Table IV: Frequency of drug interaction in the study population.

Frequency of pDDI	Male		Female		Total	
	N	%	n	%	n	%
1	52	37.14	23	16.42	75	53.57
2	25	17.85	17	12.14	42	30
3	14	10	5	3.57	19	13.57
4	2	1.42	0	0	2	1.42
5	2	1.42	0	0	2	1.42

N=140

Table V: Top 10 common pDDI.

pDDI pair	Effect	Male		Female		Total	
		N	%	N	%	n	%
Aspirin/Clopidogrel	bleeding	13	5.55	3	1.28	16	6.83
Clopidogrel/atorvastatin	Decreasedefficacy	11	4.70	5	2.13	16	6.83
Atorvastatin/amiodarone	rhabdomyolysis	7	2.99	0	0	7	2.99
Aspirin/Acenocoumarol	bleeding	3	1.28	3	1.28	6	2.56
Atorvastatin/Azithromycin	rhabdomyolysis	5	2.13	1	0.42	6	2.56
Atorvastatin/Clarithromycin	rhabdomyolysis	3	1.28	3	1.28	6	2.56
Acenocoumarol/Clopidogrel	bleeding	3	1.28	2	0.85	5	2.13
Carvedilol/aspirin	Decreased efficacy	3	1.28	2	0.85	5	2.13
Insulin/aspirin	hypoglycaemia	3	1.28	2	0.85	5	2.13
Ramipril/Spironolactone	hyperkalaemia	3	1.28	2	0.85	5	2.13

Table VI: Documentation of Pddi.

Documentation of pDDI	Male		Female		Total	
	N	%	n	%	n	%
Excellent	22	9.401	11	4.700	33	14.10
Good	64	27.35	40	17.09	104	44.44
Fair	64	27.35	33	14.10	97	41.45

Table VII: Onset of pDDI.

Onset of pDDI	Male		Female		Total	
	N	%	n	%	n	%
Rapid	12	5.12	8	3.41	20	8.54
Delayed	47	20.08	26	11.11	73	31.19
Not Specified	91	38.88	50	21.36	141	60.25

Of the pDDIs identified, 60.25% were not specified and 31.19% were of delayed onset in nature. This implies that even if there was an interaction occurring during the concomitant administration, it may not manifest itself immediately. On the off chance that these combinations of drugs were to be forged ahead an outpatient premise, this might actually prompt decreased efficacy prompting therapeutic failures or potential for delayed adverse events. Subsequently the duration of concomitant medication use ought to likewise be considered while prescribing pertinent associating drugs. Most of the interactions were documented as good (44.44%). This suggested that most of the interaction ratings were reliable.

Among 234 drug interactions aspirin (19.65%) and atorvastatin (17.09%) were the most common object drug involved in potential drug interactions. Common object drug involved in drug interaction is given in **table VIII**.

Among 234 drug interactions, aspirin (10.68%) and clopidogrel (9.48%) were the most common precipitant drug involved in drug interaction, which is shown in **table IX**.

Many of the commonly used cardiovascular drugs interact with one another. These drugs can be utilized together to treat heart conditions following a danger advantage appraisal. Numerous clinicians probably balance the dangers of pDDIs against the advantages while prescribing patients with multidrug regimens. A model would be joined anticoagulant antiplatelet treatment where an expansion in the danger of drain with the consolidated treatment should be considered against the dangers of thromboembolism without it. Benefits with multidrug regimens are unlikely to always outweigh their risks; therefore, decisions regarding prescriptions must always be tailored to suit each patient.

This study showed the median number of 1.67 pDDIs in cardiac patients. A study held earlier at ATH reported a similar median number of pDDIs in cardiac patients[23]. On analyzing the mechanism of drug interaction identified here, pharmacodynamic type interaction (57.26%) was found in a higher number compared to pharmacokinetic type (36.75%) (). The findings obtained here are in contrast to those reported by Vonbach *et al*.[24] and Aparasu *et al*.[25] who reported 76% of pharmacokinetic and 22% of pharmacodynamic interactions respectively.

The significance of pDDIs was classified according to three levels of scale. Of 234 drug interactions, the majority were moderate and major drug interactions. Moderate interaction comprised 54.11% followed by major 40.59%. The severity of pDDIs is shown in **table X**.

Of the total pDDIs identified, the interacting combination of moderate severity (58.11%) constituted the majority of pDDI. The major severity interacting combination identified was 40.59%. This finding is similar to most of the DDI studies conducted worldwide.

Among major drug interactions, aspirin/clopidogrel[16] was the most common pDDI. The important and common major drug interaction is summarized in **table XI**.

Among moderate drug interactions, clopidogrel/atorvastatin[16] was most commonly observed. The common moderated drug interaction is listed in **table XII**.

The most common interacting pair identified were aspirin/clopidogrel, clopidogrel/atorvastatin, atorvastatin/amiodarone, and atorvastatin/azithromycin. The pDDIs

Table VIII: Common object drug involved in drug interaction.

Object Drug	Male		Female		Total	
	N	%	n	%	n	%
Aspirin	28	11.96	18	7.69	46	19.65
Atorvastatin	28	11.96	12	5.12	40	17.09
Clopidogrel	18	7.69	9	3.84	27	11.53
Insulin	11	4.700	6	2.56	17	7.26
Metformin	12	5.12	5	2.13	17	7.26

Table IX: Common precipitant drug involved in drug interactions.

Precipitant Drug	Male		Female		Total	
	N	%	n	%	n	%
Aspirin	15	6.41	10	4.27	25	10.68
Clopidogrel	16	6.83	6	2.56	22	9.40
Atorvastatin	11	4.70	5	2.13	16	6.83
Amlodipine	7	2.99	5	2.13	12	5.12
Nebivolol	6	2.56	4	1.709	10	4.27

Table X: Severity of pDDIs.

Severity of pDDI	Male		Female		Total	
	N	%	n	%	n	%
Major	59	25.21	36	15.38	95	40.59
Moderate	88	37.60	48	20.51	136	54.11
Minor	3	1.28	0	0	3	1.28

involving aspirin (19.65%) and atorvastatin (17.09%) were most common. The values obtained here are similar to a study in India where Patel et al reported aspirin (44.85%) followed by atorvastatin (7.22%). Similarly, Smithburger *et al*. (2010)[26] reported the involvement of blood coagulation modifier in a maximum number of pDDIs. This might be due to the frequent use of this drug class among the cardiac patients in the present study. Decreased efficacy was the commonest clinical consequence in 56(23.93%) cases followed by bleeding (21.36%). A study conducted in the cardiology department of Kasturba Medical College reported bleeding (86.63%) as the commonest clinical consequence. The most common management plan found in the present study for most of the drug interaction was monitoring and dose adjustment; this is similar to the results reported by Bergk and colleagues[27].

The classification of potential drug-drug interactions was made based on their mechanism like pharmacodynamic, pharmacokinetic or unknown. Among 234 drug interactions, 57.26% were pharmacodynamic, 36.75% were pharmacokinetic and 5.98% were unknown. Among pharmacokinetics, 23.98% were metabolism interaction. The mechanism of pDDIs is shown in **table XIII**.

Decreased efficacy was the commonest clinical consequence in 56(23.93%) cases. Bleeding (21.36%) and hypo or hyperglycemia (19.23%) were other common clinical effects of interaction. The clinical effect of pDDIs are summarized in **table XIV**.

Table XI: Top 10 Major pDDI.

Object Drug	Precipitant Drug	Effect	Documentation	Frequency	Management
Acenocoumarol	Clopidogrel	bleeding	fair	5	Monitor INR
Aspirin	Acenocoumarol	Bleeding	Fair	6	Monitor INR
Aspirin	Clopidogrel	Bleeding	Fair	16	Monitor INR
Aspirin	Heparin	Bleeding	Fair	4	Monitor INR
Atorvastatin	Clarithromycin	Rhabdomyolysis	Good	6	Dose adjustment
Atorvastatin	Diltiazem	Rhabdomyolysis	good	4	Dose adjustment
Atorvastatin	Fluconazole	Rhabdomyolysis	fair	3	Monitor for toxicity
Domperidone	Amlodipine	QT prolong	Fair	4	Monitor ECG
	Cilnidipine	QT prolong	fair	4	Monitor ECG
Ramipril	Spironolactone	Hyperkalaemia	good	5	Monitor Serum K

Table XII: Top 10 moderate pDDI.

Object Drug	Precipitant Drug	Effect	Documentation	Frequency	Management
Aspirin	Furosemide	Decreased efficacy	good	4	Monitor BP
Aspirin	Spironolactone	toxicity	excellent	4	Monitor for toxicity
Atorvastatin	amiodarone	Rhabdomyolysis	good	7	Monitor for toxicity
Atorvastatin	azithromycin	Rhabdomyolysis	good	6	Monitor for toxicity
Atorvastatin	phenytoin	Decreased efficacy	good	4	Dose adjustment
Atorvastatin	Domperidone	QT prolong	fair	4	Monitor ECG
Carvedilol	Aspirin	Decreased efficacy	good	5	Monitor BP
Clopidogrel	atorvastatin	Decreased efficacy	excellent	16	Alternative therapy
Insulin	Aspirin	Hypoglycemia	fair	5	Monitor blood glucose
Ramipril	Aspirin	Decreased efficacy	fair	4	Monitor BP

Table XIII: Mechanism of potential drug interaction.

Mechanism		Male		Female		Total	
		N	%	N	%	n	%
Pharmacokinetic	Absorption	2	0.85	0	0	2	0.854
	Distribution	16	6.83	7	2.99	23	9.82
	Metabolism	39	16.66	17	7.26	56	23.93
	Excretion	1	0.42	4	1.70	5	2.13
Subtotal		**58**	**24.78**	**28**	**11.96**	**86**	36.75
Pharmacodynamic	Synergism	67	28.63	35	14.95	102	43.58
	Antagonism	18	7.69	14	5.98	32	13.67
Subtotal		**85**	**36.32**	**49**	**20.94**	**134**	57.26
Unknown		7	2.99	7	2.99	14	5.98

Table XIV: Clinical effect of pDDI.

Clinical effect	Male		Female		Total	
	N	%	n	%	n	%
Bleeding	33	14.10	17	7.26	50	21.36
Decreased efficacy	31	13.24	25	10.68	56	23.93
Hypotension	4	1.70	5	2.13	9	3.84
Rhabdomyolysis	20	8.54	7	2.99	27	11.53
Increased Toxicity	21	8.97	13	5.55	34	14.52
Hypo or hyperglycaemia	32	13.67	13	5.55	45	19.23
QT prolongation	9	3.84	4	1.709	13	5.55

The drug interaction software by Micromedex-2 showed that monitoring for the adverse drug effects 173 (73.93%) was the most popular interven¬tion followed by dose adjustment 32 (13.67%) and use of alternative 24 (10.25%) following potential drug-drug interactions. The detailed management of potential drug interaction is listed in **table XV**.

Conclusion

This study attempted to assess the potential drug-drug interaction in the prescription of cardiac patients in an inpatient hospital setting. This study also examined patient, drug characteristics, causality, and severity of pDDIs. This study shows that DDIs are frequent among hospitalized cardiac patients. About 234 drug interactions were reported during the study period with a median number of 1.67 pDDIs in the cardiac patients. This study emphasizes the need to consider pDDIs during therapeutic planning, protect patients from the consequence of drug interactions. In addition, providing DDI-related information to the prescribers and drug interaction alert software to the dispensing pharmacist can play a vital role in minimizing the incidence rate of DDI.

The majority of interactions were pharmacodynamic, having moderate severity. Anti-platelets and anti-coagulants were commonly implicated in many PDDIs in this study and therefore require intensive monitoring during therapy. The most common management plan found in the present study for most of the drug interaction was monitoring and dose adjustment. The study reported that about 26% of interventions proposed were accepted by physicians. The current study demonstrated the importance of routine medication review and the need for a pharmacist in a multidisciplinary team.

The incidence rate of adverse drug interactions was found to be 20%. The results provided an insight to the healthcare providers on the importance of monitoring and reporting adverse drug interactions. The active involvement of a well-trained clinical pharmacist for detecting the adverse drug interactions and delivering the awareness classes for the healthcare professionals regarding the need of reporting the incident could improve the scenario in under-reported hospitals.

Interests conflict

The authors declare no conflict of interest.

Table XV: Management of pDDI.

Management of pDDI	Male		Female		Total	
	N	%	n	%	n	%
Avoid concurrent use	0	0	1	0.42	1	0.42
Use of alternative drug	15	6.41	9	3.84	24	10.25
Discontinuation of drug	3	1.28	1	0.42	4	1.70
Dose adjustment	17	7.26	15	6.41	32	13.67
Continue with monitoring	115	49.14	58	24.78	173	73.93

References

1. Forouzanfar MH, Liu P, Roth GA, Ng M, Biryukov S, Marczak L, Alexander L, Estep K, Abate KH, Akinyemiju TF, Ali R. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990-2015. Jama. 2017 Jan 10;317(2):165-82.

2. Isetts BJ, Schondelmeyer SW, Artz MB, Lenarz LA, Heaton AH, Wadd WB, Brown LM, Cipolle RJ. Clinical and economic outcomes of medication therapy management services: the Minnesota experience. Journal of the American Pharmacists Association. 2008 Mar 1;48(2):203-14.

3. Murtaza G, Khan MY, Azhar S, Khan SA, Khan TM. Assessment of potential drug–drug interactions and its associated factors in the hospitalized cardiac patients. Saudi Pharmaceutical Journal. 2016 Mar 1;24(2):220-5.

4. Kovačević M, Vezmar Kovačević S, Radovanović S, Stevanović P, Miljković B. Adverse drug reactions caused by drug-drug interactions in cardiovascular disease patients: introduction of a simple prediction tool using electronic screening database items. Current medical research and opinion. 2019 Nov 2;35(11):1873-83.

5. Shakeel F, Khan JA, Aamir M, Hannan PA, Zehra S, Ullah I. Risk of potential drug-drug interactions in the cardiac intensive care units: a comparative analysis between 2 tertiary care hospitals. Saudi medical journal. 2018;39(12):1207.

6. Diksis N, Melaku T, Assefa D, Tesfaye A. Potential drug–drug interactions and associated factors among hospitalized cardiac patients at Jimma University Medical Center, Southwest Ethiopia. SAGE open medicine. 2019 Jun;7:2050312119857353.

7. Abraham RR. Drug related problems and reactive pharmacist interventions for inpatients receiving cardiovascular drugs. International Journal of Basic Medical Sciences and Pharmacy (IJBMSP). 2014 Jan 26;3(2).

8. Andreazza RS, De Castro MS, Köche PS, Heineck I. Causes of drug-related problems in the emergency room of a hospital in southern Brazil. Gaceta Sanitaria. 2011 Nov 1;25(6):501-6.

9. Zaredar N, Koneri R, Swamy T. Assessment of Drug Interactions in Hospitalized Cardiac Patients at a Tertiary Care Hospital, Baptist Hospital, Bangalore. World J Pharm Med Res. 2017;3(1):210-5.

10. Nascimento YD, Carvalho WD, Acurcio FD. Drug-related problems observed in a pharmaceutical care service, Belo Horizonte, Brazil. Brazilian Journal of Pharmaceutical Sciences. 2009;45:321-30.

11. Rashid K, Khan Y, Ansar F, Waheed A, Aizaz M. Potential Drug-Drug Interactions in Hospitalized Medical Patients: Data From Low Resource Settings. Cureus. 2021 Aug;13(8).

12. Garin N, Sole N, Lucas B, Matas L, Moras D, Rodrigo-Troyano A, Gras-Martin L, Fonts N. Drug related problems in clinical practice: a cross-sectional study on their prevalence, risk factors and associated pharmaceutical interventions. Scientific reports. 2021 Jan 13;11(1):1-1.

13. Origgi FC, Jacobson ER. Diseases of the respiratory tract of chelonians. Veterinary Clinics of North America: Exotic Animal Practice. 2000 May 1;3(2):537-49.

14. Gattis WA, Hasselblad V, Whellan DJ, O'Connor CM. Reduction in heart failure events by the addition of a clinical pharmacist to the heart failure management team: results of the Pharmacist in Heart Failure Assessment Recommendation and Monitoring (PHARM) Study. Archives of internal medicine. 1999 Sep 13;159(16):1939-45.
15. Hartshorn EA. Drug Interaction 1. General Considerations. Drug Intelligence. 1968 Jan;2(1):4-7.

16. Murtaza G, Khan MY, Azhar S, Khan SA, Khan TM. Assessment of potential drug–drug interactions and its associated factors in the hospitalized cardiac patients. Saudi Pharmaceutical Journal. 2016 Mar 1;24(2):220-5.

17. Nolan Jr PE, Marcus F. Cardiovascular drug use in the elderly. The American journal of geriatric cardiology. 2000 May;9(3):127-9.

18. Parthasarathi G, Ramesh M, Kumar JK, Madaki S. Assessment of drug-related problems and clinical pharmacists' interventions in an Indian teaching hospital. Journal of Pharmacy practice and Research. 2003 Dec;33(4):272-4.

19. Patel VK, Acharya LD, Rajakannan T, Surulivelrajan M, Guddattu V, Padmakumar R. Potential drug interactions in patients admitted to cardiology wards of a south Indian teaching hospital. The Australasian medical journal. 2011;4(1):9.

20. Sharma S, Chhetri HP, Alam K. A study of potential drug-drug interactions among hospitalized cardiac patients in a teaching hospital in Western Nepal. Indian journal of pharmacology. 2014 Mar;46(2):152.

21. Nag KA, Umesh M, Churi SH. Assessment of drug-drug interactions in hospitalised patients in India. Asian J Pharm Clin Res. 2011;4(1):62â.

22. Murtaza G, Khan MY, Azhar S, Khan SA, Khan TM. Assessment of potential drug–drug interactions and its associated factors in the hospitalized cardiac patients. Saudi Pharmaceutical Journal. 2016 Mar 1;24(2):220-5.

23. Ismail M, Iqbal Z, Khattak MB, Khan MI, Javaid A, Khan TM. Potential drug-drug interactions in cardiology ward of a teaching hospital. Health Med. 2012 Jan 1;6:1618-24.

24. Vonbach P, Dubied A, Krähenbühl S, Beer JH. Prevalence of drug–drug interactions at hospital entry and during hospital stay of patients in internal medicine. European journal of internal medicine. 2008 Oct 1;19(6):413-20.

25. Aparasu R, Baer R, Aparasu A. Clinically important potential drug-drug interactions in outpatient settings. Research in Social and Administrative Pharmacy. 2007 Dec 1;3(4):426-37.

26. Smithburger, P. L., Kane-Gill, S. L., & Seybert, A. L. (2010). Drug-drug interactions in cardiac and cardiothoracic intensive care units. Drug safety, 33(10), 879-88.

27. Bergk V, Gasse C, Rothenbacher D, Loew M, Brenner H, Haefeli WE. Drug interactions in primary care: impact of a new algorithm on risk determination. Clinical Pharmacology & Therapeutics. 2004 Jul;76(1):85-96.

eISSN 2255-0569

ORIGINAL

Drug utilization and evaluation of antihypertensive medications among patients with hypertension and type 2 diabetes mellitus in a tertiary care hospital, India

Utilización y evaluación de medicamentos antihipertensivos entre pacientes con hipertensión y diabetes mellitus tipo 2 en un hospital de atención terciaria, India

Seyedeh Golnoosh Mortazavi, Ramesh C, Dharshini N.M.

Doctors of Pharmacy, Department of Pharmacy Practice, East-West College of Pharmacy, Bengaluru, India.

Corresponding author
Seyedeh Golnoosh Mortazavi
Department of Pharmacy Practice,
East-West College of Pharmacy, Bengaluru, India
E-mail: drgolnoosh.mortazavi70@gmail.com

Received: 19 - X - 2021
Accepted: 17 - XII - 2021

doi: 10.3306/AJHS.2022.37.01.118

Abstract

Objective: To find out drug utilization evaluation of antihypertensive medications among patients with hypertension and type 2 diabetes mellitus in a tertiary care hospital.

Methodology: This was a Prospective Observational study that was performed on 195 patients. The Source of data was collected from the patient's case sheets obtained from the record section. Ethical clearance was taken from the institutional ethical committee. Drugs data on the utilization of antihypertensive medications among patients with hypertension and type 2 diabetes mellitus and patient's data were computed using MS Excel and statistical analysis was done by using SPSS (Statistical Package for the social sciences).

Result: Our study shows that the majority 83(42.56%) of patients were of age group 51-60 years, 115 (58.97%) of patients belonging to male and 80 (41.02%) of patients female. Treatment was 101(51.79%) of patients with single anti-hypertensive drugs and 94 (48.20%) patients with combination therapy Monotherapy shows that patients 29 (28.71%) were prescribed with CCB and very less number of patients 2 (1.98%) were prescribed with α blockers and most of the patients 23(24.46%) were prescribed with ARB, CCB and ARB + β- blockers.

Conclusion: a study on the assessment of prescribing patterns for hypertension confirmed that monotherapy was prescribed more than combination therapy. Specify with the guidelines, CCB was the most frequently prescribed drug class followed by ACE inhibitors, ARBs, diuretics, β-blockers, and α blockers. In combination therapy, ARB + CCB was mostly prescribed.

Keywords: Hypertension, Antihypertensive medication, Diabetes mellitus type2.

Resumen

Objetivo: Averiguar la evaluación de la utilización de medicamentos antihipertensivos entre los pacientes con hipertensión y diabetes mellitus tipo 2 en un hospital de atención terciaria.

Metodología: Se trata de un estudio observacional prospectivo que se realizó en 195 pacientes. La fuente de datos se recogió de las hojas de los casos de los pacientes obtenidas de la sección de registros. Se obtuvo la autorización ética del comité ético institucional. Los datos sobre la utilización de medicamentos antihipertensivos entre los pacientes con hipertensión y diabetes mellitus de tipo 2 y los datos de los pacientes se calcularon con MS Excel y el análisis estadístico se realizó con SPSS (Statistical Package for the social sciences).

Resultados: Nuestro estudio muestra que la mayoría 83 (42,56%) de los pacientes eran del grupo de edad de 51-60 años, 115 (58,97%) de los pacientes pertenecientes a los hombres y 80 (41,02%) de los pacientes mujeres. El tratamiento fue 101 (51,79%) de los pacientes con fármacos antihipertensivos únicos y 94 (48,20%) de los pacientes con terapia combinada La monoterapia muestra que los pacientes 29 (28,71%) fueron prescritos con BCC y un número muy reducido de pacientes 2 (1,98%) fueron prescritos con α-bloqueantes y la mayoría de los pacientes 23 (24,46%) fueron prescritos con ARB, CCB y ARB +β-bloqueantes.

Conclusión: un estudio sobre la evaluación de las pautas de prescripción para la hipertensión confirmó que se prescribió más la monoterapia que el tratamiento combinado. De acuerdo con las directrices, los BCC fueron los fármacos más prescritos, seguidos de los IECA, los ARA, los diuréticos, los β-bloqueantes y los α-bloqueantes. En la terapia combinada, se prescribió mayoritariamente BRA + BCC.

Palabras clave: Hipertensión, Medicación antihipertensiva, Diabetes mellitus tipo 2.

Introduction

Diabetes mellitus and hypertension are interrelated diseases that strongly predispose an individual to atherosclerotic cardiovascular complications.[1] The incidence of hypertension in patients with type 2 diabetes mellitus is approximately two-fold higher than in age-matched subjects without the disease.[2] The prevalence of hypertension coexisting with diabetes appears to be increasing mainly in the aging population as both hypertension and non-insulin-dependent diabetes mellitus incidence increases with age.[3] Hypertension has been recognized as a significant risk factor for the improvement of diabetes as well as for the advancement of miniature and macrovascular inconveniences, that is, neuropathy, nephropathy, retinopathy, coronary artery disease, stroke, peripheral vascular disease in diabetic patients.[4,5]

Effective management and treatment for hypertension need proper screening and diagnosis. Treatment includes both non-pharmacologic (lifestyle changes, dietary changes) and pharmacological i.e., medication therapy to lower blood pressure and prevent cardiovascular events such as a heart attack, stroke. There are many classes of antihypertensives, which lower blood pressure by different means. Non-pharmacological interventions should be used throughout the management of all patients with high blood pressure.[6,7]

The World Health Organization projected that 300 million people will suffer from diabetes and 1.5 billion[8] from hypertension by 2025[9]. As per the Diabetes Atlas 2006 published by the International Diabetes Federation, the number of individuals with diabetes in India as of now around 40.9 million, is relied upon to ascend to 69.9 million by 2025 except if urgent preventive advances are taken[10]. The incidence of hypertension in patients with T2DM is approximately two-overlay higher than in age-coordinated with subjects without the disease[11].

Hypertension has been identified as a significant risk factor for the development of diabetes as well as for the development of miniature and macrovascular complications, that is, neuropathy, nephropathy, retinopathy, coronary supply route disease (CAD), stroke, fringe vascular disease (PVD) in diabetic patients. It has been obvious from Framingham heart study, UKPDS (the United Kingdom Prospective Study-39), Hypertension Optimal Treatment (HOT), Systolic Hypertension in the Elderly Program (SHEP), Systolic Hypertension in Europe (SYST-Eur), Hypertension in the Very Elderly Trial (HYVET-Pilot) that diminishing in either isolated systolic or systolic-diastolic hypertension fundamentally reduces the risk of miniature and macrovascular complications and cardiovascular (CV) death or diabetes-related death[12-18]. Lowering blood pressure (BP) in patients with diabetes mellitus is more cost-effective than tight blood glucose control, and beneficial results are apparent earlier[15]. Therefore, all of the hypertension management guidelines, that is, Seventh Report of Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure-2003 (JNC-7), American diabetes association (ADA) 2010, European Society of Hypertension (ESH) [18], WHO guideline[15,17,19] focused aggressively on blood pressure (BP) control in diabetic patient to below 130-135/80–85 mmHg[15,16,19].

Materials and methods

This was a Prospective and Observational study that was conducted for a period of six months from November 2017 to April 2018. A total of 195 patients from the department of cardiology and medicine, Apollo multispecialty hospital, and research center, those who have satisfied with the study criteria and consent to participate in this study were included for the study. all data were documented in data collection form and patients were followed up for any further addition of antihypertensive drugs. The blood pressure at the time of admission and during the hospital stay also was recorded. The antihypertensive drugs utilization pattern will be compared with international guideline JNC-8 to find out the extent of conformity with the guideline.

To interpret the outcome of the study, proper descriptive analysis has been carried out in this study. This model was Descriptive statistics, frequency and percentage were drawn and charts were used to represent the consolidated data for inferential statistics. Chi-square tests of independent of attribution were used to test the categorized data. The Statistical software namely SPSS 15.0, was used for the analysis of the data, and Microsoft Word and Excel have been used to generate graphs, tables, etc.

Result and discussion

Our study in **table I** represent that out of 195 patients, majority 83(42.56%) of patients were from the age group 51-60 years, followed by 59 (30.25%) of patients were from the age group 61-70, 15 (7.69%) of patients were from the age group41- 50, 12 (6.15%)of patients were from the age group 71-80, 9 (4.61%) of patients were from the age group 31-40, 8(4.10%) of patients were from the age group18-30, 6 (3.07%) of patients were from the age group81-90, 3(1.53%) of patients were from the age group >90. This result is similar to Georgy M. Varghese, *et al*.[20] study on the drug utilization pattern of antihypertensive agents in a tertiary care hospital. We observed the majority of 83 (42.56%) of patients were from the age group 51-60 years. more precautions should be taken in this age group.

Table I: Age-wise distribution.

Age distribution	Number of patients	Percentage
18-30	8	4.10%
31-40	9	4.61%
41-50	15	7.69%
51-60	83	42.56%
61-70	59	30.25%
71-80	12	6.15%
81-90	6	3.07%
>90	3	1.53%
Totals	195	99.96%

The study of body mass index distribution in **table II**, shows that out of 195 patients, 120 (61.53%) patients were obese, and the remaining 75 (38.46%) patients were under normal weight. A patient who is obese must be recommended more about reducing of weight will be healthful to in reducing blood pressure. This result is similar to Vikas Pandey, et al.[21] study on the evaluation of prescribing patterns in diabetic and hypertensive patients in a South Delhi Hospital.

Results on the vital parameter of patients in **table II**, show that out of 195 patients, 95 (48.71%) of patients were under stage 2 hypertension, followed by 60 (30.76%) of patients under stage 1 hypertension and the remaining 35 (17.94%) of patients were in prehypertension stage. This result is following JNC 8.

Table II: Demography of of the study patients.

Gender	Number of patients	Percentage
Male	115	58.97%
Female	80	41.02%
Totals	195	99.99%
BODY MASS (CATEGORY)		
Normal	75	38.46%
Obese	120	61.53%
Totals	195	99.99%
Socio-economic status		
Rural	75	38.46%
Urban	120	61.53%
Totals	195	99.99%
Social status		
Smoker	105	53.84%
Non smoker	90	46.15%
Totals	195	99.99%
Social status		
Alcoholic	101	51.79%
Non alcoholic	94	48.20%
Totals	195	99.99%
Diet pattern		
Under diet	73	37.43%
Without diet	122	62.56%
Totals	195	99.99%
Vital parameters		
Pre-hypertension 120-139 / 80-89	35	17.94%
Stage1 hypertension 130-139/ 80-89	60	30.76%
Stage2 hypertension =140mmHg/=90mmHg	95	48.71%
Totals	195	99.99%
Antihypertensive therapy		
Monotherapy	101	51.79%
Two drug combination	94	48.20%
Totals	195	99.99%

In the treatment of patients with the antihypertensive drug in **table II** represent among diabetic hypertensive patients, 101(51.79%) of patients were treated with single anti-hypertensive drugs, and 94 (48.20%) of patients were treated with antihypertensive drug combinations. This result was similar to Bipin b panda, et al.[22] study on a survey of the prescription pattern of antihypertensive drugs in hypertensive and diabetic hypertensive patients. So in this study 101 (51.79%) of patients were treated with single antihypertensive drugs.

Study on monotherapy of hypertension in **table III** shows that, out of 101 patients who underwent monotherapy for the treatment of hypertension, 29 (28.71%) of patients were prescribed with CCBs, followed by 23 (22.77%) of patients with ACE inhibitors, 20 (19.95%) of the patients with ARBs, 18 (17.82 %) of the patients with diuretics, 11 (10.89%) of the patients with β-blockers and 2 (1.98%) of the patients with α blocker. In this study, most of the patients 29 (28.71%) were prescribed calcium channel blockers, and a very less number of patients 2 (1.98%) were prescribed α blockers. This result is similar to Georgy M. Varghese, *et al*.[20] studies on drug utilization pattern of antihypertensive agents in a tertiary care hospital on utilization pattern of antihypertensive drugs in Chinese diabetic we observed calcium channel blockers with 28.71% was the most prescribed drug among patients underwent monotherapy.

A study on combination therapy in **table IV**, reveals that out of 94 patients in whom two antihypertensives were prescribed, 23 (24.46%) patients were prescribed with a combination of ARB and CCB and followed by 21 (22.34%) of patients who were prescribed with ARB

Table III: Various antihypertensive drugs prescribed to hypertensive diabetic patients.

Class of drug	Name of the drug	Number of patients	Percentage
ACE Inhibitors	Ramipril	7	6.93%
	Enalapril	12	11.88%
	Lisinopri	4	3.96%
Totals		23	22.77%
ARBs	Losartan	5	4.95%
	Telmisartan	3	2.97%
	Olmesartan	2	1.98%
	Valsartan	10	9.90%
Totals		20	19.95%
β blockers	Atenolol	4	3.96%
	Metoprolol	5	4.95%
	Carvedilol	2	1.98%
Totals		11	10.89%
α blocker	Prazosin	2	1.98%
Totals		2	1.98%
CCB	Nifedipine	3	2.97%
	Amlodipine	24	26.73%
Totals		27	28.71%
Diuretics	Hydrochlorothiazid	10	9.90%
	Furosemide	8	7.92%
Totals		18	17.82
All Totals		101	99.99%

and Diuretics, 19 (20.21%) of patients were prescribed with Diuretics and ACE I, 10(10.63%) of patients were prescribed with CCB and ACE-I, 7 (7.44%)of patients were prescribed with calcium channel blockers and β-blockers, 5 (5.31%) of patients were prescribed with CCB and Diuretics, 4 (4.25%) of patients with BB and ACE I, 3 (3.19%) of patients were prescribed with ARB + β-blockers and 2 (2.12%) of patients were prescribed with β-blockers and diuretics. In this study, most of patients 23 (24.46%) were prescribed a combination of ARB and CCB, and ARB +β-blockers was the least combination therapy prescribed among 2 (2.12%) of patients. We observed that calcium channel blockers, angiotensin-converting enzyme inhibitors, and diuretics were the most prescribed combination therapy. To some extent, this part is following JNC 8 guidelines[21,22].

Other class of medication in **table V**, prescribed along with antihypertensive therapy shows that the most commonly prescribed category of drugs among these medications was analgesics (15.38%) followed by Muscle relaxants (11.79%) multivitamins (10.70%), Anti asthmatic and COPD (8.71%), Antiarrhythmic drugs (7.17%), Miscellaneous anti-inflammatory (6.15%), Laxatives (5.64%), Drugs for anxiety and sleep disorders (5.12%), anti-malarial (4.10%), Anti-anemic drugs and Antiulcer drugs (3.58%), Antibacterial drugs (3.07%), Corticosteroids and Anti rheumatoid agents (2.56%), Lipid regulating drugs (2.05%), Cytotoxic drugs, Antidepressants Expectorants and cough syrups and (1.53%), Anticonvulsants and Anti allergies (1.02%), Anti amoebic and Systemic antifungal drugs (0.51%) Cytotoxic drugs and BCG vaccines (0.1%) respectively are the least prescribed. We observed that the analgesic group of drugs were the most prescribed drug with15.38%. this result is similar to J.M. Okonta, *et. al*[23] study on prescribing Patterns of Antihypertensive and Antidiabetic Agents in a Secondary Healthcare Institution in Nigeria.

Table IV: Antihypertensive drug therapy among hypertensive diabetic patients.

Two drug combinations	Number of patients	Percentage
ARB + D	21	22.34%
CCB + ACE-I	10	10.63%
CCB + BB	7	7.44%
ARB + CCB	23	24.46%
CCB + D	5	5.31%
ARB + BB	3	3.19%
BB + D	2	2.12%
BB + ACE I	4	4.25%
ACE I + D	19	20.21%
TOTALS	94	99.95%

Table V: Class of other medications.

Class	Number of patients	Percentage
Drugs for anxiety and sleep disorders	10	5.12%
Antiulcer drugs	7	3.58%
Laxatives	11	5.64%
Antiarrhythmic drugs	14	7.17%
Lipid regulating drugs	4	2.05%
Anti-anaemia drugs	7	3.58%
Multivitamins	21	10.70%
Anti-asthmatic and COPD	17	8.71%
Antidepressants	3	1.53%
Anti-allergies	2	1.02%
Antibacterial drugs	6	3.07%
Antimalarial drugs	8	4.10%
Anti-amoebic	1	0.51%
Corticosteroids	5	2.56%
Anticonvulsants	2	1.02%
Cytotoxic drugs	3	1.53%
Analgesics	30	15.38%
Anti-rheumatoid agents	5	2.56%
Miscellaneous anti-inflammatory	12	6.15%
Muscle relaxants	23	11.79%
Systemic antifungal	1	0.51%
Expectorants and cough syrups	3	1.53%
Totals	195	99.82%

Conclusion

This was a prospective observational study, assessment of prescribing patterns in hypertensive patients with type 2 diabetes mellitus and it confirmed that out of 195 patients, the majority of patients were from the age group 51-60 years, six patients were from the age group 81-90, 3 patients were from the age group >90. Out of 195 patients, 115 patients belonging to males and 80 of patients belonging to a female. Out of 195 patients, Most of them were obese and only 75 patients were under normal weight. The number of patients who were smoker was more compared to the patients were a non-smoker. The number of alcoholic patients was higher than the number of non-alcoholic patients. The majority of patients are without diet and only around a third of the patients were under diet. Out of 195 patients, 95 patients were under stage 2 hypertension, followed by 60 patients under stage 1 hypertension, and the remaining patients were in the pre-hypertension stage. Approximately half of the patients were treated with single anti-hypertensive drugs and half of the patients were treated with antihypertensive drug combinations. Out of 101 patients who underwent monotherapy for the treatment of hypertension, most of them were prescribed calcium channel blockers, and a very less number of patients2 were prescribed with α blockers. Out of 94 patients in whom two antihypertensives were prescribed, most of the patients were prescribed a combination of ARB and CCB, and ARB +β-blockers was the least combination therapy prescribed among patients. We observed that calcium channel blockers, angiotensin-converting enzyme inhibitors, and diuretics were the most prescribed combination therapy. The most commonly prescribed category of drugs among these medications was analgesics followed by Muscle relaxants multivitamins, Anti asthmatic and COPD, Antiarrhythmic drugs, Miscellaneous anti-inflammatory, Laxatives, Drugs for anxiety and sleep disorders, anti-malarial, Anti-anaemia drugs and Antiulcer drugs, Antibacterial drugs, Corticosteroids and Anti rheumatoid agents. Role of pharmacist Drug utilization and evaluation of antihypertensive medications among patients with type 2 diabetes mellitus.

Interests conflict

The authors declare no conflict of interest.

References

1. Riaz F, Al Shaikh A, Anjum Q, Mudawi Alqahtani Y, Shahid S. Factors related to the uncontrolled fasting blood sugar among type 2 diabetic patients attending primary health care center, Abha city, Saudi Arabia. International Journal of Clinical Practice. 2021 Mar 23:e14168.

2. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. The lancet. 2005 Jan 15;365(9455):217-23.

3. Venugopal K, Mohammed MZ. Prevalence of hypertension in type-2 diabetes mellitus. CHRISMED Journal of Health and Research. 2014 Oct 1;1(4):223.

4. Muntner P, Woodward M, Mann DM, Shimbo D, Michos ED, Blumenthal RS, et al.. Comparison of the Framingham Heart Study hypertension model with blood pressure alone in the prediction of risk of hypertension: the Multi-Ethnic Study of Atherosclerosis. Hypertension. 2010 Jun 1;55(6):1339-45.

5. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. Jama. 2015 Feb 10;313(6):603-15.

6. Viera AJ. Screening for hypertension and lowering blood pressure for prevention of cardiovascular disease events. Medical Clinics. 2017 Jul 1;101(4):701-12.

7. Nelson MR, Reid CM, Krum H, Muir T, Ryan P, McNeil JJ. Predictors of normotension on withdrawal of antihypertensive drugs in elderly patients: prospective study in second Australian national blood pressure study cohort. Bmj. 2002 Oct 12;325(7368):815.

8. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes care. 2004 May 1;27(5):1047-53.

9. Heizhati M, Li N, Shi Q, Yao X, Zhang D, Zhou K, et al. Effects of Simplified Antihypertensive Treatment Algorithm on Hypertension Management and Hypertension-Related Death in Resource-Constricted Primary Care Setting between 1997 and 2017. International journal of hypertension. 2021 Jul 13;2021.

10. Ramachandran A, Snehalatha C, Kapur A, Vijay V, Mohan V, Das AK, et al. High prevalence of diabetes and impaired glucose tolerance in India: National Urban Diabetes Survey. Diabetologia. 2001 Sep;44(9):1094-101.

11. Miller GJ, Maude GH, Beckles GL. Incidence of hypertension and non-insulin dependent diabetes mellitus and associated risk factors in a rapidly developing Caribbean community: the St James survey, Trinidad. Journal of Epidemiology & Community Health. 1996 Oct 1;50(5):497-504.

12. Zhao H, Ma Z, Sun Y. Predict Onset Age of Hypertension Using CatBoost and Medical Big Data. In2020 International Conference on Networking and Network Applications (NaNA) 2020 Dec 10 (pp. 405-409). IEEE.

13. UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. Bmj. 1998 Sep 12;317(7160):713-20.

14. Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. The Lancet. 1998 Jun 13;351(9118):1755-62.

15. Kostis JB, Davis BR, Cutler J, Grimm RH, Berge KG, Cohen JD, et al. Prevention of heart failure by antihypertensive drug treatment in older persons with isolated systolic hypertension. Jama. 1997 Jul 16;278(3):212-6.

16. Fuller J, Stevens LK, Chaturvedi N, Holloway JF. Antihypertensive therapy for preventing cardiovascular complications in people with diabetes mellitus. The Cochrane database of systematic reviews. 2007 Jul 18(4):CD002188-.

17. Bakris GL, Williams M, Dworkin L, Elliott WJ, Epstein M, Toto R, et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. American journal of kidney diseases. 2000 Sep 1;36(3):646-61.

18. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. hypertension. 2003 Dec 1;42(6):1206-52.

19. Staessen JA, Gasowski J, Wang JG, Thijs L, Den Hond E, Boissel JP, et al. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. The Lancet. 2000 Mar 11;355(9207):865-72.

20. Varghese GM, Imran M, Pavan Gara CT, Suresh V, Basavaraj K. Study On Drug Utilization Pattern Of Antihypertensive Agents In A Tertiary Care Hospital. World Journal of Pharmacy and Pharmaceutical Sciences. 2016;5:1078-89.

21. Pandey V, Hoda U, Aqil M, Sharma M, Akhtar M, Khandelwal R, et al. Evaluation of prescribing patterns in diabetic and hypertensive patients in a South Delhi Hospital. International Journal of Basic & Clinical Pharmacology. 2014 May;3(3):490.

22. Panda BB, Pati MR, Sahu PK. Survey of prescription pattern of antihypertensive drugs in hypertensive and diabetic hypertensive patients. Asian J Pharm Clin Res. 2015;8(1):250-2.

23. Okonta JM, Nduka SO, Idodo VE. Prescribing pattern of antihypertensive and antidiabetic agents in a secondary healthcare institution in Nigeria. Journal of pharmaceutical sciences and research. 2013;5(1):12.

eISSN 2255-0569

ORIGINAL

The relationship between anxiety and sleep quality in iranian pregnant women

Relación entre la ansiedad y la calidad del sueño en mujeres embarazadas iraníes

Maryam Mohammad Ibrahim[1], Fatima Muhammad Ibrahim[1], Hadya Abboud Abdel Fattah[2]

1. PhD Reproductive Health Department, School of Nursing and Midwifery, Tehran University of Medical Sciences, International Campus (TUMS-IC), Tehran, Iran.
2. BSN, M.Ed., PhD, Senior Lecturer Fatima College of Health Sciences, United Arab Emirates

Corresponding author
Maryam Mohammad Ibrahim
School of Nursing and Midwifery, Tehran University of Medical Sciences, International Campus (TUMS-IC), Tehran, Iran
E-mail: maryam.mohammad.87@gmail.com

Received: 20 - X - 2021
Accepted: 20 - XII - 2021

doi: 10.3306/AJHS.2022.37.01.123

Abstract

Objectives: Sleep disturbances are common in women, especially during pregnancy. Anxiety is a common disorder that can be accompanied by obstetric, neonatal and postnatal complications. This can result in emotional and psychological consequences in pregnant women. We aimed to evaluate the relationship between the anxiety and the sleep quality among pregnant women in Mashhad - Iran, in 2020.
Materials and methods: This cross-sectional study was conducted on 565 pregnant women who were referred to Mashhad health centers. Two-stage cluster sampling method was used to choose the patients. The data were collected using a socio-demographic questionnaire, state-trait anxiety inventory (STAI) and Pittsburgh Sleep Quality Index (PSQI). A general linear model was used in order to estimate the effect of independent variables (sleep quality and socio-demographic characteristics) on the dependent variable (anxiety).
Results: The mean ± standard deviation (SD) sleep quality score was 3.6 ± 1.4 (range: 0-21), and the mean anxiety score was 4.7 ± 3.7 (range: 0-30). A significant correlation was found between anxiety score and total score of sleep quality and all its sub-domains except delay in sleeping. According to the adjusted general linear model, sleep quality, age, marital relationship, the satisfaction of husband job, place of residence and place of receiving prenatal care were predictors of anxiety.
Conclusion: Considering the significant relationship between anxiety and sleep quality in pregnant women, sleep hygiene education will be necessary in order to decrease the anxiety of pregnant women.

Keywords: Anxiety, pregnancy, sleep, Pittsburgh Sleep Quality Index, state-trait anxiety inventory.

Resumen

Objetivos: Los trastornos del sueño son frecuentes en las mujeres, especialmente durante el embarazo. La ansiedad es un trastorno común que puede acompañarse de complicaciones obstétricas, neonatales y postnatales, esto puede provocar consecuencias emocionales y psicológicas en las mujeres embarazadas. Nuestro objetivo es evaluar la relación entre la ansiedad y la calidad del sueño entre las mujeres embarazadas en Mashhad - Irán, en 2020.
Materiales y métodos: Este estudio transversal se llevó a cabo en 565 mujeres embarazadas que fueron remitidas a los centros de salud de Mashhad. Se utilizó el método de muestreo por conglomerados en dos etapas para elegir a las pacientes. Los datos se recogieron mediante un cuestionario sociodemográfico, el inventario de ansiedad estado-rasgo (STAI) y el índice de calidad del sueño de Pittsburgh (PSQI). Se utilizó un modelo lineal general para estimar el efecto de las variables independientes (calidad del sueño y características sociodemográficas) sobre la variable dependiente (ansiedad).
Resultados: La puntuación media ± desviación estándar (DE) de la calidad del sueño fue de 3,6 ± 1,4 (rango: 0-21), y la puntuación media de la ansiedad fue de 4,7 ± 3,7 (rango: 0-30). Se encontró una correlación significativa entre la puntuación de ansiedad y la puntuación total de la calidad del sueño y todos sus subdominios, excepto el retraso en el sueño. Según el modelo lineal general ajustado, la calidad del sueño, la edad, la relación conyugal, la satisfacción del trabajo del marido, el lugar de residencia y el lugar donde se recibe la atención prenatal fueron predictores de la ansiedad.
Conclusiones: Teniendo en cuenta la relación significativa entre la ansiedad y la calidad del sueño en las mujeres embarazadas, la educación en higiene del sueño será necesaria para disminuir la ansiedad de las mujeres embarazadas.

Palabras clave: Ansiedad, embarazo, sueño, Índice de calidad del sueño de Pittsburgh, inventario de ansiedad estado-rasgo.

Introduction

Sleep is a systematic and organized behavior that is repeated on a regular basis. Sleep substantially contributes to revitalization of mental and physiological processes and is required for accepting new tasks[1]. Common sleep disturbances consist of insomnia, frequent waking in the night, increasing sleepiness during the daytime, mood complaints and unusual feelings during sleep[2]. About two-thirds of pregnant women complain of abnormal sleep patterns. Sleep disorders during pregnancy usually increase with every trimester. Furthermore, total sleep time and night sleep increase during the first trimester[3,4]. Pregnant women suffer from sleep onset problems, frequent awakenings, reduced night sleep hours, and decreased sleep efficiency, which starts as early as week 12 of pregnancy to 2 months postpartum[5].

Okun and colleagues indicated that 25% of pregnant women suffer from significant sleep disorders in the first gestational trimester, and it increases up to 15% in the third trimester. Meanwhile, sleep duration during pregnancy decreases progressively 6. Guendelman et al. also reported that 26% of healthy nulliparous women who were interviewed between 6 and 20 weeks of pregnancy had a night sleep of < 7 hours[7,8].

Sleep quality refers to an individual's mental characteristics and sleep experience (e.g. feeling relaxed and satisfied after waking up). Various factors such as illness, pain, mental stresses etc. can affect the sleep quality and quantity[9]. In addition, diseases such as colic, iron deficiency anemia and allergies[10,11].

Pregnancy is a highly critical period for developing mental health problems, and anxiety disorders are common mental disorders during pregnancy with a prevalence rate of 1 to 26% in low- and middle-income countries[12]. Any person may experience anxiety due to various stressors or environmental pressures[13].

This serious psychological factor extremely affects mothers and fetuses during pregnancy[14]. Prenatal anxiety may also affect the fetus through specific mechanisms. First, hormones such as catecholamines are released due to maternal stress, and pass across the placenta which affects fetal brain development at 12-22 weeks of pregnancy.

These hormones also result in umbilical artery contraction which in turn reduces oxygen and nutrients supply to the fetus[15]. In addition, maternal anxiety leads to preterm birth, emotional problems, attention deficit hyperactivity disorder (ADHD) symptoms, growth retardation, crying and restlessness, and low mental development in infants[16,17]. In a study, depression and anxiety disorders were shown to predict infant sleep disorder[18], such that newborns with anxious mothers experience higher restlessness rates[19]. In this regard, 874 mothers between 20 and 34 years of age and their infants participated in a cohort study, and researchers found that maternal psychological distress affects infants sleep quality[20].

Materials and methods

Study Design and Participants

This cross-sectional study was conducted on 565 pregnant women with pregnancy ages equal to 15 weeks or more (the second or third trimester of pregnancy) who visited health centers, based in Mashhad-Iran in 2020. The inclusion criteria consisted of Iranian nationality, being a Muslim, living in Mashhad, being willing to participate in the study, having a singleton pregnancy, living with the husband during the study, and having no employment at night shift. The exclusion criteria included having multiple pregnancies, pregnancy with fetal abnormalities, history of anxiety during the non-pregnancy period, intense family dispute with husband as asserted by the individual, having infertility history, the record of visiting a physician for mental problems, history of taking medicines or hospitalization, medical problems during pregnancy such as thyroid, hypertension and high-risk pregnancy, history of mental illness –especially anxiety– in first degree relatives, taking medicines for sleep disorders such as insomnia, oversleeping and frequent waking, facing with problems such as the death of relatives, severe accident, serious illness of family members, financial problems, losing one's and husband's jobs and/or the stress caused by changing residence within last six months.

Sampling

A 2-stage cluster sampling method was used. Sampling was conducted in the health centers and bases of Mashhad city. Among 45 centers and 20 bases in this city, one-third of the health centers and bases (10 centers and 5 bases) were selected randomly through: https://www.random. org/. Twenty-one centers were governmental and 8 centers were private. These centers are not referral ones. The number of pregnant women selected from each health center was proportional to the size of the women covered by each center. For sampling, first, the number of pregnant women covered by the selected health center was determined; Then, the names of eligible women were listed, and they were numbered. The final participants to be included in the study were randomly selected based on the quota of each center. The selected pregnant women were called and invited for the study. The participants were first assessed in terms of basic information and eligibility criteria. If they were eligible for being included in the study, comprehensive information was provided for them about the aims of the study and confidentiality. If they were willing to participate in the research, the informed consent form was filled out by participants and the data collection tool was completed via an interview with participants.

Data Collection Tool

Data collection tool included socio-demographic characteristics questionnaire, state-trait anxiety inventory (STAI) and Pittsburgh Sleep Quality Index (PSQI).

The PSQI measures an individual's attitude toward sleep quality during 4 weeks. It has 7 subscales including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medication and daily daytime dysfunction. The score of each subscale is between 0 and 3. The sum of the scores of these seven components comprises the total score of the scale ranging from zero to 21. The lower score shows the better situation of sleep. A score higher than 5 indicates the unfavorable quality of sleep. The reliability of the scale was 0.83. Its validity was reported by scale's creators at the appropriate level with the sensitivity of 89.6% and specificity of 86.5% in patient participants compared with the control group[21]. The scale was also used in a study on pregnant women in Mashhad-Iran[22].

Sample Size

Sample size was estimated 377 individuals with respect to the study of Baghi et al and considering d = 0.05 about the mean score of sleep quality (m = 10.5, standard deviation [SD] = 2.5, and α = 0.05). As it was a cluster sampling, final sample size was calculated 565 individuals with respect to the design effect of 1.5. Statistical analysis of the data was performed using SPSS version 21. Descriptive statistics including frequency and percentage, mean, median, percentile 25 to percentile 75 and SD were used for describing socio-demographic characteristics, sleep quality, and anxiety. Normality of the quantitative data was measured by skewness and kurtosis and they had normal distribution except components of sleep duration, habitual sleep efficiency and use of sleeping medication. Pearson correlation test was used for determining the relationship between anxiety and sleep quality and its components with normal distribution. The Spearman correlation was used for abnormal variables. Any variable was included in the general linear model (GLM) individually in an unadjusted form to determine the relationship between socio-demographic characteristics and the score of anxiety. Then the variables with P value lower than 0.05 based on unadjusted GLM were entered into the adjusted GLM. The P value lower than 0.05 was considered significant

Results

In this study, 612 pregnant women were assessed according to eligibility criteria and 47 women were excluded because they were not eligible. Finally, 565 women participated in the study by filling out the questionnaires. Mean (SD) age of participants was 28.7 years (5.5) and body mass index was 25.2 (3.2) kg/m2. One-third of participants (33.5%) had diploma education and majority of them (98.0%) were housewives. Almost two-thirds of women (63.8%) reported that their monthly income is less than enough amount. Ninety-five percent of women received prenatal care from health centers and about two thirds of respondents (64%) were satisfied with their husband job. More than three-quarters of women (76.5%) reported that they were willing to pregnancy. Seventy-eight percent of women and 76% of their husbands were satisfied with fetal sex (**Table I**). The mean (SD) sleep quality score was 3.6 (1.4) from attainable score of 0-21 and mean (SD) anxiety score was 4.7 (3.7) from attainable score of 0-30. About 6% of women suffered from sleep disorders. Women had the highest mean score or the worst status in subscale of impaired daily dysfunction and the lowest mean score or the best status in the subscale of hypnotic drugs consumption. According to Pearson test, there was statistically significant correlation between anxiety score and total score of sleep quality ($P < 0.001$) and sub-domains of subjective sleep quality (0.016), sleep disturbance ($P < 0.001$) and daytime dysfunction ($P < 0.001$). According to Spearman test, there was statistically significant correlation between anxiety score and sub-domains of sleep duration ($P < 0.001$), and sleep hypnotic drugs ($P < 0.001$; **Table II**).

Discussion

Sleep disturbances are common in women, especially during pregnancy, and are associated with emotional and psychological consequences. In the State Anxiety Inventory, the highest prevalence of mild anxiety was in the first trimester, for moderate anxiety in the second trimester, and for severe anxiety in the third trimester. In the trait anxiety inventory, higher prevalence of moderate anxiety was in the first trimester, for mild and severe anxiety in the second trimester, and for moderate and relatively severe anxiety in the third semester. In a research raised by Signal et al., on 406 pregnant women using Edinburgh Postnatal Anxiety Scale, by the end of pregnancy, 22%, 25%, and 55% of the women experienced symptoms of depression, anxiety, and stress, respectively. Less than 55% of women reported depressed mood for more than 2 weeks, and factors such as the history of maternal depression and younger age were important predictors of depression, stress, and anxiety caused by a feeling of inefficiency. Maternal mental health should be considered equally important in pregnancy period and the postpartum period[23]. Rallis et al. revealed that the rate of anxiety, and stress during pregnancy trimesters differ, increased anxiety and stress in the late pregnancy[24]. Consistent with other studies, current findings underline the importance of mental problems incidence in early pregnancy and a history of it even before pregnancy on sleep quality of pregnant women. Accordingly, in the current study, moderate depression, mild anxiety, and moderate anxiety were reported in the first trimester. Severe anxiety had a higher incidence in the third trimester. Thus, to have a

good mental and physical health during pregnancy, the prevalence of psychiatric disorders and its treatment should be taken into account, and mental-emotional health screening in early pregnancy seems to have much importance.

In analyzing sleep quality trimesters, the results showed that poor sleep quality has a higher prevalence in the third trimester. Sleep quality scales such as sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction were disrupted. A review of sleep quality during pregnancy indicates that sleep problems increase gradually from the first trimester to the last trimester. A research performed by Swanson *et al*. on pregnant and postpartum women indicated a high prevalence of psychiatric and sleep disorders including insomnia, and anxiety; among which insomnia had a higher frequency in the perinatal period[25]. Mindell et al. examined sleep pattern during pregnancy and showed that the subjects during pregnancy have a poor quality of sleep, decreased sleep efficiency at night, and high daytime sleepiness. Nearly all of the subjects reported repeated awakenings at night, nap during the day, symptoms of insomnia, respiratory disorders, and restless legs syndrome. No difference was seen in terms of sleep-disordered breathing, daytime sleepiness, and fatigue. Furthermore, physical problems related to pregnancy such as frequent urination and lack of convenient

Table I: Socio-Demographic Characteristics of the Participants (n = 565).

	Characteristic		Characteristic
No. (%)a	**Body mass index (kg/m²)**	**No. (%)a**	**Age (y)**
11 (2.0)	<19.8	6 (1.1)	<18
388 (70.8)	19.8-25.9	152 (27.4)	18-25
125 (22.8)	26-29	194 (35.0)	25-30
24 (4.4)	>29	202 (36.5)	>30
25.2 (2.3)	Mean (SD)b	28.7 (5.5)	Mean (SD)b
	Husbands education level		**Education level**
10 (1.8)	Illiterate	19 (3.4)	Illiterate
165 (29.2)	Elementary	151 (26.7)	Elementary
145 (25.7)	Guidance	116 (20.5)	Secondary
38 (6.7)	High school	49 (8.7)	High school
152 (26.9)	Diploma	189 (33.5)	Diploma
55 (9.7)	University	41 (7.3)	University
	Sufficiency of income for expenses		**Job**
197 (36.2)	Fairly sufficient	549 (98.0)	Housewife
347 (63.8)	Insufficient	11 (2.0)	Employed
	History of abortion		**Residence**
154 (27.3)	yes	207 (36.6)	Personal
411 (72.7)	no	358 (63.4)	Rental
	History of preterm labor		**Place of prenatal care**
7 (1.2)	yes	538 (95.9)	Health center
558 (98.8)	no	5 (0.9)	Private clinic
		18 (3.2)	Health center and Private clinic
	Satisfaction of husband job		**Marital relationship**
202 (35.8)	Fairly satisfied	92 (16.3)	Very good
362 (64.2)	Completely satisfied	368 (65.4)	Good
		103 (18.3)	Fairly good
	Woman interest in fetal sex		**Wanted Pregnancy**
443 (78.8)	yes	432 (76.5)	yes
122 (21.5)	no	133 (23.5)	no
	Husband interest in fetal sex		**History of anxiety**
427 (76.3)	yes	2 (0.4)	yes
138 (24.4)	no	563 (99.6)	no

a Valid Percent has been reported in all the variables because of missed data.
b All data indicate number (percent), unless has been specified.
c Two cases reported that the income was completely sufficient.

Table II: Status of Anxiety, Sleep Quality and its Components and Their Relationship (n = 565)

Variable	Mean (SD)	Relationship With Quality of Life	
		r	P
Sleep quality total score	3.6 (1.4)	0.292	<0.001b
Components			
Subjective sleep quality	0.8 (0.4)	0.102	0.016b
Sleep latency	0.8 (0.5)	0.020	NS b
Sleep duration	0 (0-0)a	0.164	<0.001c
Habitual sleep efficiency	0 (0-0)a	0.238	<0.001c
Sleep disturbance	0.8 (0.4)	0.291	<0.001b
Use of sleeping medication	0 (0-0)a	0.138	0.001c
Daytime dysfunction	0.9 (0.4)	0.225	<0.001b
Anxiety	4.7(3.7)	-	-

sleep can lead to sleep disturbance. Thus, such sleep disorders during pregnancy should be treated, because sleep disturbance and poor sleep can negatively impact maternal and fetus health after pregnancy[26]. Sharma et al. reported that sleep disturbance during pregnancy can have a considerable impact on pregnancy out-comes. For example, strong snoring could be a risk factor for hypertension during pregnancy and cesarean section[27,28]. Moreover, lack of sleep (short and inadequate sleep, and insomnia) during pregnancy leads to low mental and social performance. Poor sleep is a risk factor in creating side effects during pregnancy[29]. In reviewing the quality of sleep and sleep disturbances during pregnancy, Rezaei et al. reported that poor sleep and poor quality of sleep can be more prevalent in the second trimester of pregnancy[30].

There are several researches performed on sleep during pregnancy that can confirm the results obtained from the present research. In the research performed by Rezaei *et al*., it is indicated that sleep disturbance can be more prevalent in the third trimester of pregnancy[31], while we found that maternal sleep disturbance is lower in the third trimester. Given the increasing psychiatric problems at the past 3 months of pregnancy, sleep problems and low quality of sleep are more tolerable by women, such that most research con-firms the results obtained from the present research.

We also found that there is a significant correlation between sleep quality and psychiatric dis-orders, and increased level of anxiety and depression would decrease sleep quality. A community-based study by Dorheim et al. on women in week 32 of pregnancy showed that the prevalence of insomnia according to DSM-IV-TR was high (61.9%), significantly higher than the general population. Dorheim et al. results implied that the symptoms of anxietyare highly correlated with insomnia, including sleep duration of 5 or 10 hours, sleep efficiency < 75%, everyday sleep disturbances, and long sleep with a delayed onset in late pregnancy[32,33].

As sleep may be disrupted due to anxiety and available evidence, there is a definite association between the variables, and it is of significance to address maternal emotional and mental health in the early pregnancy. Along with routine prenatal care and treatments, psychiatric and psychological treatments should be done leading to the mental and physical health of pregnant women, future mothers, and newborns.

Conclusion

Due to the high prevalence of mental disorders in pregnant mothers and its significant effect on the fetus, it is recommended to pay attention to the problems that increase vulnerability and affect the sleep rhythm of pregnant mothers.

Funding

This study was funded by the research committee of Mashhad University of Medical Sciences, Mashhad, Iran.

Interests conflict

The authors declare no conflict of interest.

References

1. Lee KA, Gay CL. Sleep in late pregnancy predicts length of labor and type of delivery. Am J ObstetGynecol 2004; 191: 2041-6.

2. Kryger MH, Roth T, Dement WC. Principles and practice of sleep medicine. 6th ed. Philadelphia, PA: US Elsevier, 2017.

3. Lopes EA, Carvalho LB, Seguro PB, Mattar R, Silva AB, Prado LB, Prado GF. Sleep disorders in pregnancy. Arq Neuropsiquiatr. 2004 Jun;62(2A):217-21.

4. Hedman C, Pohjasvaara T, Tolonen U, Suhonen-Malm AS, Myllylä VV. Effects of pregnancy on mothers' sleep. Sleep Med. 2002 Jan;3(1):37-42.

5. Elliott AC. Primary care assessment and management of sleep disorders. J Am Acad Nurse Pract 2001; 13: 409-17.

6. Okun ML, Roberts JM, Marsland AL, Hall M. How disturbed sleep may be a risk factor for adverse pregnancy outcomes. Obstet Gynecol Surv. 2009 Apr;64(4):273-80.

7. Guendelman S, Pearl M, Kosa JL, Graham S, Abrams B, Kharrazi M. Association between preterm delivery and pre-pregnancy body mass (BMI), exercise and sleep during pregnancy among working women in Southern California. Matern Child Health J. 2013 May;17(4):723-31.

8. Amir Ali Akbari S, Bolouri B, Sadegh Niat Haghighi KH. Impacts of sleeping disturbances in the last month of pregnancy on the length of labor and way of delivery in women referring to the health centers of Saghez, 2006. J Ilam Univ Med Sci 2007; 15: 8-16.

9. Dewald JF, Meijer AM, Oort FJ, Kerkhof GA, Bögels SM. The influence of sleep quality, sleep duration and sleepiness on school performance in children and adolescents: a meta-analytic review. Sleep Med Rev. 2010;14(3): 179–89

10.Arasteh M, Yousefi F, Sharifi Z. Investigation of sleep quality and itsinfluencing factors in patients admitted to the gynecology and generalsurgery of besat hospital in Sanandaj. Med J Mashhad Univ Med Sci. 2014;57(6):762-9.

11. Tikotzky L, De Marcas G, Har-Toov J, Dollberg S, Bar-Haim Y, Sadeh A. Sleep and physical growth in infants during the first 6 months. J Sleep Res. 2010;19(1-Part-I):103-10.

12. Goldberg WA, Lucas-Thompson RG, Germo GR, Keller MA, Davis EP, Sandman CA. Eye of the beholder? Maternal mental health and the quality of infant sleep. Soc Sci Med. 2013;79:101-8.

13. Haghighat M, Mirghafourvand M, Mohammad-Alizadeh-Charandabi S,Malakouti J, Erfani M. The effect of spiritual counseling on stress and anxiety in pregnancy: A randomized controlled clinical trial. Iran Red Crescent MedJ. 2018;20(4):e64094.

14. Nath A, Venkatesh S, Balan S, Metgud CS, Krishna M, Murthy GV. The prevalence and determinants of pregnancy-related anxiety amongst pregnant women at less than 24 weeks of pregnancy in Bangalore, Southern India. Int J Women's Health. 2019;11:241-8.

15. Bazrafshan M, Mahmoodi RA. The relationship between women's anxiety during pregnancy and labor outcomes in Larestan hospitals. Mandish. 2009;1(1):1-12.

16. Hasanjanzadeh P, Faramarzi M. Relationship between maternal general and specific pregnancy stress, anxiety, and depression symptoms and pregnancy outcome. J Clin Diagn Res. 2017;11(4):VC04.

17. Rahimi f, Ahmadi m, Rosta f, Alavimajd H, Valiani M. Effect of relaxation training on pregnancy anxiety in high risk women. J Saf Promot Inj Prevent 2014; 2(3):180-9.

18. Glover V. Maternal depression, anxiety and stress during pregnancy and child outcome; what needs to be done. Best Pract Res Clin Obstet Gynaecol. 2014;28(1):25-35.

19. Cardwell MS. Stress: pregnancy considerations. Obstet Gynecol Surv. 2013;68(2):119-29.

20. Maryam GA, Shohre GS, Javad K. Effectiveness of hardiness training on anxiety and quality of life of pregnancy women. Procedia Soc Behav Sci.2013;84:1785-9.

21. Shahhosseini Z, Pourasghar M, Khalilian A, Salehi F. A review of the effects of anxiety during pregnancy on children's health. Mater Sociomed. 2015;27(3):200.

22. Baird J, Hill CM, Kendrick T, Inskip HM, Group SS. Infant sleep disturbance is associated with preconceptional psychological distress: findings from the Southampton Women's survey. Sleep. 2009;32(4):566-8.

23. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res.1989;28(2):193-213. doi:10.1016/0165-1781(89)90047-4.

24. Mirghafourvand M, Mohammad ACS, Mansouri A, NajafiM, Khodabande F. The effect of vitamin d and calcium plus vitamin d on sleep quality in pregnant women with leg cramps: a controlled randomized clinical trial. J Isfahan Med Sch. 2015;32(320):2444-53.

25. Signal TL, Paine SJ, Sweeney B, Muller D, Priston M, Lee K, Gander P, Huthwaite M. The prevalence of symptoms of depression and anxiety, and the level of life stress and worry in New Zealand Māori and non-Māori women in late pregnancy. Aust N Z J Psychiatry. 2017 Feb;51(2):168-76.

26. Rallis S, Skouteris H, McCabe M, Milgrom J. A prospective examination of depression, anxiety and stress throughout pregnancy. Women Birth. 2014 Dec;27(4):e36-42.

27. Swanson LM, Pickett SM, Flynn H, Armitage R. Relationships among depression, anxiety, and insomnia symptoms in perinatal women seeking mental health treatment. J Womens Health (Larchmt). 2011 Apr;20(4):553-8.

28. Mindell JA, Cook RA, Nikolovski J. Sleep patterns and sleep disturbances across pregnancy. Sleep Med 2015; 16: 483-8.

29. Sharma SK, Nehra A, Sinha S, Soneja M, Sunesh K, Sreenivas V, Vedita D. Sleep disorders in pregnancy and their association with pregnancy outcomes: a prospective observational study. Sleep Breath. 2016 Mar;20(1):87-93.

30. Williams MA, Miller RS, Qiu C, Cripe SM, Gelaye B, Enquobahrie D. Associations of early pregnancy sleep duration with trimester-specific blood pressures and hypertensive disorders in pregnancy. Sleep. 2010 Oct;33(10):1363-71.

31. Okun ML, Kline CE, Roberts JM, Wettlaufer B, Glover K, Hall M. Prevalence of sleep deficiency in early gestation and its associations with stress and depressive symptoms. J Womens Health (Larchmt). 2013 Dec;22(12):1028-37.

32. Rezaei E, Moghadam ZB, Saraylu K. Quality of life in pregnant women with sleep disorder. J Family Reprod Health 2013; 7: 87-93.

33. Dorheim SK, Bjorvatn B, Eberhard-Gran M. Insomnia and depressive symptoms in late pregnancy: A population-based study. Behav Sleep Med 2012; 10: 152-66.

eISSN 2255-0569

ORIGINAL

Colon cancer screening in the balearic islands: current situation and proposals

Cribado del cáncer de colon en las islas baleares: situación actual y propuestas

José Reyes[1], **Javier Cortés**[2]

1. Head of the Digestive System Section. Regional Hospital of Inca.
President of the Board of the Balearic Islands of the Spanish Association against Cancer.
2. Full Member of the Royal Academy of Medicine of the Balearic Islands

Corresponding author
José Reyes
Head of the Digestive System Section.
Regional Hospital of Inca
E-mail: josereyesdigestivo@gmail.com

Received: 22 - X - 2021
Accepted: 22 - XII - 2021

doi: 10.3306/AJHS.2022.37.01.129

Abstract

There is evidence that screening for colorectal cancer (CRC), a cancer whose natural history is well known, is very effective and efficient. The recommendations of Scientific Societies and National and Supra-National Health Institutions for its population application are clear and forceful.

The bases of this evidence, the recommendations made and in force, and the current circumstances of application of the CRC screening in the Balearic Islands are reviewed in the text, establishing at the end recommendations for its improvement, which is much needed.

Keywords: Cancer, colon, screening.

Resumen

Está demostrado que el cribado del cáncer colorrectal (CCR), un cáncer cuya historia natural es bien conocida, es muy eficaz y eficiente. Las recomendaciones de Sociedades Científicas e Instituciones Sanitarias Nacionales y Supranacionales para su aplicación poblacional son claras y contundentes.

Las bases de esta evidencia, las recomendaciones realizadas y vigentes, y las circunstancias actuales de aplicación del cribado de CCR en Baleares se revisan en el texto, estableciendo al final recomendaciones para su mejora, que es muy necesaria.

Palabras clave: Cáncer, colon, cribado.

Introduction

The importance of colorectal cancer (CRC) in our society is very great, although little is known by the general population. In Spain, CRC is the most common cancer, with about 40,000 new cases / year; in the Balearic Islands, over 800 cases are diagnosed annually[1].

Most CRC cancers develop from adenomatous polyps. The probability that a polyp progresses to cancer depends on the histological type, its size, and the degree of cellular dysplasia. The average time required to complete this progression is long, probably 10 years or more, which creates a long period of time that allows preventing or detecting CRC early and improving its prognosis. After the removal of polyps, the incidence of carcinomas decreases by approximately 88-90%, in the following 6 years[2,3,4].

The incidence of CRC clearly increases after the age of 50 5. The progressive aging of the population, exposure to environmental risks and, more recently, screening for CRC, influence the increase in observed cases of CRC.

The main factor associated with the survival of CRC is the degree of extension at the time of diagnosis: 60% of CRC cases are diagnosed when the disease is already advanced at a regional or distant level, that is, with metastases. However, when the diagnosis is made in early stages (stages I and II), overall survival can exceed 90%: this fact highlights the great importance of screening programs (early diagnosis, secondary prevention) of CRC and that in this context most neoplasms are diagnosed in early stages[6,7] (The clinical stages - TNM - of the CRC can be consulted in annex 1).

Given the great importance of CRC and its enormous capacity to be prevented through specific screening programs, as has been demonstrated in the Balearic Islands in areas where the program already operates, we consider it essential to promote the expansion of the program in the Balearic Islands.

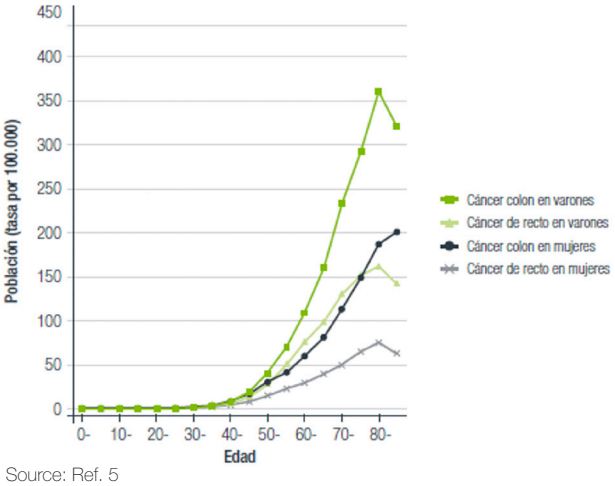
This text aims to explain the importance of the CRC and its screening and thus be able to base its implementation in the Balearic Islands.

Epidemiology of colorectal cancer

CRC is one of the most frequent neoplasms in western countries. In Spain, CRC is globally the most frequent cancer, with a total of 39,553 new cases per year, and it occupies the second position among men, behind prostate cancer, and among women, behind breast cancer[1,6]. **Table I** details the incidence of the main types of tumors and their distribution by sex.

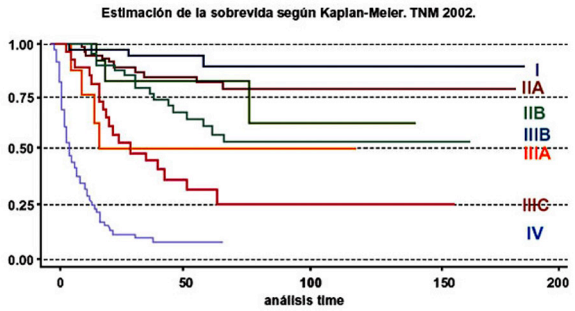
The incidence of CRC varies according to age, increasing markedly after the age of 50 5, as can be seen in **figure 1**. The progressive aging of the population, exposure to environmental risks and CRC screening have a very marked influence on the evolution of the number of observed CRC cases.

Figure 1: Colon and rectal cancer incidence rates by age in Spain.



Source: Ref. 5

Figure 2: Survival based on CRC staging .



Source: Ref. 7

Table I: Most frequent tumors in Spain according to sex. 2017.

Men			Women			Total		
Cancer	**n**	**%**	**Cancer**	**n**	**%**	**Cancer**	**n**	**%**
Prostate	33370	22,42	Breast	27747	28.04	CRC	41441	16,73
CRC	24764	16,63	CRC	16677	16,85	Prostate	33370	13,47
Lung	22430	15,07	Uterus	6160	6,23	Lung	28347	11,44
Bladder	17439	11,71	Lung	5917	5,98	Breast	28047	11,32
Stomach	5150	3,46	Bladder	3654	3,69	Bladder	21093	8,51
Total	148827	100	Total	98944	100	Total	247771	100

Source: Refs 1, 6.

60% of CRC cases are diagnosed when the disease is already advanced at a regional or distant level, that is, with metastasis, and this is the main factor influencing overall survival. However, when the diagnosis is made in early stages (stages I and II), a situation that occurs only in 37% of cases, overall survival can exceed 90%[7].

Most CRC develop from adenomatous polyps. The probability that a polyp progresses to cancer depends on its histological type, its size and the degree of cellular dysplasia it shows[3].
The removal of colon polyps (polypectomy) has two direct consequences, a reduction in the incidence of CRC of 88-90% at 6 years and a decrease in mortality from CRC both after ten and twenty years[3,4].

In recent years, mortality from CRC shows a downward trend, both for colon and rectal cancer and in men and women 8 (**Table II**). This trend observed in Spain since 1995 could be related to the improvement in the diagnosis and treatment of CRC.

Early detection of colon and rectal cancer

CRC is, together with cervical and breast cancer, one of the tumors that can be subjected to a screening program, since all three meet the classically required characteristics of knowledge[9] , namely:

- Constitute a major public health problem
- Have a well-established and identifiable natural history
- Have screening evidence of proven effectiveness and efficiency

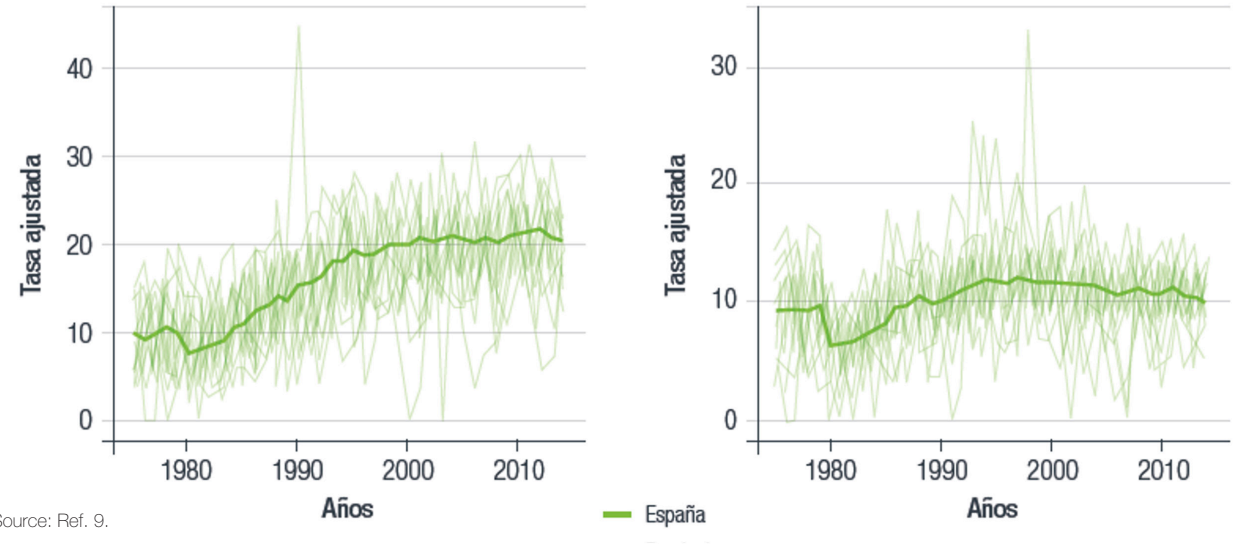
The CRC screening tests are grouped into four categories:

1. Stool tests for occult blood (SOB)
2. Endoscopic tests: sigmoidoscopy and colonoscopy
3. Imaging tests: computed tomography (CT), colonography and capsule endoscopy of the colon
4. Biomarkers in peripheral blood: Septin9 methylated DNA and miRNA.

The predominant strategy for population screening in European, Anglo-Saxon and Asian countries is the detection of biennial SOB followed by colonoscopy in positive cases, and annual sigmoidoscopy with or without immunological fecal occult blood test[10,11,12,13].
The ability to measure fecal Hb concentration is the main advantage of the quantitative SOBi tests over the qualitative ones and the guaiac SOB tests (SOBg). It is universally accepted that the ideal test for organized population screening is the quantitative SOBi test, which should replace chemical tests (SOBg test)

The fecal Hb concentration increases as the lesion is more advanced. For this reason, the rate of positive results obtained with the SOBi test varies according to the cut-off point chosen, which makes it possible to select the most appropriate one (best balance between sensitivity and specificity) for a population screening program based on the availability of colonoscopies. The screening programs are aimed at the population at medium risk for developing colon cancer, that is, people aged 50 to 69 years with no symptoms and without the presence of a family or personal history of CRC.

Table II: Evolution of adjusted mortality rates from colon and rectal cancer in Spain during the 1975-2018 period for men and women.



Source: Ref. 9.

In the first round of screening of the COLONPREV Randomized Clinical Trial[14] the effect on CRC detection and its impact on saving colonoscopies of increasing the cut-off point from 15 to 40 µg Hb / g of stool was analyzed. In women under 60 years of age, increasing the cut-off point to 40 µg Hb / g reduced the detection of advanced adenoma by 35% without altering the detection of CRC, which would mean a saving of 44.5% in colonoscopies. Likewise, increasing the cut-off point to 30 µg Hb / g of stool in men under 60 years of age and up to 25 µg Hb / g of stool in women over 60 years of age did not modify the CRC detection rate, assuming savings in colonoscopies 28.6 and 32.9%, respectively. However, in men older than 60 years, any increase in the cut-off point above 15 µg Hb / g of stool leads to a loss of CRC diagnosis, which reaches up to 25% with the cut-off point of 40 µg Hb / g of feces. This study suggests that the cut-off point for the SOHi test can be optimized based on age, sex, and existing resources for colonoscopy. Ultimately, in groups selected by age and sex, the cut-off point for SOBi could be increased, which would result in savings in endoscopy resources without loss of diagnosis of CRC cases.

The COLONPREV study has provided fundamental data for the justification of SOB-based screening in medium-risk populations, since it has shown that in the long term in two overlapping cohorts, the effect in terms of diagnosis and prevention of colon cancer was equivalent if compared doing an initial colonoscopy with doing SOBi every 2 years with colonoscopy when the result was positive.

Of the different types of tests to detect occult blood in feces, the immunological (OC-Sensor®) is used in the colorectal cancer prevention program of most Autonomous Communities. The sensitivity of immunological PDSOH to detect cancer varies between 85% and 95%; specificity, between 39% and 94%. The sensitivity to detect polyps with a higher probability of malignancy (>1cm) is 10-20%. With non-rehydrated tests, the positive predictive value varies between 10% and 15% for CRC, and between 30% and 40% for adenomas[15].

There is extensive experience in previous programs both at a Spanish and international level that show the high efficiency (cost / benefit) of CRC screening programs[16] based on the fact that the diagnosis of pre-cancerous lesions (adenomas) or cancers in very early stages of their development represents a great cost saving in health and social terms compared to those generated by the treatment of advanced invasive cancer, with, in addition the great improvement in the vital prognosis of the disease.

A clear example is found in France[17], where it is expected that with the application of the population screening program for CRC in a medium-risk population, the number of deaths from CRC will decrease from 15,000 / year to 12,000 / year. Furthermore, in population-based studies the reduction in mortality from CRC has been 15-18%, although it is estimated that this reduction may reach 30%[18,19].

During the period 2005-2008, after carrying out and evaluating a pilot CRC screening test carried out by the Catalan Institute of Oncology in order to determine the acceptance and viability of a program on a population scale, the Master Catalunya Oncology Plan, determined that colorectal cancer screening should be extended to the entire population. For this reason, it was implemented at the population level in Barcelona city[20].

A recent Spanish cooperative study[21], shows how the development of screening programs reduces the incidence and mortality from colon cancer 7 years after their introduction. This work is of great importance since it is developed on the Spanish population of different territories and not selected, that is, the population of the colon cancer screening programs.

There are recommendations made by the European Commission urging all member countries to develop screening programs since 2003, as well as a European guide for the development of screening programs[22]. There is also an order from the Ministry of Health of Spain in 2014 establishing the CRC screening program as part of the portfolio of common services of the National Health System[23].

Consequently, and based on these solid evidence of effectiveness and efficiency, there are currently CRC screening programs in activity in all the Spanish Autonomous Communities with the endorsement and legal and administrative support of both the European Commission and the Spanish Ministry of Health .

Current situation of the CRC screening program in the balearic islands

In view of the enormous potential benefits, the current situation of the program in the Balearic Islands is not acceptable based on the results published in the last day of the Alliance against colon cancer of the year 2019[24].

The CRC screening program in the Balearic Islands began in January 2015, in the form of biannual rounds, using the quantitative immunological SOH (OC-Sensor) as a screening test. At present, the program covers the areas of Ibiza-Formentera and the Inca District Hospital in Mallorca.

We have the general results of the first two rounds of the program (January 2015-December 2018). They can be consulted in **table III**.

The results of the endoscopic activity are detailed in the following **table IV**.

It should be noted that 77% of the colonoscopies performed found lesions directly related to CRC, while only 23% of the colonoscopies were negative for CRC or colon polyps.

That is, summarizing:

- Detection of 116 cases of CRC, 80% in stages I and II: that is, less therapeutic aggressiveness with better prognosis and lower personal and social cost.
- Detection of 472 people with high-risk adenomas, which implies a clear task of preventing CRC cases in the future

These excellent results are those of a program that covers 29% of the population of the Balearic Islands. The estimate in the case of 100% coverage of the population would produce the following results:

- Detection of 400 cases of CRC in 4 years
- Detection of 1,628 high-risk adenomas

If we do the calculation by doubling the participation rate to 50% then the estimated results are even more relevant:

- Detection of 689 cases of CRC in 4 years
- Detection of 2806 high-risk adenomas

In the whole of Spain, other Autonomous Communities have already reached 100% coverage of the program or have a clear objective on when to achieve it, while in the case of the Balearic Islands, from the Spanish Association against Cancer with the Balearic Government, we are finally working on planning to achieve a total population coverage, or at least greater than 85% as neighboring Communities and with a similar socio-sanitary structure have already achieved.

Participation is another synergistic objective to cover. The global participation rate of the population in the areas of the Balearic Islands where the program has been carried out is 28.8%, clearly lower than the national average of 48% and the participation rate recommended by the European Union 45%[22]. **Table V** details the coverage achieved by the program in the Spanish Autonomous Communities. It can be seen that the Community of the Balearic Islands has the penultimate worst participation rate.

The collaboration of Civil Society has been fundamental during the current development of the screening program. This is due to the clear perception that the population has of the benefit of the diagnosis of cancer in the asymptomatic phase and the fact that almost everyone has a family member or friend who has benefited from the program. Volunteers from the Spanish Cancer Association (SCA) carried out a work of personalized phone calls at the beginning of the second round of the program that was very effective in almost doubling the very low initial participation rate.

Table V: Participation rates by Autonomous Communities.

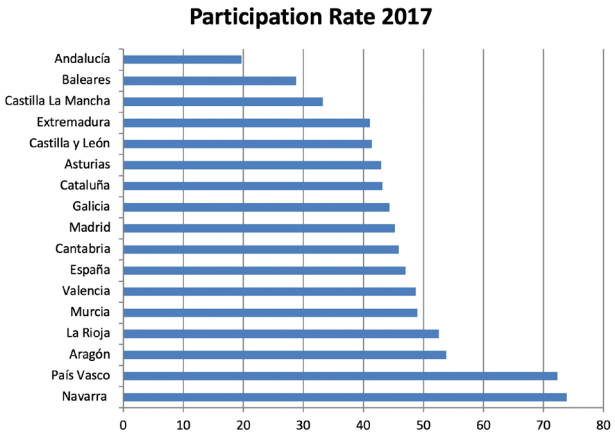


Table III: General results of the January 2015- December 2018 Program.

	INCA		IBIZA-FORM		MENORCA	TOTAL
	1st Round	2nd Round	1st Round	2nd Round	1st Round	
Letters sent	25,352	25,498	25,090	26,267	19,871	122,078
Total SOB	8,362	8,991	5,363	6,618	5,826	35,160
SOBi (+)	616	533	388	379	373	2289
Exclusions	50	39	18	19	27	153
Waivers	17	15	11	10	17	70
Colonoscopias	539	478	359	350	329	2055
Participation rate	32,98	35,26	21,37	25,19	29,31	28,80

Table IV: Endoscopic activity of the Program January 2015- December 2018.

	FIRST ROUND	SECOND ROUND	TOTAL (%)
Colonoscopies performed	1233	816	2049
High-risk polyps	276	196	472 (23,03%)
Medium risk polyps	325	181	506 (24,7%)
Low risk polyps	283	200	483 (23,6%)
Normal colonoscopies	275	197	472 (23,03%)
CRC	74	42	116 (5,66%)
Stage I	53	22	75
Stage II	8	5	13
Stage III	12	5	17
Stage IV	1	4	5

Impact of the Covid19 pandemic on the program

The impact of the Covid-19 pandemic on all screening programs in Europe has been enormous. In this sense, it should be considered that the Balearic Islands have not been an exception: the CRC screening program was stopped in March 2020 and restarted in October 2020. A national survey conducted in December 2020 and directed by the SCA with the strategic collaboration of the Spanish Societies of Medical Oncology, Radiotherapy Oncology, Pathology, Hematology and Hemotherapy and Oncology Nursing[25] showed that between March / June 2019 and March / June 2020 34% fewer cytologies and 24% fewer biopsies had been performed nationwide, in addition to objectifying the very strong impact that the pandemic had caused on job stability and the psychological balance of cancer patients and their families. It is legitimate to assume and hope that this activity stoppage will have a harsh impact in the coming years in the form of an increase in cancer cases diagnosed in more advanced stages.

Conclusions

1. It is urgent to complete the implementation of the Screening Program in all health areas of the Balearic Islands 26. At the present time, the program covers only 20% of the population of the Balearic Islands. The lack of extension to the population as a whole, generates a situation of inequity within the population that, although in the initial phases of the development of the program can be acceptable, at this time they are very difficult to justify before the population.

2. Through preventive education programs, the population should be made aware of the benefits of participating in the Screening Program, to avoid rejection of the invitation and thus achieve high coverage.

3. The diagnostic results obtained in the Balearic Islands in the first rounds of the program are equivalent to those obtained in other Autonomous Communities, in line with those required by good practice, demonstrating the quality of the Program and the technical preparation of all the team that It is carried out, which makes it possible to ensure that a population expansion of the Program, with adequate organizational planning, can and should –extremely high efficiency– be assumed.

ANNEX 1. Tumor stages of colon cancer.

Stage I: The cancer has grown, crossed the mucosa, and invaded the muscle layer of the colon or rectum. It has not spread to nearby tissues or lymph nodes (T1 or T2, N0, M0).

Stage II

A: The cancer has grown through the wall of the colon or rectum, but has not spread to nearby tissues or lymph nodes (T3, N0, M0).

B: The cancer has grown through the muscle layers to the lining of the abdomen, called the visceral peritoneum. It has not spread to nearby lymph nodes or elsewhere (T4a, N0, M0).

Stage III

A: The cancer has grown through the inner lining or into the muscular layers of the intestine. It has spread to 1 to 3 lymph nodes, or to a tumor node in tissues around the colon or rectum that do not appear to be lymph nodes, but has not spread to other parts of the body (T1 or T2, N1 or N1c, M0; or T1, N2a, M0).

B: The cancer has grown through the intestinal wall or into surrounding organs and into 1 to 3 lymph nodes, or into a tumor node in tissues surrounding the colon or rectum that do not appear to be lymph nodes. It has not spread to other parts of the body (T3 or T4a, N1 or N1c, M0; T2 or T3, N2a, M0; or T1 or T2, N2b, M0).

C: Regardless of how deep it has spread, the cancer has spread to 4 or more lymph nodes, but not to other distant parts of the body (T4a, N2a, M0; T3 or T4a, N2b, M0; or T4b, N1 or N2, M0).

Stage IV: The cancer has spread to one or more distant organs of the body.

Interests conflict

The authors declare no conflict of interest.

References

1. Available in https://seom.org/seomcms/images/stories/recursos/Las_cifras_del_cancer_en_Esp_2017.pdf Access 02.08.2020

2. Cubiella J, Marzo-Castillejo M, Mascort-Roca JJ, Amador-Romero FJ, Bellas-Beceiro B, Clofent-Vilaplana J et al.: Clinical practice guideline. Diagnosis and prevention of colorectal cancer. 2018 Update. Gastroenterol Hepatol. 2018; 41: 585-96.

3. Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic Polypectomy and Long-Term Prevention of Colorectal-Cancer Deaths. N Engl J Med. 2012; 366: 687-96.

4. Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS et al.: Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med. 1993; 329: 1977-81.

5. Cortés J.: Cancer, vellesa i SARS-CoV-2. AJHS 2021; 36 (4): 155-160.

6. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A et al.: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries CA Cancer J Clin.: 2018; 68: 394-424.

7. Oh Hs, Chung HJ, Kim HK, Choi JS: Differences in overall survival when colorectal cancer patients are stratified into new TNM staging strategy. Cancer Res Treat. 2007; 39(2): 61-4.

8. Instituto Nacional de Estadística (INE). Estadística de defun¬ciones según la causa de muerte. 2018.
Available in: https://www.ine.es/dyngs/INEbase/es/operacion.htm?c=Estadistica_C&cid=1254736176780&menu=ultiDatos&idp=1254735573175
Access 19.10.2021.

9. Conference on Screening and Early Detection of Cancer 18 – 19. Nov. 1999, Viena, Austria. Eur J Cancer 2000; 36: 1473-8. Conclusions contained in a Recommendation of the Council of the European Union of 2.12.2003 and published in Official Journal of the European Union L327 / 34, 16.12.2003.

10. Sung JJ, Ng SC, Chan FK, Chiu HM, Kim HS, Matsuda T et al.: An updated Asia Pacific Con¬sensus Recommendations on colorectal cancer screening. Gut. 2015; 64: 121-32.

11. Lin JS, Piper MA, Perdue LA, Rutter CM, Webber EM, O'Connor E et al.: Screening for Colorectal Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2016; 315: 2576-94.

12. Levin B, Lieberman DA, McFarland B, Levin B1, Andrews KS, Brooks D, Bond J, et al.: Screening and Surveillance for the Early Detection of Colorectal Cancer and Adenomatous Polyps, 2008: A Joint Guideline From the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Gastroenterology. 2008; 134: 1570-95.

13. European Commission. European guidelines for quality assuran¬ce in colorectal cancer screening and diagnosis. Luxembourg: International Agency for Research on Cancer (IARC); 2010. Available in https://op.europa.eu/es/publication-detail/-/publication/e1ef52d8-8786-4ac4-9f91-4da2261ee535
Access 20.10.2021.

14. Quintero E, Castells A, Bujanda L, Cubiella J, Salas D, Lanas A et al.: Colonoscopy versus Fecal Immunochemical Testing in Colorectal-Cancer Scree-ning. New Engl J Med. 2012; 366: 697-706.

15. Informe de la Agencia de Evaluación de Tecnologías Sanitarias, AATRM nº. 2006/01. Available in https://www.sergas.es/Docs/Avalia-t/AATRM200601.pdf. Access 20.10.2021

16. Servicio Canario de Salud. Análisis coste-efectividad del cribado del cáncer colorrectal en la población general.
Available in https://www3.gobiernodecanarias.org/sanidad/scs/contenidoGenerico.jsp?idDocument=c33938dd-222b-11e0-964e-f5f3323ccc4d&idCarpeta=6f285035-7af0-11e4-a62a-758e414b4260. Access 20.10.2021.

17. Denis B, Gendre I, Perrin P.: Bilan des 18 premiers mois du programme français de dépistage du cancer colorectal par test immunologique. Côlon&Rectum. 2017 / 5 Vol. 11; Iss. 2.

18. Shaukat A, Mongin SJ, Geisser MS, Lederle FA, Bond JH, Mandel JS et al.: Long-term mortality after screening for colorectal cancer. N Engl J Med. 2013; 369: 1106-14.

19 Jorgensen B, Knudtson J: Stop cancer colon. Colorectal cancer screening-updated guidelines. S D Med. 2015; Spec No: 82-7.

20. Navarro M, Peris M, Binefa G, Vanaclocha M, Losa F, Fernández E: Colorectal cancer in a population with a guaiac-based screening programme. Med Clin (Barc). 2009; 13 : 495-500.

21. Keys MT, Serra-Burriel M, Martínez-Lizaga N, Pellisé M, Balaguer F, Sánchez A et Al.: Population-based organized screening by faecal immunochemical testing and colorectal cancer mortality: a natural experiment. Int J Epidemiol. 2021; 50: 143-155.

22. Available in
https://eurlex.europa.eu/legal-content/ES/TXT/?uri=uriserv:OJ.L_.2003.327.01.0034.01.SPA&toc=OJ:L:2003:327:TOC Access 21.10.2021.

23. Boletín Oficial del Estado, de 6 de noviembre de 2014. Número 269, sec. I, pág. 91369. Orden Ministerial SSI/2065/2014

24. Available in
https://www.youtube.com/watch?v=r0JIIISYDo4&list=PLfsdzqFH59eFGruh7co8CygL4oi3eO2nm&index=3&t=0s Access 21.10.2021

25. Available in http://observatorio.aecc.es/sites/default/files/informes/Impacto-COVID19_Personas_Cancer_0.pdf Access 21.10.2021

26. Dolz C, Cortés J.: El cribado del cáncer colo-rectal: Situación en las Islas Baleares propuestas de acción- Medicina Balear. 2019; 34 (2): 9-11.

eISSN 2255-0569

ORIGINAL

Antimicrobial resistance of *Staphylococcus aureus* isolated from dental plaques

Resistencia a los antimicrobianos de Staphylococcus aureus aislado de placas dentales

Nima Khamisi[1], Amirhossein Fathi[2], Amir Yari[3]

1. Faculty of Dentistry, Khorasgan Branchg, Islamic Azad University, Isfahan, Iran. 2. Dental Material Research Center, Department of Prosthodontics, School of Dentistry, Isfahan University of Medical Sciences, Isfahan, Iran. 3. Doctor of Dental Surgery, School of Dentistry, Dental Research Center, Tehran University of Medical Sciences, Tehran, Iran.

Corresponding author
Amirhossein Fathi
Dental Material Research Center, Department of Prosthodontics,
School of Dentistry, Isfahan University of Medical Sciences, Isfahan, Iran
E-mail: amir_alty@yahoo.com

Received: 24 - X - 2021
Accepted: 18 - XII - 2021

doi: 10.3306/AJHS.2022.37.01.136

Abstract

Background: *Staphylococcus aureus* is considered the pathogenic agent of dental implant infections. The present survey was performed to assess the prevalence and antimicrobial resistance of *S. aureus* strains amongst the swab samples taken from the site of dental implant infection and also periimplant sulcular fluid (PISF).

Methods: A total of 70 individuals were included in this survey. Swab samples of the site of infection and also PISE fluid were taken and applied for microbial culture. Disk diffusion was used to assess the antimicrobial resistance of *S. aureus* isolates. Twenty out of 70 (28.57%) swab samples taken from the site of dental implant infection and PISF.

Results: The mean age of the studied population was 50.4 years, with a male to female ratio of 45/25. A history of alcohol and smoking was found in 25.71% and 77.5714 of the studied population. Statistically significant differences were found between male to female ratio (P <0.05), distribution of non-alcoholic and alcoholic individuals (P <0.05), and smokers with non-smoker individuals (P <0.05). *S. aureus* strains harbored the highest resistance levels toward penicillin (90%), gentamicin (85%), tetracycline (85%), and ciprofloxacin (75%). Resistance toward rifampin (25%) and trimethoprim-sulfamethoxazole (45%) was lower than other antimicrobials.

Conclusion: The role of antibiotic resistant-*S. aureus* strains was found as a reason of dental implant infections. However, some additional studies are needed to found more epidemiological aspects of antibiotic resistant-*S. aureus* in dental implant samples.

Keywords: Staphylococcus aureus, antimicrobial resistance, dental implants, prevalence.

Resumen

Antecedentes: El *Staphylococcus aureus* se considera el agente patógeno de las infecciones de los implantes dentales. El presente estudio se realizó para evaluar la prevalencia y la resistencia a los antimicrobianos de las cepas de *S. aureus* en las muestras tomadas de la zona de infección de los implantes dentales y del líquido sulcular periimplantario de la infección de los implantes dentales y del líquido sulcular periimplantario (PISF).

Métodos: Se incluyó a un total de 70 individuos en este estudio. Se tomaron muestras de hisopos del lugar de la infección y del líquido periimplantario y se aplicaron para el cultivo microbiano. Se utilizó la difusión en disco para evaluar la resistencia antimicrobiana de los aislados de *S. aureus*. Veinte de 70 (28,57%) muestras de hisopo tomadas del lugar de la infección del implante dental y del PISF.

Resultados: La edad media de la población estudiada fue de 50,4 años, con una proporción de hombres y mujeres de 45/25. Los antecedentes de alcohol y tabaquismo en el 25,71% y 77,5714 de la población estudiada. Se encontraron diferencias estadísticamente significativas entre la proporción de hombres y mujeres (P <0,05), la distribución de individuos no alcohólicos y alcohólicos (P <0,05), y los fumadores con los no fumadores (P <0,05). Las cepas de *S. aureus* presentaron los niveles más altos de resistencia a la penicilina (90%), la gentamicina (85%), tetraciclina (85%) y ciprofloxacino (75%). La resistencia a la rifampicina (25%) y al trimetoprim-sulfametoxazol (45%) fue menor que a otros antimicrobianos.

Conclusión: Se constató el papel de las cepas de *S. aureus* resistentes a los antibióticos como motivo de las infecciones de los implantes dentales. Sin embargo, se necesitan estudios adicionales para encontrar más aspectos epidemiológicos del *S. aureus* resistente a los antibióticos en muestras de implantes dentales.

Palabras clave: *Staphylococcus aureus*, resistencia antimicrobiana, implantes dentales, prevalencia.

Introduction

Dental implant treatment is important for the recovery process in patients with developmental and acquired dental defects. Dental implants directly improve the oral cavity function and esthetics as well as a patient's speech and general well-being[1]. In recent years, medical professionals have increasingly used dental implant procedures for tooth replacement. Consequently, there has been an increase in the number of patients with systemic diseases requesting dental implants to replace their missing teeth. However, the increase in demand for dental implants is also associated with an increase in complications associated with the procedure[2,3].

One of the major issues regarding dental implants is the infections occurrence in the site of dental plants[4]. In this regard, a small proportion of implants are not successful and may fail due to infection. The microbiota of implants is similar to that of teeth in similar clinical states. Implants that fail because of mechanical stress are colonized by species associated with healthy teeth. Infected implants are colonized by subgingival species, including Staphylococcus aureus (*S. aureus*)[5-7].

S. aureus is a Gram-positive and catalase-positive bacterium responsible for different kinds of infections, including Urinary Tract Infections (UTIs), Respiratory Tract Infections (RTIs), wound and burn infections, soft tissue infections, food-borne infections and etc[8]. *S. aureus* has been reported to be a common cause of infection-related implant failure, which involves multiple stages, including adherence, maturation, and dispersal of bacteria[9].

Dental implant *S. aureus* is able to cause several soft tissue infections and also infection expansion through head and neck[10]. Research reports that *S. aureus* bacteria harbor high resistance to diverse kinds of antibiotic drugs, particularly penicillins, cephalosporins, tetracyclines, aminoglycosides, macrolides, and fluoroquinolones[11-13]. Resistant strains cause more severe infections for a longer period of time with higher economic losses owing to the costs of control and treatments[14-16].

Rendering the high importance of this matter, the present survey was done to assess the prevalence and antimicrobial resistance of *S. aureus* strains isolated from dental implant infections.

Materials and methods

Study criteria

The present cross sectional survey was conducted between January 2020 to January 2021 on 200 individuals who were treated with dental implants at least 12 months ago. All individuals had signs of inflammation, pain, and redness in the site of dental implant. The inclusion and exclusion criteria were as follow:

The inclusion criteria:
1. Dental implant treatment at least 12 months ago
2. Presence of inflammation, pain and redness in the site of dental implant
3. Age > 18
4. No relevant medical conditions
5. Lack of antibiotic therapy in the past 2 months

The exclusion criteria:
1. Presence of the coronavirus diseases 2019 (COVID-19)
2. Presence of hepatitis viruses
3. Antibiotic uses in the past 2 months
4. Pregnancy or lactation
5. Malignant diseases or other diseases
6. Treated with radiotherapy or chemotherapeutic agents (chemotherapy) during the past five years
7. A history of head and neck radiation treatment owing to certain medical conditions

Written informed consents were taken from all individuals and their personal information kept secret.

Samples

Seventy out of 200 individuals were included into the study. Swab samples were taken from the site of dental implant infection without any contact with other parts of the oral cavity. Swabs were taken from both implant surfaces with inflammation and periimplant sulcular fluid (PISF) of each implant. All swabs were separately transferred to laboratory in cool boxes using the nutrient broth media.

S. aureus isolation and identification

A loopful sample of each broth media were transferred to blood agar media and incubated at 37ºC for 24 h in aerobic atmosphere. *S. aureus* identification was done using some biochemical tests, including Gram staining, , catalase activity, coagulated test (rabbit plasma), oxidase test, glucose O/F test, resistance to bacitracin (0.04 U), mannitol fermentation on Mannitol salt agar (Merck, Germany), urease activity, nitrate reduction, phosphatase, deoxyribonuclease (DNase, Merck, Germany) test, voges-proskaver (Merck, Germany) test and carbohydrate (xylose, sucrose, trehalose and maltose, fructose, lactose, mannose) fermentation tests[17].

Antimicrobial resistance

Patterns of antibiotic resistance of the *S. aureus* isolates were studied using the simple disk diffusion technique. The Mueller-Hinton agar (Merck, Germany) medium was used for this purpose. Susceptibility of *S. aureus* isolates were tested against several types of antibiotic groups including penicillin (10 µg/disk), methicillin (5 µg/disk), gentamicin (10 µg/disk), azithromycin (15 µg/disk), erythromycin (15 µg/disk), tetracycline (30 µg/disk), ciprofloxacin (5 µg/disk), levofloxacin (5 µg/disk),

clindamycin (2 µg/disk), trimethoprim-sulfamethoxazole (25 µg/disk), and rifampin (5 µg/disk) antibiotic agents (Oxoid, UK) using the instruction of Clinical and Laboratory Standards Institute. The plates containing the discs were allowed to stand for at least 30 min before incubated at 37°C for 24 h. The diameter of the zone of inhibition produced by each antibiotic disc was measured and interpreted using the CLSI zone diameter interpretative standards. *Staphylococcus aureus* ATCC 25923 was used as quality control organism in antimicrobial susceptibility determination[19-21].

Data analysis

SPSS software and chi-square test were used for data analysis. At first, obtained data were kept at the Microsoft Excel software and then transferred to the SPSS[22,23]. *P* value > 0.05 was recognized as a significant level[24, 25].

Results

S. aureus distribution

A total of 70 swab samples were taken from the site of dental implant and assess for the prevalence and antimicrobial resistance of *S. aureus* isolates. **Table I** shows the distribution of *S. aureus* amongst the examined samples. Twenty out of 70 (28.57%) swab samples taken from the site of dental implant infection and PISF.

Table I: *S. aureus* distribution amongst the examined samples.

Samples	N. collected	N. positive (%)
Dental implant swab	70	20 (28.57)

Demographical characters

Table II shows the demographical characters of the examined individuals. As shown, the mean age of the studied population was 50.4 years, with a male to female ratio of 45/25. A history of alcohol and smoking was found in 25.71% and 77.5714 of the studied population. Statistically significant differences were found between male to female ratio (*P* <0.05), distribution of non-alcoholic and alcoholic individuals (*P* <0.05), and smokers with non-smoker individuals (*P* <0.05).

Table II: Demographical characters of the examined individuals.

Demographic characters	Individuals (n= 70)
Mean age (SD)	50.4 (13.5)
Sex (M/F)	45/25
Mean weight (SD)	70.6 (12.2)
Mean BMI (SD)	25.6 (3.8)
Alcohol (%)	18 (25.71)
Smoking (%)	54 (77.14)

Antimicrobial resistance

Table III shows the antimicrobial resistance of *S. aureus* strains isolated from dental implants. *S. aureus* strains harbored the highest resistance levels toward penicillin (90%), gentamicin (85%), tetracycline (85%), and ciprofloxacin (75%). Resistance toward rifampin (25%) and trimethoprim-sulfamethoxazole (45%) was lower than other antimicrobials. Statistically differences were found for the resistance levels between diverse antimicrobials (*P* <0.05).

Discussion

Several infections have been threated the human life in recent years[26-30]. *S. aureus* is considered one of the most prevalence causes of hospital infections, globally[31,32]. It is also considered the reason of some infectious cases in the dental implants[33].

The present survey showed that the *S. aureus* was isolated from 28.57% of the swab samples taken from the sites of the implant infections. Isolates were resistant to diverse classes of antimicrobial agents, particularly penicillin, gentamicin, tetracycline, and ciprofloxacin. A study conducted on Yemen[34], reported that 4.10% of examined samples of dental infections. Reports of this survey showed that isolates were resistant toward vancomycin (22.20%), clindamycin (26%), ciprofloxacin (29.70%), ceftizoxime (40.70%), clarithromycin (37%), augmentin (55.60%), tetracycline (74%), and erythromycin (23.30%). Minkiewicz-Zochniak et al. (2021)35 reported that *S. aureus* isolates of dental implants samples were resistant toward cefoxitin (9%), gentamycin (15.20%), tobramycin (18.20%), ciprofloxacin (33.30%), levofloxacin (15.20%), erythromycin (66.70%), clindamycin (54.50%), tetracycline (12.10%), and trimethoprim-sulfamethoxazole (3%).

Unauthorized and improper use of antibiotics and disinfectants in medical clinics, self-medication of patients with antibiotics, over-the-counter sales of antibiotics, over-prescribing of antibiotics are the main reasons for the high incidence of antibiotic resistance in bacteria.

About the main sources of dental implant infections, antibiotic-resistant bacteria can transmit from food[36-41], dental interventions, ear, nose and throat infections, sore throats, bloodstream infections, and finally imported infections from the outside of the mouth. The main important reality about these infections are their main

Table III: Antimicrobial resistance of *S. aureus* strains isolated from dental implants

	Resistance toward antimicrobials (%)										
Samples (N. positive)	P10	Met	Gen	Az	Ert	Tet	Cip	Lev	Cln	Tr-Sul	Rif
Dental implants (20)	18 (90)	14 (70)	17 (85)	13 (65)	14 (70)	17 (85)	15 (75)	10 (50)	8 (40)	9 (45)	5 (25)

*P10: penicillin (10 µg/disk), Met: methicillin (5 µg/disk), Gen: gentamicin (10 µg/disk), Az: azithromycin (15 µg/disk), Ert: erythromycin (15 µg/disk), Tet: tetracycline (30 µg/disk), Cip: ciprofloxacin (5 µg/disk), Lev: levofloxacin (5 µg/disk), Cln: clindamycin (2 µg/disk), Tr-Sul: trimethoprim-sulfamethoxazole (25 µg/disk), Rif: rifampin (5 µg/disk),

roles in the expansion of infections into other parts of the body, such as sinuses, head and neck, blood, root canals, and other parts of the body[42]. Thus, it is essential to know and understand other epidemiological aspects of the dental implants infections.

Conclusion

To put it in a nutshell, the present work show the role of antibiotic-resistant *S. aureus* is one of the main sources of dental implant infections. Isolates had a high resistance toward some kinds of antimicrobials and low resistance toward others. It seems that, rifampin and trimethoprim-sulfamethoxazole owing to their low prevalence of resistance level can be suitable choices for the treatment of dental implant infections. Male was more prone to implant infections than females. Additionally, smoking is maybe the predisposing factor. However, the role of alcohol is not determined. Thus, more epidemiological surveys are needed to found more details about the *Staphylococcal* implant infections.

Interests conflict

The authors declare no conflict of interest.

References

1. Dewan, S.; Khullar, A.; Sehgal, M.; Arora, A. Implant failures: A broader perspective. J. Dent. Implants 2015, 5, 53.

2. Missika, P.; Bessade, J. Dental implants. Rev. Prat. 2018, 68, 827–830.

3. Manor, Y.; Simon, R.; Haim, D.; Garfunkel, A.; Moses, O. Dental implants in medically complex patients—A retrospective study. Clin. Oral Investig. 2016, 21, 701-708.

4. Mayta-Tovalino F, Rosas J, Mauricio-Vilchez C, Luza S, Alvitez-Temoche D, Mauricio F. Management of Postsurgical Complication in Multiple Implant-Infected Postextraction Sites in the Lower Arch. International Journal of Dentistry. 2020 Sep 29;2020.

5. Minkiewicz-Zochniak A, Jarzynka S, Iwańska A, Strom K, Iwańczyk B, Bartel M, Mazur M, Pietruczuk-Padzik A, Konieczna M, Augustynowicz-Kopeć E, Olędzka G. Biofilm Formation on Dental Implant Biomaterials by Staphylococcus aureus Strains Isolated from Patients with Cystic Fibrosis. Materials. 2021 Jan;14(8):2030.

6. Pye AD, Lockhart DE, Dawson MP, Murray CA, Smith AJ. A review of dental implants and infection. Journal of Hospital infection. 2009 Jun 1;72(2):104-10.

7. Aguayo S, Donos N, Spratt D, Bozec L. Nanoadhesion of Staphylococcus aureus onto titanium implant surfaces. Journal of dental research. 2015 Aug;94(8):1078-84.

8. Madahi H, Rostami F, Rahimi E, Dehkordi FS. Prevalence of enterotoxigenic Staphylococcus aureus isolated from chicken nugget in Iran. Jundishapur journal of microbiology. 2014 Aug;7(8).

9. Abdolmaleki Z, Mashak Z, Dehkordi FS. Phenotypic and genotypic characterization of antibiotic resistance in the methicillin-resistant Staphylococcus aureus strains isolated from hospital cockroaches. Antimicrobial Resistance & Infection Control. 2019 Dec;8(1):1-4.

10. Rokadiya S, Malden NJ. An implant periapical lesion leading to acute osteomyelitis with isolation of Staphylococcus aureus. British dental journal. 2008 Nov;205(9):489-91.

11. Momtaz H, Dehkordi FS, Rahimi E, Asgarifar A, Momeni M. Virulence genes and antimicrobial resistance profiles of Staphylococcus aureus isolated from chicken meat in Isfahan province, Iran. Journal of Applied Poultry Research. 2013 Dec 1;22(4):913-21.

12. Rahi A, Kazemeini H, Jafariaskari S, Seif A, Hosseini S, Dehkordi FS. Genotypic and phenotypic-based assessment of antibiotic resistance and profile of staphylococcal cassette chromosome mec in the methicillin-resistant Staphylococcus aureus recovered from raw milk. Infection and drug resistance. 2020;13:273.

13. Hasanpour Dehkordi A, Khaji L, Sakhaei Shahreza MH, Mashak Z, Safarpoor Dehkordi F, Safaee Y, Hosseinzadeh A, Alavi I, Ghasemi E, Rabiei-Faradonbeh M. One-year prevalence of antimicrobial susceptibility pattern of methicillin-resistant Staphylococcus aureus recovered from raw meat. Trop Biomed. 2017;34(2):396-404.

14. Ranjbar R, Seif A, Dehkordi FS. Prevalence of antibiotic resistance and distribution of virulence factors in the shiga toxigenic Escherichia coli recovered from hospital food. Jundishapur Journal of Microbiology. 2019;12(5):8.

15. Ranjbar R, Yadollahi Farsani F, Safarpoor Dehkordi F. Antimicrobial resistance and genotyping of vacA, cagA, and iceA alleles of the Helicobacter pylori strains isolated from traditional dairy products. Journal of Food Safety. 2019 Apr;39(2):e12594.

16. Abdolmaleki Z, Mashak Z, Safarpoor Dehkordi F. Molecular and virulence characteristics of methicillin-resistant Staphylococcus aureus bacteria recovered from hospital cockroaches. Jundishapur Journal of Microbiology. 2019 Dec 31;12(12).

17. Dehkordi FS, Gandomi H, Basti AA, Misaghi A, Rahimi E. Phenotypic and genotypic characterization of antibiotic resistance of methicillin-resistant Staphylococcus aureus isolated from hospital food. Antimicrobial Resistance & Infection Control. 2017 Dec;6(1):1-1.

18. CLSI. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fifth Informational Supplement. In: CLSI document M100-S25, Wayne: Clin and Laboratory Standards Institute. 2015.

19. Mashak Z, Jafariaskari S, Alavi I, Shahreza MS, Dehkordi FS. Phenotypic and genotypic assessment of antibiotic resistance and genotyping of vacA, cagA, iceA, oipA, cagE, and babA2 alleles of Helicobacter pylori bacteria isolated from raw meat. Infection and drug resistance. 2020;13:257.

20. Ranjbar R, Farsani FY, Dehkordi FS. Phenotypic analysis of antibiotic resistance and genotypic study of the vacA, cagA, iceA, oipA and babA genotypes of the Helicobacter pylori strains isolated from raw milk. Antimicrobial Resistance & Infection Control. 2018 Dec;7(1):1-4.

21. Abdolmaleki Z, Mashak Z, Dehkordi FS. Phenotypic and genotypic characterization of antibiotic resistance in the methicillin-resistant Staphylococcus aureus strains isolated from hospital cockroaches. Antimicrobial Resistance & Infection Control. 2019 Dec;8(1):1-4.

22. Rahimi E, Yazdanpour S, Dehkordi FS. Detection of Toxoplasma gondii antibodies in various poultry meat samples using enzyme linked immuno sorbent assay and its confirmation by polymerase chain reaction. J Pure Appl Microbiol. 2014;8(1):421-7.

23. Dehkordi FS, Saberian S, Momtaz H. Detection and segregation of Brucella abortus and Brucella melitensis in Aborted Bovine, Ovine, Caprine, Buffaloes and Camelid Fetuses by application of conventional and real-time polymerase chain reaction. The Thai Journal of Veterinary Medicine. 2012 Mar 1;42(1):13.

24. Nejat S, Momtaz H, Yadegari M, Nejat S, Safarpour Dehkordi F, Khamesipour F. Seasonal, geographical, age and breed distributions of equine viral arteritis in Iran. Kafkas Univ Vet Fak Derg. 2015 Jan 1;21(1):111-6.

25. Dehkordi FS. Prevalence study of Coxiella burnetii in aborted ovine and caprine fetuses by evaluation of nested and real-time PCR assays. American Journal of Animal and Veterinary Sciences. 2011.

26. Mirzaie A, Halaji M, Dehkordi FS, Ranjbar R, Noorbazargan H. A narrative literature review on traditional medicine options for treatment of corona virus disease 2019 (COVID-19). Complementary therapies in clinical practice. 2020 Aug 1;40:101214.

27. Halaji M, Farahani A, Ranjbar R, Heiat M, Dehkordi FS. Emerging coronaviruses: first SARS, second MERS and third SARS-CoV-2: epidemiological updates of COVID-19. Infez Med. 2020;28(suppl):6-17.

28. Sheikhshahrokh A, Ranjbar R, Saeidi E, Dehkordi FS, Heiat M, Ghasemi-Dehkordi P, Goodarzi H. Frontier therapeutics and vaccine strategies for sars-cov-2 (COVID-19): A review. Iranian Journal of Public Health. 2020 Jul 11.

29. Ranjbar R, Mahmoodzadeh Hosseini H, Safarpoor Dehkordi F. A review on biochemical and immunological biomarkers used for laboratory diagnosis of SARS-CoV-2 (COVID-19). The Open Microbiology Journal. 2020 Dec 15;14(1).

30. Ranjbar R, Dehkordi FS, Heiat M. The frequency of resistance genes in Salmonella enteritidis strains isolated from cattle. Iranian Journal of Public Health. 2020 May;49(5):968.

31. Momeni Shahraki M, Shakerian A, Rahimi E, Safarpoor Dehkordi F. Study the frequency of enterotoxin encoding genes and antibiotic resistance pattern of methicillin-resistant Staphylococcus aureus isolated from vegetable and salad samples in Chaharmahal Va Bakhtiari province. Journal of Food Microbiology. 2020 Jun 21;7(2):55-69.

32. Madahi H, Rostami F, Rahimi E, Safarpoor Dehkordi F, Jalali M. Detection of classical enterotoxins of Staphylococcus aureus isolates from chicken nugget and ready to eat foods in Esfahan province by ELISA technique. Food Hygiene. 2013 Nov 22;3(3 (11)):1-0.

33. Harris LG, Richards RG. Staphylococcus aureus adhesion to different treated titanium surfaces. Journal of Materials Science: Materials in Medicine. 2004 Apr;15(4):311-4.

34. Al-Akwa A, Zabara AQ, Al-Shamahy HA, Al-labani MA, Al-Ghaffari KM, Al-Mortada AM. Prevalence of Staphylococcus aureus in dental infections and the occurrence of MRSA in isolates. Univers J Pharm Res. 2020;5(2):23-7.

35. Minkiewicz-Zochniak A, Jarzynka S, Iwańska A, Strom K, Iwańczyk B, Bartel M, Mazur M, Pietruczuk-Padzik A, Konieczna M, Augustynowicz-Kopeć E, Olędzka G. Biofilm Formation on Dental Implant Biomaterials by Staphylococcus aureus Strains Isolated from Patients with Cystic Fibrosis. Materials. 2021 Jan;14(8):2030.

36. Hosseini SS, Makkie SA, Far BT, Dehkordi FS. Genotypic and phenotypic assessment of antibiotic resistance of MRSA bacteria isolated from food stuffs. Academic Journal of Health Sciencies: Medicina balear. 2021;36(3):76-80.

37. Shakerian A, Rahimi E, Dehkordi FS. Identification and characterization of resistant Arcobacter spp. isolated from meat products. Online Journal of Veterinary Research. 2017;21(12):766-76.

38. Mousavi S, Safarpoor Dehkordi F, Valizadeh Y. Genotyping of Helicobacter pylori strains isolated from raw milk and dairy products. Journal of Food Microbiology. 2017 Nov 22;4(3):41-53.

39. Mashak Z, Banisharif F, Banisharif G, Reza Pourian M, Eskandari S, Seif A, Safarpoor Dehkordi F, Alavi I. Prevalence of listeria species and serotyping of Listeria monocytogenes bacteria isolated from seafood samples. Egyptian Journal of Veterinary Sciences. 2021 Apr 1;52(1):1-9.

40. Ghorbani F, Gheisari E, Dehkordi FS. Genotyping of vacA alleles of Helicobacter pylori strains recovered from some Iranian food items. Tropical Journal of Pharmaceutical Research. 2016 Sep 5;15(8):1631-6.

41. Mousavi S, Dehkordi FS. Virulence factors and antibiotic resistance of Helicobacter pylori isolated from raw milk and unpasteurized dairy products in Iran. Journal of Venomous Animals and Toxins including Tropical Diseases. 2015 Jan 20;20:1-7.

42. Dehkordi FS, Tavakoli-Far B, Jafariaskari S, Momtaz H, Esmaeilzadeh S, Ranjbar R, Rabiei M. Uropathogenic Escherichia coli in the high vaginal swab samples of fertile and infertile women: virulence factors, O-serogroups, and phenotyping and genotyping characterization of antibiotic resistance. New Microbes and New Infections. 2020 Nov 1;38:100824.

eISSN 2255-0569

ORIGINAL

Cardiovascular risk stratification using the globorisk scale in the population of the Czech Republic

Estratificación del riesgo cardiovascular empleando la escala globorisk en población de la República Checa

Jitka Mudrychová[1], Kristýna Mudrychová[2], Martina Houšková Beránková[2], Bárbara Altisench Jané[1], Maria del Mar Torrens Darder[1], José Ignacio Ramírez Manent[1,3]

1. Family Doctor Practice, Calvià Primary Care Center, Health Service of Baleares.
2. Czech University of Life Sciences, Prague.
3. Spain, University of the Balearic Islands, Palma de Mallorca.

Corresponding author
Kristýna Mudrychová
Czech University of Life Sciences, Prague
E-mail: kmudrychova@gmail.com

Received: 26 - X - 2021
Accepted: 21 - XII - 2021

doi: 10.3306/AJHS.2022.37.01.141

Abstract

Introduction: The risk of cardiovascular disease can be determined with a multitude of scales. The present study aims to determine the level of cardiovascular risk in population of the Czech Republic by applying the Globorisk scale.
Methods: A descriptive, cross-sectional study of 28234 persons aged 40-74 years in whom cardiovascular risk was assessed using the Globorisk scale adapted to the population of the Czech Republic. The influence of sociodemographic variables (age, sex and social class) and tobacco consumption on the values of this scale was assessed.
Results: Both the mean values and the prevalence of high values of the Globorisk scale are higher in males, in older people, in people with lower socioeconomic status and in smokers. The variable that most influences the occurrence of high values of the scale is male sex with an odds ratio of 39.71 (95% CI 29.79-52.92).
Conclusions: All the sociodemographic variables analyzed, as well as tobacco consumption, influence the values of the Globorisk scale.

Keywords: Globorisk, cardiovascular disease, social class.

Resumen

Introducción: El riesgo de padecer enfermedades cardiovasculares se puede determinar con multitud de escalas. El presente estudio pretende determinar el nivel de riesgo cardiovascular en población de la República Checa aplicando la escala Globorisk.
Material y métodos: Estudio descriptivo y transversal en 28234 personas de edades comprendidas entre los 40 y 74 años en los que se valora el riesgo cardiovascular aplicando la escala Globorisk adaptada a la población de la República Checa. Se valora la influencia de variables sociodemográficas (edad, sexo y clase social) y consumo de tabaco en los valores de esta escala.
Resultados: Tanto los valores medios como la prevalencia de valores elevados de la escala Globorisk son más elevados en los varones, en las personas de mayor edad, en las personas con menor nivel socioeconómico y en los fumadores. La variable que más influye en la aparición de valores altos de la escala es el sexo masculino con una odds ratio de 39,71 (IC 95% 29,79-52,92).
Conclusiones: Todas las variables sociodemográficas analizadas, así como el consumo de tabaco influyen en los valores de la escala Globorisk.

Palabras clave: Globorisk, enfermedad cardiovascular, clase social.

Introduction

Cardiovascular disease (CVD) is defined as disease associated with ischemic vascular disorders, with symptomatic development of ischemic heart disease or coronary artery disease (acute myocardial infarction, stable or unstable angina), stroke (ictus) or peripheral vascular disease (peripheral arterial disease[1].

Cardiovascular risk (CVR) is the probability that an individual will develop a cardiovascular disease (angina, AMI, stroke, heart failure or peripheral vascular disease) in the next 10 years. It is calculated according to the number of risk factors present in the individual (qualitative risk) or taking into account the magnitude of each of them (quantitative risk). The determination of the GCR is used to: –Classify individuals and populations according to high, medium, low risk.– Determine the frequency of each factor individually. –Establish prevention strategies, according to risk levels and available resources.– Evaluate the impact of the preventive actions implemented in order to plan new measures[2].

Many scales exist to assess CVR, from the classic Framingham scales[3,4] with their corresponding adaptations to different countries[5] to other models that assess the probability of death, such as the SCORE scale[6]. In recent years, new scales have appeared, such as Globorisk[7], which present different models for each country.

In the Globorisk study, data from multiple cohorts were combined, which also allowed the inclusion of interaction terms between age or sex and risk factors. In addition, the risk score was used to estimate the 10-year risk of fatal cardiovascular disease using national health examination surveys from different countries around the world, including the Czech Republic[7].

The aim of this study is to determine how CVR is stratified by applying the Globorisk model in the population of the Czech Republic.

Methods

A descriptive, cross-sectional study was carried out in 29,168 persons in the Czech Republic, of whom 934 were eliminated for different reasons, 69 for not wishing to participate and 865 for not having all the data necessary to calculate CVR with the Globorisk model. The final number of persons included in the study was 28,234 (11,181 women and 17,053 men). See Flow chart in **figure 1**.

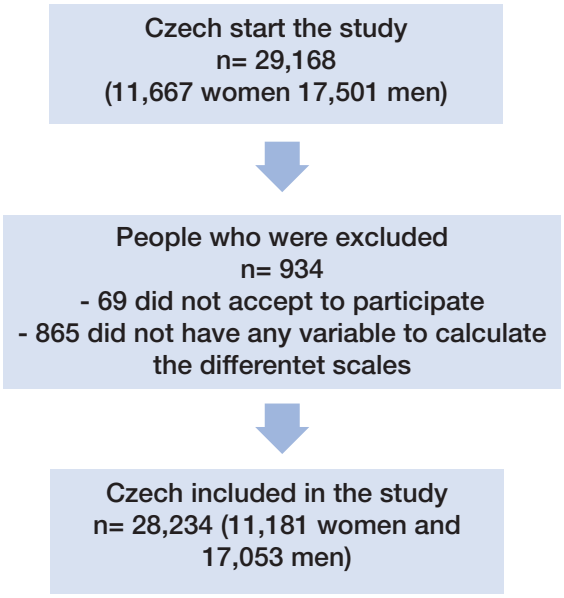
Inclusion criteria were as follows:

- Acceptance to participate in the study.
- Age between 40 and 74 years (as established by Globorisk).

Anthropometric height and weight measurements, both clinical and analytical, are performed by healthcare personnel after standardizing the measurement techniques.

Height and weight are determined with a SECA 700 scale with an attached SECA 220 telescopic measuring rod. Abdominal waist circumference is measured with an approved tape measure. Blood pressure is measured in the supine position with a calibrated OMRON M3 automatic sphygmomanometer after a 10-minute rest. Three measurements were taken at one-minute intervals and the mean of the three was obtained.

Figure 1: Flow chart of the study participants.



The analytical parameters are obtained by peripheral venipuncture after a 12-hour fast. Automated enzymatic methods are used for glycemia, total cholesterol and triglycerides. Values are expressed in mg/dl. HDL is determined by precipitation with dextran sulfate Cl2Mg, and values are expressed in mg/dl. LDL is calculated using the Friedewald formula (provided that triglycerides are less than 400 mg/dl). Values are expressed in mg/dl.

A person is considered to be a smoker if he/she has regularly consumed at least 1 cigarette/day (or the equivalent in other types of consumption) in the last month, or has stopped smoking less than one year ago.

The social class is determined from the 2011 National Classification of Occupations (CNO-11), based on the proposal of the group of social determinants of the Spanish Society of Epidemiology8. It is classified into 3 categories: Class I. Directors/managers, university professionals, athletes and artists. Class II. Intermediate occupations and self-employed workers without employees. Class III. Unskilled workers.

To determine the CVR with the Globorisk model, the table adapted to the population of the Czech Republic[9] was used.

Statistical analysis

A descriptive analysis of the categorical variables was performed, calculating the frequency and distribution of responses for each variable. For quantitative variables, the mean and standard deviation are calculated, and for qualitative variables the percentage is calculated. The bivariate association analysis was performed using the 2 test (with correction of Fisher's exact statistic when conditions required it) and Student's t test for independent samples. For the multivariate analysis, binary logistic regression was used with the Wald method, with calculation of the Odds ratio and the Hosmer-Lemeshow goodness-of-fit test. Statistical analysis was performed with the SPSS 27.0 program, with an accepted statistical significance level of 0.05.

Ethical considerations and aspects

The study was approved by the Clinical Research Ethics Committee. All procedures were performed in accordance with the ethical standards of the institutional research committee and with the 2013 Declaration of Helsinki. All patients signed written informed consent documents before participating in the study.

Of the sample, 60.4% were male. The mean age of the participants was about 49 years. The values of both anthropometric and clinical or analytical parameters are more unfavorable in males. The majority of people of both sexes are between 40 and 49 years of age. The percentage of smokers is slightly more than 32% in both sexes. All the characteristics of the sample can be consulted in **table I**.

Table II shows how the values of the Globorisk scale increase as the age of the person increases and as one descends in social class; this situation is seen in both men and women. Tobacco consumption also increases the risk in both sexes. All the data can be consulted in **table II**.

The prevalence of high values (≥ 10) increases with age in both sexes. An elevation of these values is also seen as one moves down in social class. Tobacco use also increases the percentage of people at high risk. The complete data are presented in **table III**.

Table I: Characteristics of the Czech Republic population.

	Men n=17,053	Women n=11,181	
	Mean (SD)	Mean (SD)	p-value
Age (years)	49.1 (6.4)	48.6 (6.3)	<0.0001
Height (cm)	173.5 (6.9)	160.7 (6.4)	<0.0001
Weight (kg)	83.1 (14.4)	67.6 (13.3)	<0.0001
Body mass index (kg/m²)	27.6 (4.4)	26.2 (4.9)	<0.0001
Waist circumference (cm)	87.1 (10.9)	75.2 (10.5)	<0.0001
Waist to height ratio	0.50 (0.06)	0.47 (0.06)	<0.0001
Systolic blood pressure (mmHg)	131.3 (16.4)	121.9 (16.9)	<0.0001
Diastolic blood pressure (mmHg)	81.1 (10.6)	75.3 (10.8)	<0.0001
Total cholesterol (mg/dl)	203.6 (37.1)	203.89 (35.3)	0.534
HDL-cholesterol (mmHg)	48.4 (8.4)	55.5 (8.9)	<0.0001
LDL-cholesterol (mmHg)	128.7 (35.3)	129.0 (34.0)	0.473
Triglycerides (mmHg)	136.2 (90.2)	97.4 (53.6)	<0.0001
Glycaemia (mmHg)	97.5 (23.8)	90.6 (17.3)	<0.0001
ALT (U/L)	31.8 (18.8)	21.7 (14.9)	<0.0001
AST (U/L)	24.7 (11.8)	18.7 (7.5)	<0.0001
GGT (U/L)	41.8 (46.5)	23.3 (22.2)	<0.0001
Creatinine (mg/dl)	0.93 (0.17)	0.75 (0.17)	<0.0001
	n (%)	n (%)	p-value
40-49 years	9557 (56.0)	6637 (59.3)	<0.0001
50-59 years	6221 (36.5)	3831 (34.3)	
60-79 years	1275 (7.5)	713 (6.4)	
Social class I	870 (5.1)	656 (5.9)	<0.0001
Social class II	2852 (16.7)	2619 (23.4)	
Social class III	13331 (78.2)	7906 (70.7)	
Non-smokers	11487 (67.4)	7522 (67.3)	0.445
Smokers	5566 (32.6)	3659 (32.7)	

Table II: Mean values of the Globorisk scale according age, social class and tobacco consumption by sex.

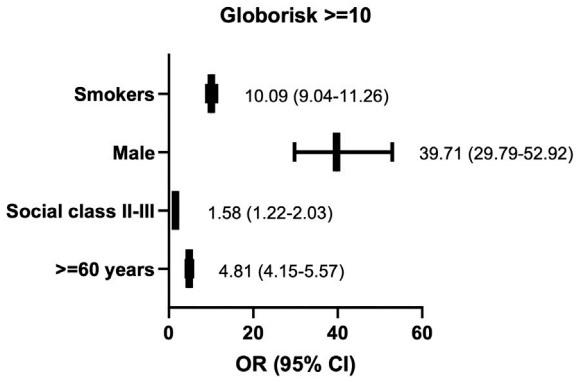
	Women			Men		
	n	Mean (SD)	p-value	n	Mean (SD)	p-value
40-49 years	6637	1.5 (1.1)	<0.0001	9557	4.1 (2.5)	<0.0001
50-59 years	3831	2.7 (1.7)		6221	7.4 (3.3)	
60-79 years	713	4.1 (2.0)		1275	8.4 (3.0)	
Social class I	656	1.8 (1.4)	<0.0001	870	5.0 (3.1)	<0.0001
Social class II	2619	1.9 (1.5)		2852	5.4 (3.1)	
Social class III	7906	2.2 (1.6)		13331	5.7 (3.4)	
Non-smokers	7522	1.5 (0.9)	<0.0001	11487	4.5 (2.5)	<0.0001
Smokers	3659	3.4 (1.9)		5566	8.0 (3.6)	

Table III: Prevalence of different values of the Globorisk scale according age, social class and tobacco consumption by sex.

		<5	5-9	≥ 10	
Women	n	% (95% CI)	% (95% CI)	% (95% CI)	p-value
40-49 years	6637	62.8 (62.1-63.5)	19.0 (18.3-19.7)	0.0 (0.0-0.0)	<0.0001
50-59 years	3831	32.5 (31.6-33.4)	54.6 (53.7-55.5)	36.7 (35.2-38.2)	
60-79 years	713	4.7 (3.2-6.2)	26.4 (25.0-27.9)	63.3 (62.4-64.2)	
Social class I	656	6.1 (4.6-7.6)	3.5 (2.2-5.0)	6.1 (4.6-7.6)	<0.0001
Social class II	2619	24.1 (23.0-25.2)	14.4 (13.3-15.5)	24.5 (23.4-26.6)	
Social class III	7906	69.8 (69.2-70.4)	82.2 (81.6-82.8)	69.4 (68.8-70.0)	
Non-smokers	7522	72.1 (71.6-72.7)	9.7 (9.1-10.3)	0.0 (0.0-0.0)	<0.0001
Smokers	3659	27.9 (27.0-28.8)	90.3 (89.4-91.2)	100.0 (99.1-100.0)	
		<5	5-9	≥ 10	
Men	n	% (95% CI)	% (95% CI)	% (95% CI)	p-value
40-49 years	9557	86.1 (85.6-86.6)	36.2 (35.7-36.7)	18.5 (18.0-19.0)	<0.0001
50-59 years	6221	12.9 (12.2-13.6)	52.5 (51.8-53.2)	19.5 (18.4-20.6)	
60-79 years	1275	0.9 (0.5-1.7)	11.3 (10.2-12.4)	64.0 (63.3-64.7)	
Social class I	870	6.0 (4.6-7.4)	4.6 (3.2-6.0)	3.5 (2.1-4.9)	<0.0001
Social class II	2852	17.4 (16.3-18.5)	16.9 (15.8-18.0)	13.6 (12.5-14.7)	
Social class III	13331	76.5 (76.2-76.8)	78.5 (78.2-78.8)	82.9 (82.6-83.2)	
Non-smokers	11487	88.5 (88.1-88.9)	58.3 (57.9-58.7)	23.8 (23.4-24.2)	<0.0001
Smokers	5566	11.5 (10.7-12.3)	41.7 (40.9-42.5)	76.2 (75.4-77.0)	

In the multivariate analysis by binary logistic regression with the Wald model, all those variables that presented statistically significant differences in the bivariate analyses were established as covariates, i.e. age 60 years and older, male sex, social classes II-III and smoking. The variable that most increased the risk of presenting high Globorisk values was male sex with an OR of 39.71 (95% CI 29.79-52.92). The other variables such as smoking, social class and age also increase the risk of presenting high Globorisk values. The complete data can be seen in **figure 2**.

Figure 2: Logistic regresión analysis.



Discussion

Nowadays, it is internationally accepted that cardiometabolic risk factors should be treated based on cardiovascular risk and not based on individual numbers[10].

In our study in the population of the Czech Republic, the prevalence of high values of the Globorisk scale increases with age, as one descends in social class and if one consumes tobacco. The variable that most increases the risk of presenting high values of this scale is the male sex. These results coincide with those of Hajifathalian et al. with regard to age, tobacco and male sex[7]. Although in this study no tables are presented for the population of the Czech Republic, in all the tables of the different countries we find the same effect, varying the cardiovascular risk according to the country and the geographical area. Neither is a relationship established with social class in this study, which we have also found has a great influence on our results.

This study, in which data from different countries were collected, showed that the prevalence of people at high risk of fatal cardiovascular disease was lower in developed countries such as South Korea, Spain and Denmark, where only 5-10% of men and women had more than a 10% cardiovascular risk at 10 years, and 62-76% of men and 79-82% of women had less than 3% risk. In contrast, the proportion of people at high risk was higher in China and Mexico. In China, 33% of men and 28% of women had a 10-year risk of fatal cardiovascular disease of 10% or more, while in Mexico, the prevalence of this high risk was 15% for men and 11% for women. The risk prevalence of less than 3% was 37% for men and 42% for women in China, and 54% for men and 68% for women in Mexico[7].

However, this higher cardiovascular risk ratio in lower social classes obtained in our study coincides with the results obtained by Ueda et al., who find a greater cardiovascular risk both in the lowest social classes and in the countries with lower or middle income[11].

In the literature reviewed, we have only found one study carried out in 182 countries that included data from the Czech population, in which the prevalence of high cardiovascular risk values is higher than that of our study. While both agree that cardiovascular risk in the Czech population is much higher in men than in women[11].

The rest of the studies found have been performed in third world populations, thus a study performed in several African countries[12] found mean risk values with the Globorisk scale of 2-6%, lower than ours. However, the results highlight different 10-year CVD risk levels by region, with lower levels of estimated risk observed in rural West African sites, higher levels in the urban Nairobi site, and higher levels in all three South African sites. Importantly, the rural sites in South Africa had populations with higher levels of estimated risk than the urban site in Nairobi. Regardless of the algorithm used, men were found to have higher levels of 10-year predicted risk than women at all sites[12]. The variability between regions and geographical areas had already been described by Hajifathalian et al. in 2015[7].

Another study in Burkina Faso also found mean values of the scale and prevalence of high Globorisk values lower than those obtained by us. However, this work comes from a secondary analysis of data from the first cross-sectional survey at the national level on risk factors for noncommunicable diseases in Burkina Faso, so there could be an under-declaration. Furthermore, the sample size was low and could cause a low precision of the measured associations[13]. A study in people with diabetes in Bangladesh found a prevalence of high values of 37%, which is much higher than ours. In this case, we must bear in mind that all people were diabetic, and that the American Heart Association warns that diabetic people are 2 to 4 times more likely to die from heart disease than non-diabetics, and at least 68% of them aged 65 and over die from some form of heart disease[14].

Other investigations[15] have also found, as we did, a positive association between higher social class and non-tobacco use and a lower CVR with the Globorisk scale.

Strenghts and limitations

As strong points we would highlight that this is the first study carried out in our country using this scale, in addition the sample size is very large (more than 28,000 people) and the influence of sociodemographic variables such as social class, which is rarely taken into account, is assessed.

The main limitation is the impossibility of comparing our results with those obtained by other authors in our country, since there are no other studies similar to ours.

Conclusion

We consider the use of the Globorisk scale to determine CVR to be of interest, since there is a scale for each of the countries adapted to the characteristics of the population.

Interests conflict

The authors declare no conflict of interest.

References

1. Vera-Remartínez EJ, Lázaro Monge R, Granero Chinesta S, Sánchez-Alcón Rodríguez D, Planelles Ramos MV. Factores de riesgo cardiovascular en adultos jóvenes de un centro penitenciario. Revista Española de Salud Pública 2018; 92,e201807037.

2. Patrón Osorno HO, Manzanero Fernández RZ, Ke Aznar EA. Values of different index related to cardiovascular risk according the Findrisc test scores in Caucasian. Academic Journal of Health Sciences 2021; 36 (3): 29-33.

3. Anderson KM, Wilson PWF, Odell PM, Kannel WB. An updated coronary risk profile. A statement for health professionals. Circulation 1991; 83(19):356-62.

4. D'Agostino RB, Grundy S, Sullivan LM, Wilson P. Validation of the Framingham Coronary Heart Disease Prediction Scores: Results of a Multiple Ethnic Groups Investigation. JAMA 2001; 286(2):180-7.

5. Marrugat J, D'Agostino R, Sullivan L, Elosua R, Wilson P, Ordovás J, et al. An adaptation of the Framingham risk function to southern Europe Mediterranean areas. J Epidemiol Community Health. 2003; 57(8):634-8.

6. Conroy R, Pyörälä K, Fitzgerald T, Sans S, Menotti A, De Backer G, et al. Estimation of ten-year risk of fatal CVD in Europe: the SCORE Project. Eur Heart J 2003; 24(11):987-1003.

7. Hajifathalian K, Ueda P, Lu Y, Woodward M, Ahmadvand A, Aguilar-Salinas CA, et al. A novel risk score to predict cardiovascular disease risk in national populations (Globorisk): a pooled analysis of prospective cohorts and health examination surveys. Lancet Diabetes and Endocrinology. 2015; 3(5): 339-55.

8. Domingo-Salvany A, Bacigalupe A, Carrasco JM, Espelt A, Ferrando J, Borrell C. Propuesta de clase social neoweberiana y neomarxista a partir de la Clasificación Nacional de Ocupaciones 2011. Gac Sanit 2013; 27(3):263-72

9. Risk Charts | Globorisk. Available at http://globorisk.org/risk-charts

10. JBS3 Board: Joint British Societies' consensus recommendations for the prevention of cardiovascular disease. Heart 2014; 100: pp. ii1. i67

11. Ueda P, Woodward M, Lu Y, Hajifathalian K, Al-Wotayan R, Aguilar-Salinas CA, et al. Laboratory-based and office-based risk scores and charts to predict 10-year risk of cardiovascular disease in 182 countries: a pooled analysis of prospective cohorts and health surveys. Lancet Diabetes Endocrinol. 2017 Mar;5(3):196-213.

12. Wagner RG, Crowther NJ, Micklesfield LK, Boua PR, Nonterah EA, Mashinya F, et al. Estimating the burden of cardiovascular risk in community dwellers over 40 years old in South Africa, Kenya, Burkina Faso and Ghana. BMJ Glob Health. 2021 Jan;6(1):e003499.

13. Cisse K, Samadoulougou S, Ouedraogo M, Bonnechère B, Degryse JM, Kouanda S, et al. Geographic and Sociodemographic Disparities in Cardiovascular Risk in Burkina Faso: Findings from a Nationwide Cross-Sectional Survey. Risk Manag Healthc Policy. 2021 Jul 7;14:2863-2876.

14. Mondal R, Ritu RB, Banik PC. Cardiovascular risk assessment among type-2 diabetic subjects in selected areas of Bangladesh: concordance among without cholesterol-based WHO/ISH, Globorisk, and Framingham risk prediction tools. Heliyon. 2021 Aug 5;7(8):e07728.

15. Geldsetzer P, Manne-Goehler J, Theilmann M, Davies JI, Awasthi A, Danaei G, Gaziano TA, Vollmer S, Jaacks LM, Bärnighausen T, Atun R. Geographic and sociodemographic variation of cardiovascular disease risk in India: A cross-sectional study of 797,540 adults. PLoS Med. 2018 Jun 19;15(6):e1002581.

eISSN 2255-0569

ORIGINAL

Trend and prevalence of skin disorders among Saudi population in different regions of Saudi Arabia

Tendencia y prevalencia de los trastornos de la piel entre la población saudí en diferentes regiones de Arabia Saudí

Fahad Alfhaid[1], Hala S. AlZuyaydi[2], Safaa A. Fahad[3], Abdulrahman M. Alkhammash[3], Weam A. Moafa[4], Mashal A. Alameer[5], Shahad D. Alsulaimani[6], Eslam S. Almarhoun[7], Sami S. Alabdulqader[8]

1. Deparment of Family Medicine, College of Medicine, Majmaah University, Majmaah, Saudi Arabia.
2. General Practitioner, East Fayzyah Primary health care center, Buraidah, Saudi Arabia.
3. Medical College, Ibn Sina National College, Jeddah, Saudi Arabia.
4. Medical College, Jazan University, Jazan, Saudi Arabia.
5. Medical College, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia.
6. Department of Dermatology, King Fahad Hospital, Jeddah.
7. Medical College, Zagazig University, Zagazig, Egypt.
8. Medical College, Majmaa University, Majmaah, Saudi Arabia.

Corresponding author
Fahad Mohammad Alfhaid
Associate Professor, Department of Family Medicine, College of Medicine, Majmaah University, Al Majmaah-11952, Saudi Arabia.
E-mail: F.Alfhaid@mu.edu.sa

Received: 28 - X - 2021
Accepted: 28 - XII - 2021

doi: 10.3306/AJHS.2022.37.01.150

Abstract

Objective: The present study aims at understanding and examining the trends of skin problems among Saudi residents in a cross-sectional qualitative study.
Methodology: The study was a cross-sectional study carried out among the adult population in Saudi Arabia from all five regions of Saudi Arabia. Data were collected through closed-ended questionnaires recruited through online means and respondents only participating in the study out of their own will. The main data collection tool was a closed-ended questionnaire that captured sociodemographic factors and the disorders experienced by the study respondents. Analysis was carried out using SPSS version 22.
Results: A sample of 1349 respondents was drawn where 751 of the respondents were aged between 18 and 35, which represented the majority of the respondents (55.7%). 77% of the respondents were females, while the rest were males. The proportion of respondents with acne significantly varied across gender p<.001, which was also the case with eczema. 17.6% of the respondents had some kind of skin problem where the acne was the most prevalent skin problem 32.4%.
Conclusion: While skin disease may have been found to significantly differ between men and women in previous studies, in the present study, only acne and eczema significantly differed. The most suffered skin problem across Saudi Arabia is acne.

Keywords: Acne, skin diseases, dermatology.

Resumen

Objetivo: El presente estudio tiene como objetivo comprender y examinar las tendencias de los problemas cutáneos entre los residentes saudíes en un estudio cualitativo transversal.
Metodología: Se trata de un estudio transversal realizado entre la población adulta de Arabia Saudí de las cinco regiones del país. Los datos se recogieron mediante cuestionarios cerrados reclutados por medios online y los encuestados sólo participaron en el estudio por su propia voluntad. La principal herramienta de recogida de datos fue un cuestionario cerrado que recogía los factores sociodemográficos y los trastornos experimentados por los encuestados del estudio. El análisis se realizó con el SPSS versión 22.
Resultados: Se extrajo una muestra de 1.349 encuestados, de los cuales 751 tenían entre 18 y 35 años, lo que representaba la mayoría de los encuestados (55,7%). El 77% de los encuestados eran mujeres, mientras que el resto eran hombres. La proporción de encuestados con acné varió significativamente según el género p<.001, lo que también ocurrió con el eczema. El 17,6% de los encuestados tenía algún tipo de problema cutáneo, siendo el acné el problema cutáneo más frecuente, el 32,4%.
Conclusión: Mientras que en estudios anteriores se ha comprobado que las enfermedades de la piel difieren significativamente entre hombres y mujeres, en el presente estudio, sólo el acné y el eczema difieren significativamente. El problema cutáneo más sufrido en toda Arabia Saudí es el acné.

Palabras clave: Acné, enfermedades de la piel, dermatología.

Introduction

Skin diseases are amongst the common health problems that are confronted by primary care physicians. The incidence of skin disorders in an area or a country is based on multiple factors; these aspects include genetics, racial background, socioeconomic status, hygienic measures, customs, nutritional trends, and climatic conditions. Also, the diagnostic aptitude and skill of doctors, proficiency of dermatologists, and the obtainability of the up-to-date diagnostic facilities play a very significant part[1].

Almost every person suffers from skin diseases at some time during his/her life, and this shows the prevalence of dermatologic ailments. Conditions or states such as formation warts and acne are almost widespread and quite common at certain ages[2]. However, whether people spot or reach out for medical care for these common conditions varies widely depending on the site of the body involved and the severity of the disease.

Epidemiological surveys to evaluate a load of dermatological diseases in an area are crucial. The information and analysis derived about the incidence and spectrum of certain disorders assist in the formation of strategies for appropriate health care planning. Such info and stats also help to develop proper preventive and research programs according to the requirement of the community[3].

The reviews and research on the trends of common and specific skin disorders are very insufficient and sparse, and only a limited number of published research papers and reports are in Saudi Arabia[3]. Although the community-based research study is the most preferred way to evaluate the incidence of a specific disorder; this method is quite hard to conduct. As it is very time-consuming and requires a vast workforce as well as a lot of effort. As most of such studies to measure the occurrence of dermatological disorders are based on hospital attendees[4-5].

The main aim of this study is to evaluate the trends of dermal diseases in patients. So that proper training programs on mostly occurring skin disorders could be started for primary health care physicians and the rest of the general practitioners.

Methodology

The study was a cross-sectional study carried out among the adult population in Saudi Arabia from all five regions of Saudi Arabia from June 2020 to December 2020. There are some minor differences between these regions geographically, environmental and socioeconomic status. The adult population, including both males and females living in Saudi Arabia, was considered in the present study. An online questionnaire was disseminated through various social media platforms like twitter, Facebook, and WhatsApp. The weblink with the prerequisite consent was sent. The questionnaire had details on sociodemographic profiles and skin disorders experienced by the study respondents. This survey was validated, and a pilot study was carried out before the commencement of the study. The sample size for the present study was determined using the formula $n = p(1-p) * (Z_{\frac{\alpha}{2}}/e)^2$ where p is the preferred population proportion set at $0.5, Z_{\frac{\alpha}{2}} = 1.96$ where alpha was 0.05, and e was the expected margin of error. The desired sample size was 382, but larger sample size was collected. Data analysis was done using Statistical Package for Social Science (SPSS) version 22 and Excel 2013. Ethical approval was obtained from King Fahad Medical City Research Centre.

Results and analysis

77% (1039 out of 1349) of the respondents were females, while the rest were males. 751 of the respondents were aged between 18 and 35, which represented the majority of the respondents (55.7%). Respondents aged older than 65 were 0.7%. Only 2.6% of the respondents were from the Northern region, while the Western Region was represented by 636 respondents (47.1%), while the Eastern region was represented by 33.7% of the respondents. The proportion of married and single respondents was almost the same as the single respondents were 54.3%, while 45.7% of the respondents were married. 861 (63.8%) of the respondents reported their highest qualification as a diploma or bachelor level, while respondents whose highest level of education was high school were represented by 27.8% of the respondents. The majority of the respondents reported their highest education level as bachelor's or diploma. For the respondents represented in the sample, income was fairly equally distributed as the percentage of respondents with income less than 5000 riyals per month was 46.2%, while those with income greater than 15000 riyals per month was 15.3%. 55.4% of the respondents confirmed that at least one of their family members had the same skin problems as the respondents, while the majority of the respondents indicated that they are not ashamed of the skin problem they are having. 98.9% of the respondents reported no instances of cancers in their life, while 1.1% of the respondents confirmed they had had some form of cancer in their life prior to the skin problem. **Table I** shows the summary statistics for the present sample data.

The inference was made on the sample data to compare whether the different age groups and gender of the study participants significantly varied with respect to the different ailments presented in the study. Acne was much more prevalent in individuals aged 18-35 (63.9%), and this ailment significantly varied across the five age groups represented in the sample data p=.000. There was no significant difference in the proportion of respondents who

suffered from psoriasis across the different age groups (p=.111), the proportion of respondents across age groups who suffered from alopecia (p=0.972). However, there was a significant difference in the proportion of respondents who reported suffering from eczema across the five age groups p=0.000. (**Table II**)

The present study also established that the proportion of males and females who suffer from acne is significantly different at 0.01 significance level p=.000. The same can be said of the proportion of males and females who suffer from eczema, where the p-value associated with the chi-square statistic was p=0.000. However, there was no significant difference between males and females in terms of proportion that suffers from psoriasis alopecia, vitiligo boils, and moles (p>.05 in all mentioned cases above), as shown in the below **table III**.

There was a significant association between blistering when exposed to the sun and application of sunscreen or any other such product p<.001 as per **table IV**.

Table I: Distribution of study respondents based on sociodemographic variables and health conditions.

Variable	Freq.	Percent
Gender		
· Male	310	23
· Female	1039	77
Age		
· <18	164	12.2
· 18-35	751	55.7
· 36-50	289	21.4
· 51-65	136	10.1
· 65>	9	0.7
Residence		
· Central Region	23	16.5
· Eastern Region	455	33.7
· Northern Region	35	2.6
· Western Region	636	47.1
Marital Status		
· Single	617	54.3
· Married	732	45.7
Education Level		
· Primary	32	2.4
· High School	375	27.8
· Higher studies	80	5.9
· Diploma/bachelor	861	63.8
Income (Riyal/month)		
· <5000	623	46.2
· 5000-10000	283	21.0
· 10000-15000	236	17.5
· >15000	207	15.3
Whether anyone else has the same problem in Family		
· Yes	748	55.4
· No	366	27.1
· Don't Know	235	17.4
Do you feel ashamed of your condition?		
· Yes	363	26.9
· No	765	56.7
· Not Applicable	221	16.4
History of Any cancer		
· Yes	15	1.1
· No	1334	98.9
Family history of any cancer?		
· Yes	353	26.2
· No	825	61.2
· I don't Know	171	12.6
Skin disease		
· Yes	238	17.6
· No	1111	82.4

Table II: Age-wise distribution of respondent's response on previous history/ present complaints of different skin conditions.

Disease	<18	18-35	36-50	51-65	65>	Sig
Acne	24.9	63.9	10.7	0.6	0	***.000***
Psoriasis	6.7	36.7	30	26.7	0	.111
Alopecia	23.1	23.1	30.8	23.1	0	.972
Eczema	4.3	58.5	22.3	13.8	1.1	***.000***
Vitiligo	22.1	22.2	33.3	22.2	0	.881
Boils	10	50	30	10	0	.221
Moles	7.1	46.4	28.6	10.7	7.1	***.002***
Freckle	0	41.2	52.9	5.9	0	***.047***

Table III: Sex-wise distribution of respondent's response on previous history/ present complaints of different skin conditions.

Disease	Male	Female	Sig.
Acne	13.6	86.4	.000
Psoriasis	43.33	56.67	.465
Alopecia	61.5	38.5	.263
Eczema	24.47	75.53	.000
Vitiligo	66.67	33.33	.157
Boils	80	20	.058
Moles	67.86	32.14	.059
Freckles	64.71	35.3	.225

Table IV: Association between blistering of skin exposed to sun and sunscreen application.

	Value	df	P value
No of cases	1349	-	-
Likelihood Ratio	48.50	6	0.00

Discussion

The present study aimed at exploring and evaluating the different situation of skin health across the different regions of Saudi Arabia. The present analysis found out that only 17.4% of the study respondents did not report any kind of skin disorders, while more than 82% of the study respondents reported some form of skin ailment. This is in contrast to the report by Thomas et al., 2019 where they found out that half of the adult population in India suffered from some form of skin ailment. That the present study predominantly consisted of female respondents as opposed to male respondents was also reflected in the other studies carried out with the aim of investigating the prevalence and patterns of skin diseases[6-10]. In this regard, the present study incorporated respondents from across Saudi Arabia as opposed to a specified region in the Kingdom of Saudi Arabia. Just like in the study by Alshamrani on the trends in skin ailments in Saudi Arabia, the average age of study participants was 35 years with a standard deviation of 3.8 years. Age was grouped in the present study, with the highest frequency of respondents being aged between 18 and 35 years[11].

That women experience more dermatological conditions generally more than men do is well documented[12]. Despite the fact that a majority of Saudi women cover the bigger portion of their bodies, leaving only the hands and the feet, the difference in men and women skin

ailments can be attributed to the use of beauty products by women[13] (Matta et al., 2019). The difference in skin ailments between male and female respondents was only observed in the present study in the cases of acne and eczema (p<.001 in both cases). In both cases, there was a significantly larger percentage of women with the said diseases than there were men. However, that alopecia was significantly different in proportion between men and women in the study done in Saudi Arabia and is not reflected in our study. The most common skin ailment in our study was acne (32.4%), while in Alshamrani was dermatitis (21.4%)[11].

As would be expected, acne hits most people in their younger adult years as compared to their old age. There was a significant difference in the prevalence of acne across the five age groups p=.0000. This finding was also observed in the study by El Akawi et al[12] and Alshamrani et al11 which could be easily attributed to the rapid growth and change in the hormonal composition during young adulthood. Women, especially in the ages between 18 and 35, could have reported higher rates of acne due to the increased image and self-awareness than men in the same age bracket. While one would expect skin conditions such as acne that are visible to everyone to induce some form of low self-esteem, the proportion of the respondents in the present study who reported low self-esteem due to skin condition was lower than those who did not report a drop in self-esteem 26.9%. This is in comparison to the findings by Alshamrani et al[11], where the bigger percentage of respondents reported a drop in self-esteem.

Sampling and the accuracy of the measurements taken form an important part in the validity of study results. The gold standard to improving validity is conducting a complete experiment where each population member has an equal chance at being included in the sample. This was not the case in the present study which rendered the results quasi-experimental hence undermining the validity of the study. However, since the study included participants from all over Saudi Arabia, the representativeness of the sample was intact.

Limitations of the study: The study was conducted online during the covid 19 pandemic, so it is affected the responses rate. In addition to that, there was no clinical confirmation, and the information collected is solely based on respondents' self-reporting of skin diseases.

Conclusion

While skin disease may have been found to significantly differ between men and women in previous studies, in the present study, only acne and eczema significantly differed. The most suffered skin problem across Saudi Arabia is acne.

Acknowledgment

I would like to acknowledge Dr. Ghaiath Hussein for reviewing the research work, and also, we would like to thank the Deanship of Scientific Research at Majmaah University for supporting this work.

Funding

This study was not funded.

Interests conflict

The authors declare no conflict of interest.

Ethical approval for study

The study was approved by the Medical Ethics Committee of Majmaah University.

References

1. Burton JL, Savin JA, Champion RH. Introduction, epidemiology and historical bibliography. In: Champion RH, Burton JL, Ebling FJ, editors. Textbook of dermatology. 5th ed. Vol. 1. Oxford: Blackwell Scientific Publications; 1992.

2.Bahamian KA, Egere JU, Khare AK, Tallab T, Ibrahim K, Mourad M. The pattern of skin diseases in Asir region, Saudi Arabia: A 12-month prospective study in a referral hospital. Ann Saudi Med 1995;15(5):455-7.

3.Kubeyinje EP. The pattern of endogenous eczema in the Northern Frontier, Kingdom of Saudi Arabia. Ann Saudi Med 1995;15(4):416-8.

4.Abu Share'ah AM, Abdel Dayem H. The incidence of skin diseases in Abu Dhabi (United Arab Emirates). Int J Dermatol 1991;30(2):121-4.

5.Agarwal PK. Pattern of skin diseases in Al-Jouf Region. Ann Saudi Med 1997;17(1):112-4.

6.Najdawi F, Fa'ouri M. Frequency and types of skin disorders and associated diabetes mellitus in elderly Jordanians. East Mediterr Health J 2002;8(5):574-8.

7.Baghestani S, Zare S, Mahboobi AA. Skin disease patterns in Hormozgan, Iran Int J Dermatol 2005;44(8):641-5.

8.Parthasaradhi A, Al Gufai AF. The pattern of skin diseases in Hail Region, Saudi Arabia. Ann Saudi Med 1998;18(6):558-61.

9.Alzahrani MK, Almanaah MAM, Alabdulatif AAM, Alshammari SMN, Almazroa AM. Prevalence of skin problems and its health impact among adolescent school children in Majmaah. Sau Area Med Sci 2021;25(114):2030-7.

10.Al Shobaili HA. The pattern of skin diseases in the Qassim region of Saudi Arabia: What the primary care physician should know. Ann Saudi Med. 2010;30(6):448-53.

11.Alshamrani HM, Alsolami MA, Alshehri AM, Salman AK, Alharbi MW, Alzuhayri AJ, et al. Pattern of skin diseases in a university hospital in Jeddah, Saudi Arabia: age and sex distribution. Ann Saudi Med. 2019 Jan-Feb;39(1):22-28.

12.El Akawi Z, Abdel Latif Nemr N, Razzak A, Al Aboosi M. Factors believed by Jordanian acne patients to affect their acne condition. East Medit Health J. 2006;12(6):840–6.

13.Thomas J, Saple DG, Jerajani HR, Netha NRG, Rangasamy DU, Shaikh R, et al. Real-World, Non-Interventional, Observational Study of Hydroxyzine Hydrochloride in Chronic Pruritus: a Prospective, Non-Comparative Study. Dermatol Ther (Heidelb). 2019;9(2):299-308.

eISSN 2255-0569

ORIGINAL

Risk of prediabetes as determined by the Prediabetes Risk Score in Qatar (PRISQ) in the european working population

Riesgo de prediabetes determinada con la escala Prediabetes Risk score in Qatar (PRISQ) en población laboral europea

Fernando Fernández García-Abril[1], Pedro Luis Cabot Nadal[2], Sonia Bravo Rodríguez[2], Vanina Elisabet Pascua Escot[2], Cristina Alonso Saiz[2], Eduardo Tejedo Benedicto[3]

1. ECHO Expert Santé / Health Expert Bureau Regional Dakar. Cameroon
2. PREVIS. Prevention Service. Palma. Balearic Islands. Spain
3. PREVIS. Prevention Service. Ibiza. Balearic Islands. Spain

Corresponding author
Fernando Fernández García-Abril
ECHO Expert Santé / Health Expert
Bureau Regional Dakar. Cameroon
E-mail: Fernando.Fernandez@echofield.eu

Received: 24 - X - 2021
Accepted: 29 - XII - 2021

doi: 10.3306/AJHS.2022.37.01.151

Abstract

Introduction: Diabetes is a chronic disease that has a major impact on people's health by increasing the risk of death from cardiovascular and other causes. Pre-diabetes is a state prior to diabetes that is also known to increase health risk. The aim of this study is to apply a tool to detect people at high risk of prediabetes.
Methods: Retrospective, cross-sectional study conducted in 134,065 European workers aged 18-69 years. The PRISQ (Prediabetes Risk Score in Qatar), which uses clinical anthropometric variables, was used to determine the risk of developing prediabetes.
Results: 13.1% of the men and 6.2% of the women in our study had high-risk PRISQ values. The different sociodemographic variables analysed, especially age, but also sex and social class increase the risk of having high PRISQ values.
Conclusion: The PRISQ scale can be useful at all levels of care to detect people at risk of prediabetes.

Keywords: Prediabetes, socio-demographic variables, prediabetes risk score in Qatar, prevention.

Resumen

Introducción: La diabetes es una patología crónica que tiene una gran repercusión en la salud de las personas incrementando el riesgo de muerte de origen cardiovascular y por otras causas. La prediabetes es un estado previo a la diabetes que también se sabe que incrementa el riesgo sobre la salud. El objetivo de este estudio es aplicar una herramienta para detectar personas con alto riesgo de prediabetes.
Metodología: Estudio retrospectivo y transversal realizado en 134.065 trabajadores europeos de 18 a 69 años. Para determinar el riesgo de presentar prediabetes se emplea el PRISQ (Puntuación de riesgo de prediabetes en Qatar) que emplea para su determinación variables antropométricas clínicas.
Resultados: El 13,1% de los hombres y el 6,2% de las mujeres de nuestro estudio presentan valores de PRISQ de alto riesgo. Las diferentes variables sociodemográficas analizadas, especialmente la edad, pero también el sexo y la clase social incrementan el riesgo de presentar valores altos en la escala PRISQ.
Conclusión: La escala PRISQ puede ser de utilidad en todos los niveles asistenciales para detectar personas con riesgo de prediabetes.

Palabras clave: Prediabetes, variables sociodemográficas, puntuación de riesgo de prediabetes en Qatar, prevención.

Introduction

The International Diabetes Federation estimates that, unless prevention programmes are implemented, the global prevalence of diabetes will be 9.9% in 2045, with 629 million people affected worldwide[1].

DM is defined as "a group of metabolic diseases characterised by hyperglycaemia resulting from deficits in insulin secretion, insulin action or both". Chronic hyperglycaemia is associated with a high incidence of micro- and macrovascular complications affecting the kidneys[2], eyes, nerves[3], coronary arteries, cerebral circulation and peripheral arteries[4]. It is clearly established that vascular risk is higher in patients with diabetes mellitus than in individuals without diabetes mellitus, such that diabetic patients have a 2- to 5-fold higher risk of cardiovascular disease than the general population[5]. This increased cardiovascular risk arises as a result of a combination of diabetes-specific alterations and the acceleration of the atherosclerosis process common to all individuals[6,7].

The possible relationship between prediabetes and cardiovascular disease risk has gained prominence in recent years, although the results are not entirely conclusive. A recent meta-analysis conducted in China[8] with 129 studies including more than 10 million people followed for more than 10 years assessed the association between prediabetes and the risk of cardiovascular disease or death from any other cause in people with and without a history of heart disease. The most interesting results were that prediabetes increased the risk of cardiovascular disease by 15% and all-cause mortality by 13% in people with no previous history compared to people with normal blood glucose levels. If there was a previous history of cardiovascular disease, the risk increased by 37% for heart disease and 36% for all-cause mortality.

5-10% of people per year with prediabetes will progress to diabetes, with the same proportion converting back to normoglycaemia. Prevalence of prediabetes is increasing worldwide and experts have projected that more than 470 million people will have prediabetes by 2030[9].

It is important to detect at an early stage those people at high risk of developing pre-diabetes, so the aim of this study is to determine those people at high risk of developing pre-diabetes using one of the few existing instruments, the Prediabetes Risk score in Qatar (PRISQ).

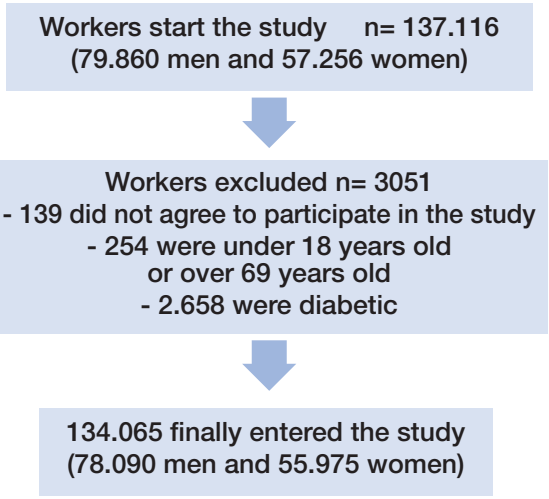
Methods

A retrospective and transversal study is carried out on 134.065 workers from different Spanish geographical areas and belonging to different productive sectors during the period from January 2019 to June 2020. The workers were selected among those who attended the periodic occupational medical examinations. The flow chart is shown in **figure 1**.

Inclusión criteria

- Age between 18 and 69 years old.
- Be an active worker
- Agree to participate in the study.
- Not being diabetic

Figure 1: Flow chart of the participants.



Data collection and management

The anthropometric measurements of height and weight, clinical and analytical, have been made by the health personnel of the different occupational health units participating in the study, after homogenizing the measurement techniques.

To measure the weight (expressed in kilograms) and the height (expressed in cm), a scale/height meter was used: model SECA 700 with capacity for 200 kg and 50 gram divisions, which has an added telescopic height meter SECA 220 with millimetric division and 60-200 cm interval. The BMI is calculated by dividing the weight by the height in meters squared.

The abdominal waist perimeter was measured in cm with a measuring tape: SECA model 20, with 1-200 cm interval and millimetric division. For evaluation, the person is placed in a standing position, feet together and trunk upright, abdomen relaxed and upper extremities hanging on both sides of the body. The measuring tape is placed parallel to the floor at the level of the last floating rib.

CUN BAE[10] (Clínica Universidad de Navarra Body Adiposity Estimator) The formula is:

$-44.988 + (0.503 \times age) + (10.689 \times gender) + (3.172 \times BMI) - (0.026 \times BMI^2) + (0.181 \times BMI \times gender) - (0.02 \times BMI \times age) - (0.005 \times BMI^2 \times gender) + (0.00021 \times BMI^2 \times age)$.

Where male sex equals 0 and female sex equals 1.

The blood pressure was examined in supine position with a calibrated OMRON M3 automatic sphygmomanometer and after 10 minutes of rest. Three determinations were made at one-minute intervals, obtaining the mean value of the three.

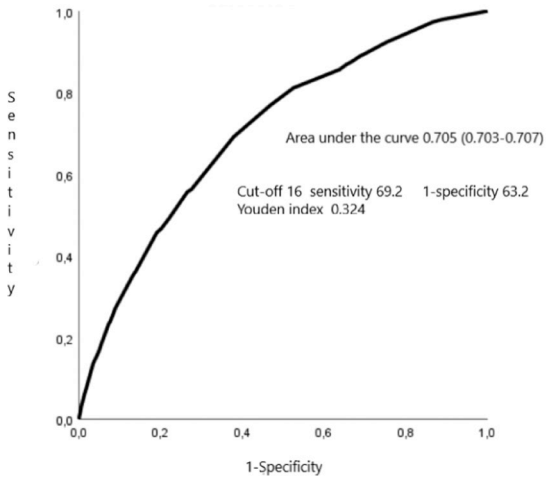
The blood samples were obtained by peripheral venipuncture after 12 hours of fasting and were sent to the reference laboratories where they were processed within a maximum time of 48-72 hours. Glycaemia, total cholesterol and triglycerides were determined by automated enzymatic methods, expressing the values in mg/dl. HDL is calculated by precipitation with dextran-sulphate Cl2Mg, and values are expressed in mg/dl. The LDL is estimated by means of the Friedewald formula (provided that the triglycerides are lower than 400 mg/dl) and is expressed in mg/dl.

Friedewald formula: LDL-c= Total cholesterol–HDL-c–triglycerides/5

The social class is determined from the 2011 National Classification of Occupations (CNO-11), based on the proposal of the group of social determinants of the Spanish Society of Epidemiology[11]. It is classified into 3 categories: Class I. Directors/managers, university professionals, athletes and artists. Class II. Intermediate occupations and self-employed workers without employees. Class III. Unskilled workers.

The risk of developing pre-diabetes is determined with the PRISQ[12] scale, which uses age, sex, waist circumference, BMI and blood pressure to calculate it. The cut-off point for high risk is 16 points for the Qatari population, the same figure as that obtained by us in the Spanish population (see **figure 2**).

Figure 2: Cut-off of PRISQ for spanish population.



Statistical analysis

A descriptive analysis of the categorical variables is carried out, calculating the frequency and distribution of responses for each of them. For quantitative variables, the mean and standard deviation are calculated, and for qualitative variables the percentage is calculated. The bivariate association analysis is carried out by means of the test of chi 2 (with correction of the exact Fisher statistic when conditions require it) and the Student t for independent samples. The statistical method of ROC curves (Receiver operating characteristic) curves were used to determine PRISQ discriminatory capacity of prediabetes). Cutoff values were derived mathematically from the ROC curves. For multivariate analysis, binary logistic regression with Wald's method has been used, with the calculation of Odds ratios and the Hosmer-Lemeshow goodness-of-fit test is performed. The statistical analysis is carried out with the program SPSS 27.0 with the accepted statistical significance level of 0.05.

Ethics statement

Approval for the study was obtained from Balearic Islands Health Area Clinical Research Ethics Committee (institutional review board approval number: IB 4383/20). The study was designed in accordance with the ethical guidelines of the Declaration of Helsinki. All participants sign written informed consent documents before participating in the study.

Results

Table I shows the anthropometric, clinical and analytical characteristics of the study population. In all cases the values are more unfavourable in males with statistically significant differences.

The mean PRISQ values increase with age, and this is true for both men and women. In women, PRISQ values get worse as social class gets worse, this situation is not observed in men. In all cases, age and social class, the values are higher in males. The complete data are presented in **table II**.

The prevalence of high-risk PRISQ values behaves similarly to what we have seen with the mean values, i.e. it increases with age and also as we move down the social class. The global prevalence of high risk of PRISQ is 13.1% in men and 6.2% in women. All data can be found in **table III**.

In the multivariate analysis using binary logistic regression, male sex, age 50 years and older, and belonging to social classes II and III were established as covariates. All three variables increase the risk of presenting a high-risk PRISQ, with age having the greatest influence with an ODDS ratio of 11.62 (95% CI 11.37-12.09). The full data are presented in **figure 3**.

Table I: Characteristics of the population.

	Men n= 78.090	Women n= 55.975	Total n= 134.065	
	Mean (SD)	Mean (SD)	Total (SD)	p-value
Age (years)	40.2 (11.0)	39.5 (10.7)	39.9 (10.9)	<0.0001
Height (cm)	174.7 (6.9)	161.9 (6.5)	169.3 (9.3)	<0.0001
Weight (kg)	81.0 (14.4)	66.2 (13.9)	74.8 (16.0)	<0.0001
BMI (kg/m²)	26.5 (4.4)	25.3 (5.1)	26.0 (4.7)	<0.0001
Waist circumference (cm)	85.9 (10.9)	74.7 (10.5)	81.3 (12.1)	<0.0001
Waist to height ratio	0.49 (0.06)	0.46 (0.06)	0.48 (0.06)	<0.0001
CUN BAE (%)	25.3 (6,5)	35.1 (7.1)	29.4 (8.3)	<0.0001
Systolic blood pressure (mmHg)	127.8 (15.3)	117.2 (15.5)	123.4 (16.2)	<0.0001
Diastolic blood pressure (mmHg)	77.5 (15.3)	72.5 (10.4)	75.4 (11.0)	<0.0001
Total cholesterol (mg/dl)	192.2 (38.6)	190.2 (35.6)	191.4 (37.4)	<0.0001
HDL-c (mg/dl)	50.5 (8.4)	56.8 (8.6)	53.1 (9.1)	<0.0001
LDL-c (mg/dl)	118.0 (36.6)	115.8 (34.6)	117.1 (35.8)	<0.0001
Triglycerides (mg/dl)	121.1 (80.7)	88.2 (46.1)	107.4 (70.3)	<0.0001
Glycaemia (mg/dl)	90.5 (11.9)	88.7 (10.7)	88.9 (11.6)	<0.0001

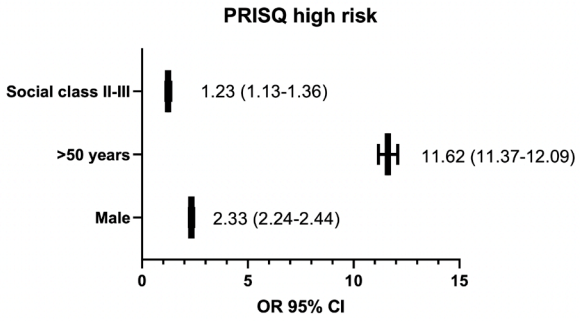
Table II: Mean values of PRISQ according sociodemographic variables by sex.

	Men			Women		
	n	Mean (SD)	p-value	n	Mean (SD)	p-value
18-29 years	15275	5.8 (4.4)	<0.0001	11706	2.5 (4.5)	<0.0001
30-39 years	21791	12.1 (7.9)		16560	8.0 (7.8)	
40-49 years	23602	20.1 (5.3)		16691	16.0 (5.4)	
50-59 years	14736	25.1 (7.4)		9306	20.9 (7.6)	
60-69 years	2686	31.8 (4.9)		1712	27.8 (5.7)	
Social class I	3851	16.8 (9.4)	<0.0001	3995	9.9 (8.6)	<0.0001
Social class II	11702	17.4 (9.4)		13121	11.4 (8.8)	
Social class III	62537	16.2 (9.8)		38859	12.4 (9.8)	

Table II: Prevalence of elevated values of PRISQ according sociodemographic variables by sex.

	Men			Women		
	n	% (95% CI)	p-value	n	% (95% CI)	p-value
18-29 years	15275	0.0	<0.0001	11706	0.0	<0.0001
30-39 years	21791	3.9 (3.8-4.0)		16560	0.9 (0.9-1.0)	
40-49 years	23602	11.3 (11.2-11.4)		16691	4.0 (3.9-4.1)	
50-59 years	14736	32.9 (32.8-33.0)		9306	19.8 (19.6-20.0)	
60-69 years	2686	68.4 (67.9-69.9)		1712	48.8 (48.1-49.5)	
Social class I	3851	12.6 (12.2-13.0)	<0.0001	3995	3.2 (2.8-3.6)	<0.0001
Social class II	11702	13.7 (13.5-13.8)		13121	4.6 (4.4-4.8)	
Social class III	62537	13.0 (12.9-13.1)		38859	7.1 (7.0-7.2)	
Total	78090	13.1 (13.0-13.2)		55975	6.2 (6.1-6.3)	

Figure 3: Binary logistic regression.



Discussion

The data from our study show that applying the PRISQ scale in the Spanish population, the prevalence of high-risk values for pre-diabetes is 13.1% in men and 6.2% in women. Other noteworthy data are that all the socio-demographic variables analysed, especially age, increase the risk of presenting high PRISQ values.

As this is a recently created scale (2021), there are no studies in the medical literature that allow us to compare our results with those obtained by other authors.

In our study age is an important risk factor for the development of pre-diabetes. Previous studies showed that some populations in Mexico and Jamaica[13], as well as non-white minorities in the UK[14] , had an earlier onset of diabetes than white people. In Israel, Arabs were found to have an earlier onset of diabetes than Jewish people[15]. Similarly, Arab men developed diabetes earlier than UK men living in Canada, probably due to an unhealthy lifestyle[16] . In the same vein, we found a study comparing the onset of diabetes in Iraqi immigrants living in Sweden versus Swedes showed that immigrants had a significantly earlier age of diabetes onset (47.6 years versus 53.4 years) and a higher risk of diabetes onset[17].

As strong points, we would highlight the large sample size, more than 134,000 people, and the assessment of the influence of different sociodemographic variables. The most important limitation is that the PRISQ is a scale

based on data from the Qatari population, so we do not know whether it can be extrapolated to the Spanish population, although the cut-off point obtained by us coincides with that obtained by the authors of the scale. Another limitation is that only people of working age (18-69 years) have been included, so the prevalence in other age groups is not known.

Conclusion

PRISQ is a non-invasive tool for detecting pre-diabetes and very easy to interpret. This scale can be easily used in any individual with risk factor measurements, or be implemented in primary care settings and used routinely by healthcare staff.

Interests conflict

The authors declare no conflict of interest.

References

1. Federación Internacional de la Diabetes. Atlas de la Diabetes. Octava edición. Update 2017. Available at: http://www.diabetesatlas.org/resources/2017-atlas.html

2. Kim GS, Oh HH, Kim SH, Kim BO, Byun YS. Association between prediabetes (defined by HbA1C, fasting plasma glucose, and impaired glucose tolerance) and the development of chronic kidney disease: a 9-year prospective cohort study. BMC Nephrol. 2019 Apr 16;20(1):130. Wilson ML. Prediabetes: beyond the borderline. Nurs Clin North Am 2017; 52: 665-77.

3. Complicaciones de la diabetes a largo plazo. Available at: medlineplus.gov/spanish/ency/patientinstructions/000327.htm

4. Rawshani A, Rawshani A, Franzén S, Eliasson B, Svensson AM, Miftaraj M, et al. Mortality and cardiovascular disease in type 1 and type 2 diabetes. N Engl J Med. 2017;376:1407-18.

5. Huang Y, Cai X, Mai W, Li M, Hu Y. Association between prediabetes and risk of cardiovascular disease and all cause mortality: systematic review and meta-analysis. BMJ. 2016 Nov 23;355:i5953.

6. Vistisen D, Witte DR, Brunner EJ, Kivimäki M, Tabák A, Jørgensen ME, Færch K. Risk of Cardiovascular Disease and Death in Individuals With Prediabetes Defined by Different Criteria: The Whitehall II Study. Diabetes Care. 2018 Apr;41(4):899-906.

7. Cai X, Zhang Y, Li M, Wu JH, Mai L, Li J, et al. Association between prediabetes and risk of all cause mortality and cardiovascular disease: updated meta-analysis. BMJ. 2020 Jul 15;370:m2297.

8. Tabák AG, Herder C, Rathmann W, Brunner EJ, Kivimäki M. Prediabetes: a high-risk state for diabetes development. Lancet. 2012 Jun 16;379(9833):2279-90.

9. Gómez-Ambrosi J, Silva C, Catalán V, Rodríguez A, Galofré JC, Escalada J, et al. Clinical usefulness of a new equation for estimating body fat. Diabetes Care 2012;35(2):383-8.

10. Domingo-Salvany A, Bacigalupe A, Carrasco JM, Espelt A, Ferrando J, Borrell C. Propuesta de clase social neoweberiana y neomarxista a partir de la Clasificación Nacional de Ocupaciones 2011. Gac Sanit 2013;27(3):263-72

11. Abbas M, Mall R, Errafii K, Lattab A, Ullah E, Bensmail H, et al. Simple risk score to screen for prediabetes: A cross-sectional study from the Qatar Biobank cohort. J Diabetes Investig. 2021 Jun;12(6):988-97.

12. Irving R, Tusié-Luna MT, Mills J, Wright-Pascoe R, McLaughlin W, Aguilar-Salinas CA. Early onset type 2 diabetes in Jamaica and in Mexico. Opportunities derived from an interethnic study. Rev Invest Clin. 2011 Mar-Apr;63(2):198-209.

13. Winkley K, Thomas SM, Sivaprasad S, Chamley M, Stahl D, Ismail K, et al. The clinical characteristics at diagnosis of type 2 diabetes in a multi-ethnic population: the South London Diabetes cohort (SOUL-D). Diabetologia. 2013 Jun;56(6):1272-81.

14. Kalter-Leibovici O, Chetrit A, Lubin F, Atamna A, Alpert G, Ziv A, et al. Adult-onset diabetes among Arabs and Jews in Israel: a population-based study. Diabet Med. 2012 Jun;29(6):748-54.

15. Tenkorang EY. Early onset of type 2 diabetes among visible minority and immigrant populations in Canada. Ethn Health 2017; 22: 266-84.

16. Bennet L, Lindblad U, Franks PW. A family history of diabetes determines poorer glycaemic control and younger age of diabetes onset in immigrants from the Middle East compared with native Swedes. Diabetes Metab 2015; 41: 45–54.

eISSN 2255-0569

ORIGINAL

Genome-scale reconstruction and systems analysis of brain microglial cells

Reconstrucción a escala del genoma y análisis de sistemas de células microgliales cerebrales

Haleh Iranmanesh

1. Department of Biotechnology, Tehran Medical Sciences Branch, Islamic Azad University, Tehran, Iran

Corresponding author
Haleh Iranmanesh
E-mail: Halehiranmanesh@gmail.com

Received: 26 - X - 2021
Accepted: 30 - XII - 2021

doi: 10.3306/AJHS.2022.37.01.156

Abstract

Introduction and objectives: Microglia are neuroglial cells found throughout the brain and spinal cord. The present study aimed to perform a metabolic comparison between normal and activated microglial cells.

Materials and methods: In the present study, the GEO database was used to access the transcript data. After selecting the appropriate data for the type of cell culture and cell treatment and how to obtain the relevant tissue, and based on the format type of these data, the corresponding package was selected from the Bioconductor and the data were normalized. P-Values were determined to evaluate the significance of statistical studies and the GIMME algorithm and GLPK linear programming solver was used in MATLAB software.

Results: Two types of samples were used in this study: normal and activated microglia. Comparison of the studied models showed that there were some metabolic differences between the two types of microglia, including the number of presented genes, the number of metabolites, and the number of metabolic reactions. The results of this study showed a decrease in the activity of both aconitase and arginase enzymes in activated microglia compared to normal microglia. On the other hand, gene expression associated with succinyl coagulase and lactate dehydrogenase as well as the activity of nitric oxide synthase increased in activated microglia, but the synthesis of fatty acids decreased in the deactivated state.

Conclusion: Reconstruction of the microglia metabolic network based on genomic, biochemical, and physiological data provides an overall outlook of cellular metabolism.

Keywords: Genome-scale of metabolic networks, brain, microglia, systemic medicine.

Resumen

Introducción y objetivos: Las microglías son células neurogliales que se encuentran en todo el cerebro y la médula espinal. El presente estudio tiene como objetivo realizar una comparación metabólica entre células microgliales normales y activadas.

Materiales y métodos: En el presente estudio se utilizó la base de datos GEO para acceder a los datos de transcripción. Tras seleccionar los datos apropiados para el tipo de cultivo celular y el tratamiento celular y la forma de obtener el tejido pertinente, y en función del tipo de formato de estos datos, se seleccionó el paquete correspondiente del Bioconductor y se normalizaron los datos. Se determinaron los valores P para evaluar la importancia de los estudios estadísticos y se utilizó el algoritmo GIMME y el solucionador de programación lineal GLPK en el software MATLAB.

Resultados: En este estudio se utilizaron dos tipos de muestras: microglía normal y activada. La comparación de los modelos estudiados mostró que había algunas diferencias metabólicas entre los dos tipos de microglía, incluyendo el número de genes presentados, el número de metabolitos y el número de reacciones metabólicas. Los resultados de este estudio mostraron una disminución de la actividad de las enzimas aconitasa y arginasa en la microglía activada en comparación con la microglía normal. Por otra parte, la expresión génica asociada a la succinil coagulasa y a la lactato deshidrogenasa, así como la actividad de la óxido nítrico sintasa, aumentaron en la microglía activada, pero la síntesis de ácidos grasos disminuyó en el estado desactivado.

Conclusión: La reconstrucción de la red metabólica de la microglía basada en datos genómicos, bioquímicos y fisiológicos proporciona una visión global del metabolismo celular.

Palabras clave: Red metabólica a escala genómica, cerebro, microglía, medicina sistémica.

Introduction

Microglia are neuroglial cells found throughout the brain and spinal cord[1]. These cells form 20% of the total population of glial cells, which account for 10 to 15% of the brain cells[2,3]. The microglia are originated from hematopoietic stem cells in the spinal cord, some of which differentiate into monocytes and then into microglia after migrating to the brain and residing in the tissue[4]. Microglia are considered the first and most important line of defense in the active immune system in the CNS because they are a type of tissue-resident macrophages[5]. They act as the main inflammatory cells in the brain and respond to pathogens and brain damage by transforming into activated form and through phagocytosis[5]. The response of these cells is the secretion of substances such as cytokines and chemokines, prostaglandins, nitric oxide, and reactive oxygen species[5].

In recent years, the development of high-throughput laboratory methods has led to the formation of large genome-scale databases for a variety of organisms and tissues[6]. Microarray technology enables researchers to study the gene expression patterns of cells and tissues. Therefore, using these new techniques makes it possible to identify cell components. Regularization of biological systems requires comprehensive models (systemic modeling) of cellular processes[7]. Hence, a rational method to achieve a biological understanding of complex datasets is via mathematical modeling, quantitative simulation, and analysis of their results. In recent years, notable efforts have been made toward developing genomic-scale metabolic models for many organisms. These models are based on new techniques and several analytical tools are developed for computational and quantitative analysis of modeled organisms[8]. In 2007, two general models of human metabolism were published that are widely used in systematic studies[9].

To date, various genome-scale metabolic models have been reconstructed for a variety of human tissues, including the genome-scale reconstruction of the astrocyte metabolic network. Among the most famous reconstructions for human tissue are various efforts for different types of cancers. Moreover, several other models have been developed for different tissues of the human body based on Recon 2. The analysis of these models using biological system methods can provide tremendous information on bioenergetic interactions and causal mechanisms underlying the aggressive behavior of these cells when invading central nervous system cells. Biological systems allow for integrating data from all levels of biology, including genomics, proteomics, and metabolomics, and analyzing them in the context of systems theory and control, thus can provide an in-depth understanding of the underlying processes of cell behavior, including microglia. The present study aims to develop the first genome-scale model of microglia cells and examine it according to the existing knowledge on the physiology of these cells. Therefore, the study was designed and conducted to reconstruct and systematically analyze the genome-scale metabolic network of the brain microglia cells.

Materials and methods

Data collection from databases

In the present study, the GEO database was used as the data source to access transcript information. This database contains transcript data from the microarray technique for a variety of tissues and microorganisms. After selecting the appropriate data for the type of cell culture and cell treatment and how to obtain the relevant tissue, and based on the format type of the data, the corresponding package was selected from the Bioconductor and the data were normalized. P-Values were determined to evaluate the significance of statistical studies and the GIMME algorithm was then applied. This algorithm eliminates the reactions with the least flux in the relevant tissue and maintains the minimum necessary reactions in the model based on the phenotype.

Model building based on the constraints

The process of model building and analyzing can be divided into four consecutive steps: **1.** reconstruction of the metabolic network, **2.** formation of the stoichiometric matrix, **3.** define and assign proper constraints on molecular components, and **4.** network analysis. The process of network reconstruction can be divided into three simultaneous sections: 1. data collection to define the target network, 2. preparing a list of all metabolic reactions within the cell, and 3. determination of gene-protein-reaction (GPR) relationships.

Solving the linear programming problem

Linear programming is a mathematical method to find the minimum or maximum value of a linear function on a convex polygon[10]. There are various algorithms for linear programming. In the present study, the GLPK algorithm was used as a free solver in MATLAB software. Moreover, to reduce the range of samples and resulting errors, sampling predictions were applied in the present study[11]. This process was performed for metabolic fluxes and the sampling results, including median, mean, and standard deviation of metabolic fluxes, were used to match previous library data.

Results

The main purpose of this study was to perform a metabolic comparison between normal (m0) and activated (m1) microglia cells. To this end, appropriate samples of microglia gene expression data were first obtained from the GEO database. These data were obtained from

microarray operations on microglia cells derived from the brain of an adult human. The microarray chip data was [HuGene-2_0-st] [HuGene-2_0-st] Affymetrix Human Gene 2.0 ST Array [transcript (gene) version]. Next, the data were normalized to achieve a list of genes that were considered to be present or absent according to the specified cut-off (P-value = 0.05).

As previously mentioned, two types of samples were used for modeling in the present study, including normal and activated microglia. Comparison of these models indicates the metabolic difference between these two types of microglia, which is visible at the genomic level. Among the apparent differences in model, structure is the number of presented genes, the number of metabolites, and the number of metabolic reactions. In general, these two types of microglia have certain metabolic differences, as presented in **table I**.

Table I: Structural differences between the metabolic models of normal and activated microglia.

genes	metabolites	reactions	Cell type
1857	2733	4954	M0
1874	2747	4988	M1

Since a decrease in aconitase activity is associated with increased cis-aconitate and decreased isocitrate, the best approach to measure these changes in metabolic models is to examine the flux sampling data of reactions in the two models and compare the mean values of the fluxes (**Table II**).

Table II: Calculation of the mean flux difference of the aconitase reaction.

Mean flux difference M0-M1	Gene ID	Reaction name	Reaction	Pathway	Enzyme
26.2444	3658.1	'ACONT'	cit[c] <=> icit[c]	'Citric Acid Cycle'	'aconitase'

The difference in mean reaction fluxes indicates a decrease or increase in enzyme activity. As articulated in previous literature, there is a decrease in the activity or down-regulation of the aconitase enzyme in M1 compared to M0. Based on previous studies[12,13], only activated microglia shows an angiogenic-like phenotype and the expression of the SUCLG2 gene, indicating the generation of mitochondrial succinyl-CoA. Therefore, we expect an increase in gene expression related to succinyl-CoA ligase in activated microglia (**Table III**).

Table III: Calculation of the mean flux difference of the succinyl-CoA ligase reaction.

Mean flux difference M0-M1	Gene ID	Reaction name	Reaction	Pathway	Enzyme
-30.6021	8801.1	'SUCOAS1m'	'coa[m]+gtp[m]+succ[m] <=> pi[m]+gdp[m]+succoa[m] '	'Citric Acid Cycle'	'Succinate--CoA ligase (GDP-forming)'

According to previous studies[14], when microglia are activated, we expect an increase in the lactate dehydrogenase-related gene expression (**Table IV**).

Table IV: Mean flux difference of the lactate dehydrogenase.

Mean flux difference M0-M1	Gene ID	Reaction name	Reaction	Pathway	Enzyme
-208.216	160287.1	'LDH_L'	nad[c] + lac_L[c] <=> ' h[c] + pyr[c] + nadh[c] '	Glycolysis/' 'gluconeogenesis	'lactate dehydrogenase'

A review of the literature showed that the overall profile of fatty acids decreases during inflammation and activation of microglia[15]. In a deactivated state, the synthesis of fatty acids is lower due to the presence of rate-limiting agents of malonyl-CoA, which is the substrate of the fatty acid synthase enzyme (**Table V**).

Table V: Mean flux difference of fatty acid synthase.

Mean flux difference M0-M1	Gene ID	Reaction name	Reaction	Pathway	Enzyme
-4.11215707	FASN	'FAS100COA'	'3 h[c] + 2 nadph[c] + malcoa[c] + occoa[c] -> h2o[c] + 2 nadp[c] + co2[c] + coa[c] + dcacoa[c] '	'Fatty acid synthesis'	'fatty acyl-CoA synthase (n-C10:0CoA)'

According to the literature review[16,17], it is expected to occur an increase in nitric oxide synthase activity in activated microglia and, conversely, an increase in arginase activity in deactivated microglia. In the present study, as expected, there was a decrease in the arginase-related reaction flux in M1, indicating a decrease in the activity of the enzyme arginase (**Table VI**).

Table VI: Mean flux difference of arginase activity.

Mean flux difference M0-M1	Gene ID	Reaction name	Reaction	Pathway	Enzyme
0.28380	'ARGN'	'R00551'	h2o[c] + arg_L[c] -> orn[c] ' ' + urea[c]	'Arginase'	'Urea cycle'

Since the mean flux difference is negative, we concluded that the reaction flux of nitric oxide synthase in M1 is higher than M0, so the difference is less than zero (**Table VII**).

Table VII: Mean flux difference of nitric oxide synthase reaction.

Mean flux difference M0-M1	Gene ID	Reaction name	Reaction	Pathway	Enzyme
-11.4605906	'NOS2'	'R00557'	o2[c] + nadph[c] + ' nwharg[c] -> h2o[c] + h[c] + nadp[c] + citr_L[c] ' + no[c]	Arginine ' and Proline 'Metabolism	Nitric Oxide ' Synthase (NO 'forming)

The main characteristic of microglia M1 is the production of reactive oxygen species (ROS) (17). It is expected to see a decrease in pyruvate dehydrogenase activity in microglia M1 (**Table VIII**).

Table VII: Mean flux difference of pyruvate dehydrogenase reaction.

Mean flux difference M0-M1	Gene ID	Reaction name	Reaction	Pathway	Enzyme
-594.4252	'PDHm'	'R01699'	'coa[m] + ' nad[m] + pyr[m] -> co2[m] + nadh[m] + ' accoa[m]	'Glycolysis /gluconeogenesis'	'Pyrovate dehydrogenase'

Discussion

Genome-scale analysis of microglial cells can reveal their metabolic capacity, the biosystem mechanisms of invasion as well as the mechanism of transformation into neurons, and lead to strategies to prevent or treat the neuro-destructive effects of these cells. In the present study, two types of samples were used for modeling in the present study, including normal and activated microglia. Comparison of these models indicates the metabolic difference between these two types of microglia, which is visible at the genomic level. However, the most important metabolic differences are presented below, which are consistent with previous studies, indicating the accuracy of the developed models. As mentioned previously, various statistical tools were used to compare the two models of this study. Our comparative method was based on calculating and comparing the mean flux differences of each metabolic reaction between the two models. According to previous studies, the common symptoms of neurodegenerative diseases are microglia activation, oxidative stress, impaired mitochondrial energy metabolism, and accumulation of intracellular iron. Microglia activation is a common process in neurodegenerative diseases. The essential role of nitric oxide in the incidence and continuation of neurodegenerative disorders and activation of microglia has been discussed in several studies[18-20]. However, it should be noted that although the presence of nitric oxide is essential to maintain the iron cycle, its excessive increase is problematic. Long-term production of nitric oxide leads to suppression of cytochrome C oxidase and reduced activity of complexes I and II. As a result of these two processes, ATP levels decreased, while ATPase activity remained unchanged. Nitric oxide and peroxynitrite inhibit several mitochondrial enzymes, including respiratory chain complexes and a Krebs cycle enzyme called aconitase[12,21,22]. According to these studies, the first difference in microglia M1 compared to M0 is expected to be a decrease in aconitase activity. Recent studies on the metabolic status of the central nervous system during the development of neurodegenerative diseases have shown that the release of lactate dehydrogenase from existing cells is associated with increased inflammation and angiogenesis[14].

Autophagic activity is one of the main characteristics of microglia because microglia are a type of tissue-resident macrophage. This process disrupts in the case of neurodegenerative diseases and aging. Research has been conducted on metabolic processes involved in autophagy, disruption of which is manifested as activated microglia phenotype. When exposed to microbes and foreign substances, microglia undergo an oxidative burst, producing reactive oxygen-based compounds that kill the microbes[16]. The association between oxidative burst and reorientation of arginine metabolism has been investigated in previous studies[17]. According to these studies, an increase in the content of nitric oxide causes metabolic disorders, and to reduce the subsequent damage, more arginine is secreted into the phagocytic cell to form a blood clot in the area. After entering the cell, arginine follows one of the following two pathways. If nitric oxide is present in the cell environment, arginine is affected by the enzyme nitric oxide synthase, producing citrulline. If arginine enters a cell with a normal condition, it is affected by the arginase enzyme and produces urea and ornithine. Accordingly, it is expected to observe an increase in nitric oxide synthase activity in activated microglia and, conversely, an increase in arginase activity in deactivated microglia.

Another key feature of microglia M1 is the production of reactive oxygen species (ROS)[17]. These species enable the phagocytic cell to kill pathogens. As the glutathione reduction process begins, some NADPH is produced that prevents further ROS damage to the intercellular area[23]. Meanwhile, NO species are produced with the occurrence of arginine oxidation by the NOS enzyme and using electrons derived from NADPH[17]. At high concentrations, NO competes with oxygen in cytochrome C oxidase, disrupting mitochondrial respiration. As mitochondrial respiration decreases, ROS species are increased into superoxide anion and converted to hydrogen peroxide by superoxide dismutase, which is finally transported to the cytoplasm. With the advance of this process, NO reacts with the superoxide anion to produce peroxynitrite, which inhibits the enzyme pyruvate dehydrogenase. This enzyme produces acetyl CoA from pyruvate, which later enters the Krebs cycle. Therefore, it is expected to occur a decrease in pyruvate dehydrogenase activity in M1 microglia.

Conclusion

Reconstruction of the microglia metabolic network based on genomic, biochemical, and physiological data provides an overall outlook of cellular metabolism. In this

study, a genome-scale metabolic model of microglia was developed that can be used in future studies, and gap-filling operation can also be applied to this model in the suitable cultural medium for microglia. To increase the accuracy of such models, it is recommended to use valid transcript data, i.e., using diverse samples in the microarray technique and donors with high age diversity. Moreover, other algorithms can also be used to systematically study and analyze other neurodegenerative disorders for future research.

Interests conflict

The authors declare no conflict of interest.

References

1. Ginhoux F, Lim S, Hoeffel G, Low D, Huber T. Origin and differentiation of microglia. Frontiers in cellular neuroscience. 2013 Apr 17; 7: 45.

2. Kreutzberg GW. Microglia, the first line of defence in brain pathologies. Arzneimittel-Forschung. 1995 Mar; 45(3A): 357.

3. Lawson LJ, Perry VH, Gordon S. Turnover of resident microglia in the normal adult mouse brain. Neuroscience. 1992 May 1; 48(2): 405-15.

4. Ritter MR, Banin E, Moreno SK, Aguilar E, Dorrell MI, Friedlander M. Myeloid progenitors differentiate into microglia and promote vascular repair in a model of ischemic retinopathy. The Journal of clinical investigation. 2006 Dec 1; 116(12): 3266-76.

5. Filiano AJ, Gadani SP, Kipnis J. Interactions of innate and adaptive immunity in brain development and function. Brain research. 2015 Aug 18; 1617: 18-27.

6. Sayers EW, Barrett T, Benson DA, Bolton E, Bryant SH, Canese K, Chetvernin V, Church DM, DiCuccio M, Federhen S, Feolo M. Database resources of the national center for biotechnology information. Nucleic acids research. 2010 Nov 20; 39(suppl_1): D38-51.

7. Radrich K, Tsuruoka Y, Dobson P, Gevorgyan A, Swainston N, Baart G, Schwartz JM. Integration of metabolic databases for the reconstruction of genome-scale metabolic networks. BMC systems biology. 2010 Dec 1; 4(1): 114.

8. Price ND, Reed JL, Palsson BØ. Genome-scale models of microbial cells: evaluating the consequences of constraints. Nature Reviews Microbiology. 2004 Nov; 2(11): 886-97.

9. Duarte NC. Becker S. a, Jamshidi N, Thiele I, Mo ML, Vo TD, Srivas R, Palsson BØ, 2007. Global reconstruction of the human metabolic network based on genomic and bibliomic data. Proc. Natl. Acad. Sci. US A; 104: 1777-82.

10. Noyes J, Weisstein EW. Linear Programming. From MathWorld–A Wolfram Web Resource.

11. Hubbard D. How to Measure Anything: Finding the Value of" Intangibles" in Business. People and Strategy. 2011; 34(2): 58.

12. Brown GC. Nitric oxide and mitochondrial respiration. Biochimica et Biophysica Acta (BBA)-Bioenergetics. 1999 May 5; 1411(2-3): 351-69.

13. Dobolyi A, Bagó AG, Gál A, Molnár MJ, Palkovits M, Adam-Vizi V, Chinopoulos C. Localization of SUCLA2 and SUCLG2 subunits of succinyl CoA ligase within the cerebral cortex suggests the absence of matrix substrate-level phosphorylation in glial cells of the human brain. Journal of bioenergetics and biomembranes. 2015 Apr 1; 47(1-2): 33-41.

14. Vallon M, Chang J, Zhang H, Kuo CJ. Developmental and pathological angiogenesis in the central nervous system. Cellular and molecular life sciences. 2014 Sep 1; 71(18): 3489-506.

15. Mor F, Izak M, Cohen IR. Identification of aldolase as a target antigen in Alzheimer's disease. The Journal of Immunology. 2005 Sep 1; 175(5): 3439-45.

16. Plaza-Zabala A, Sierra-Torre V, Sierra A. Autophagy and microglia: novel partners in neurodegeneration and aging. International journal of molecular sciences. 2017 Mar; 18(3): 598.

17. Assumpção CR, Brunini TM, Matsuura C, Resende AC, Mendes-Ribeiro AC. Impact of the L-arginine-nitric oxide pathway and oxidative stress on the pathogenesis of the metabolic syndrome. The Open Biochemistry Journal. 2008; 2: 108.

18. Dawson VL, Dawson TM. Nitric oxide in neurodegeneration. InProgress in brain research 1998 Jan 1 (Vol. 118, pp. 215-229). Elsevier.

19. Heales SJ, Bolaños JP, Stewart VC, Brookes PS, Land JM, Clark JB. Nitric oxide, mitochondria and neurological disease. Biochimica et Biophysica Acta (BBA)-Bioenergetics. 1999 Feb 9; 1410(2): 215-28.

20. Hirsch EC. Glial cells and Parkinson's disease. Journal of neurology. 2000 Apr 1; 247(2): II58-62.

21. Drapier JC. Interplay between NO and [Fe-S] clusters: relevance to biological systems. Methods. 1997 Mar 1; 11(3): 319-29.

22. Clementi E, Brown GC, Feelisch M, Moncada S. Persistent inhibition of cell respiration by nitric oxide: crucial role of S-nitrosylation of mitochondrial complex I and protective action of glutathione. Proceedings of the National Academy of Sciences. 1998 Jun 23; 95(13): 7631-6.

23. Orihuela R, McPherson CA, Harry GJ. Microglial M1/M2 polarization and metabolic states. British journal of pharmacology. 2016 Feb; 173(4): 649-65.

eISSN 2255-0569

ORIGINAL

Study of the expression rates of *RORA* and *COX5b* genes amongst MS patients compared with healthy individuals as an emerging diagnostic biomarker

Estudio de los índices de expresión de los genes RORA y COX5b entre los pacientes con EM en comparación con los individuos sanos como biomarcador diagnóstico emergente

Ali Shahali[1,2], Niloofar Sadeghi Ghorogh Aghaei[3], Amin Mosharraf[4], Shiva Sharestani[5], Avicenna Madani[6,7]

1. College of Pharmacy, University of Punjab, Lahore, Pakistan
2. Department of Pharmaceutical Biotechnology, Faculty of Pharmacy, Isfahan University of Medical Sciences, Isfahan, Iran.
3. Department of Genetics, Faculty of Basic Sciences, Guilan University, Guilan, Iran.
4. Faculty of Veterinary Medicine, Shahrekord Branch, Islamic Azad University, Shahrekord, Iran.
5. MSc of Medical Genetics, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.
6. George Washington University, United States.
7. School of Medicine, University of California San Diego (UCSD), United States.

Corresponding author
Avicenna Madani
E-mail: Usasdca@gmail.com

Received: 29 - X - 2021
Accepted: 30 - XII - 2021

doi: 10.3306/AJHS.2022.37.01.161

Abstract

Background: Multiple Sclerosis is a degenerative disease of the central nervous system accompanied with both environmental and genetic backgrounds. The present survey was performed to assess the expression rates of *COX5B* and *RORA* genes in MS and healthy individuals.

Methods: Sixty blood samples were taken from MS (n= 30) patients and healthy (n= 30) individuals. RNA was extracted from blood samples and used for cDNA synthesis. DNA samples were subjected to real-time PCR to assess the *COX5B* and *RORA* genes expression by specific primers.

Results: MS patients had the higher history of smoking and alcohol. Statistically significant differences were obtained for the history of alcohol and smoking between MS and healthy population (P <0.05). There were no statistical differences between MS patients and healthy individuals for age, sex, BMI, and weight. *COX5B* gene expression was significantly decreased in MS patients compared to healthy individuals (P = 0.0433). *RORA* gene expression was increased in MS patients compared to the control group (P = 0.481).

Conclusion: *COX5B* gene expression analysis can be used as an emerging biomarker for MS diagnosis in individuals. It seems that RORA gene expression should be studied more to find its specific role in MS pathogenicity.

Keywords: Multiple sclerosis, *RORA, COX5B*, Gene expression, Real-Time PCR.

Resumen

Antecedentes: La esclerosis múltiple es una enfermedad degenerativa del sistema nervioso central acompañada de antecedentes tanto ambientales como genéticos. El presente estudio se realizó para evaluar los índices de expresión de los genes *COX5B* y *RORA* en la EM y en individuos sanos.

Métodos: Se tomaron sesenta muestras de sangre de pacientes con EM (n= 30) y de individuos sanos (n= 30). Se extrajo el ARN de las muestras de sangre y se utilizó para la síntesis de ADNc. Las muestras de ADN se sometieron a PCR en tiempo real para evaluar la expresión de los genes *COX5B* y *RORA* mediante cebadores específicos.

Resultados: Los pacientes con EM tenían mayores antecedentes de tabaquismo y alcohol. Se obtuvieron diferencias estadísticamente significativas para los antecedentes de alcohol y tabaquismo entre la población con EM y la población sana (*P* <0,05). No hubo diferencias estadísticas entre los pacientes con EM y los individuos sanos para la edad, el sexo, el IMC y el peso. La expresión del gen *COX5B* disminuyó significativamente en los pacientes con EM en comparación con los individuos sanos (*P* = 0,0433). La expresión del gen *RORA* aumentó en los pacientes con EM en comparación con el grupo de control (*P* = 0,481).

Conclusión: El análisis de la expresión del gen *COX5B* puede utilizarse como un biomarcador emergente para el diagnóstico de la EM en individuos. Parece que la expresión del gen *RORA* debería estudiarse más para encontrar su papel específico en la patogenicidad de la EM.

Palabras clave: Esclerosis múltiple, *RORA, COX5B*, expresión génica, PCR en tiempo real.

Introduction

Despite the high advances of the medical sciences[1-5], some diseases remain threat for human health[6-10]. Multiple sclerosis (MS) is a neurodegenerative, demyelinating disease of the nervous system that respects few demographic boundaries. It has an autoimmune basis, which leads to widespread nervous system tissue lesions and dysfunction, resulting in communication breakdown between neurons[11]. As MS research has progressed, it has become clearer that environmental and genetic factors underlie the etiology of MS. The cooperation of these two factors in the etiology raises the question of whether one is more important than the other in posing risk, and whether co-morbidities elevate risk[12].

Several genetic markers are involved in the pathogenesis of MS. *COX* is composed of 13 subunits, of which the three largest are encoded by the mtDNA and form the catalytic core of the enzyme. The remaining ten, evolutionary younger, nuclear-encoded subunits are involved in assembly and regulation of the enzyme. *COX* can be physiologically modulated and the enzyme represents one of the key regulatory sites of energy metabolism. *COX* gene has also some functions on the immunological reaction in the human body and its expression can decrease or increase the exacerbation of different diseases[13]. The retinoid acid-related orphan receptor (ROR) subfamily of orphan nuclear receptors consists of three members, α, β, and γ, that regulate multiple cellular processes including cell growth, differentiation, and apoptosis[14]. The *RORA* gene is expressed in several tissues and it regulates inflammatory responses, neuronal cell development, bone metabolism, and arteriosclerosis and also it is involved in the differentiation of Th17 cells[15].

Rendering the high importance of the MS and role of genetic markers in its pathogenesis, the present survey was done to assess the role of *COX5B* and *RORA* genes expression in MS patients and compared it with healthy individuals.

Materials and methods

Study designs

This survey was designed to assess the expression rates of *RORA* and *COX5b* genes in blood samples taken from MS patients and healthy individuals. For this purpose, 35 MS patients and 35 healthy individuals were examined.

Inclusion and exclusion criteria

Thirty MS patients of both sexes and all ages who were confirmed by the neurologist were included in the study. For a control group, 30 healthy individuals with no personal or family history of autoimmune diseases were also included. Written informed consent was obtained from each individual.

Samples

Peripheral blood samples (5 ml) were obtained from the cubital vein and collected in cell preparation tubes containing an anticoagulant Ethylene diamine tetraacetic acid (EDTA). Peripheral blood mononuclear cells were isolated by EDTA density centrifugation

RNA extraction and cDNA synthesis

Total RNA was extracted from the blood samples using a RNeasy kit ((Qiagen, Gaithersburg, MD, USA), according to the manufacturer's instructions. The RNA samples were incubated with RNAse-free DNAse I at 37°C for 15 min. RNA samples were purified with a RNeasy kit. Extracted RNA were immediately stored at -80°C. Total RNA concentration was assessed by ultraviolet absorbance at 260 nm (1 absorbance unit at 260 nm = 40 ng/µl RNA). Total RNA was run on 1% agarose gels to check size and integrity. The quality of RNA was confirmed by the detection of 18S and 28S bands after 1% agarose gel electrophoresis.

Total extracted RNA was used to generate cDNA with a Reverse Transcriptase cDNA synthesis kit (Roche, Germany) with oligo deoxythymine (dT) primers, according to the manufacturer's protocol. Synthetic cDNA samples were stored at -20°C. The quality and quantity of extracted DNA were assessed according to previous studies[16-22].

Real-Time PCR analysis

The real-time PCR technique was used to assess the expression rates of *RORA* and *COX5b* genes amongst the DNA samples of MS patients and healthy individuals. **Table I** shows the primer sequences used in this regard. The Biosystems TaqMan R, Universal PCR Master Mix was used to perform the real-time PCR, using the real-time PCR thermal cycler (Corbett Research, Rotor Gene 6000). The GAPDH and β-actin were applied as house-keeping genes for *COX5b* and *RORA* genes, respectively. The data were evaluated by the Δ Δ CT method, which measures the expression level of the target genes normalized to a reference gene and relative to the expression of the genes in the calibrator samples.

Statistical analysis

Statistically significant differences were calculated by the Student's t-test, using the SPSS 21.0 and Excel. Finally a P-value <0.05 was accepted as the level of significance[25-28].

Results

Study principles

The present survey was performed to assess the expression rates of COX5b and RORA genes amongst the MS patients and healthy individuals as an emerging biomarkers of MS.

Table I: Primer sequences used in this study.

Targeted genes	Primer sequence (5'-3')	References
COX5B	F: CCCAAAGGGAGCTTCAGG R: CGACGCTGGTATTGTCCTCT	23
GAPDH	F: CCACTCCTCCACCTTTGAC R: ACCCTGTTGCTGTAGCCA	
RORA	F: GTCAGCAGCTTCTACCTGGAC R: GTGTTGTTCTGAGAGTGAAAGGCACG	24
β-actin	F: TCTACAATGAGCTGCGTGTGG R: GGAACCGCTCATTGCCAATG	

Table II: Demographic charters of the examined MS patients and healthy individuals.

Demographic characters	Individuals (60 people)		P value
	MS (30 cases)	Healthy (30 cases)	
Mean age (SD)	61.32	60.72	0.87
Sex (M/F)	18/12	14/16	0.52
Mean weight (SD)	70.02 (8.14)	68.33 (9.69)	0.63
Mean BMI (SD)	24.6 (2.7)	25.1 (3.1)	0.89
History of alcohol (%)	19 (63.33)	12 (40)	0.042
History of smoking (%)	22 (73.33)	10 (33.33)	0.028

Figure 1: The expression rate of *COX5B* gene amongst the MS patients and healthy individuals.

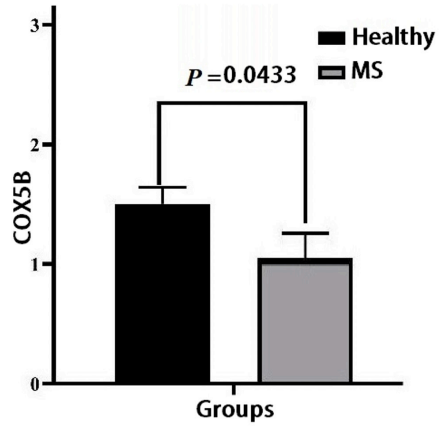
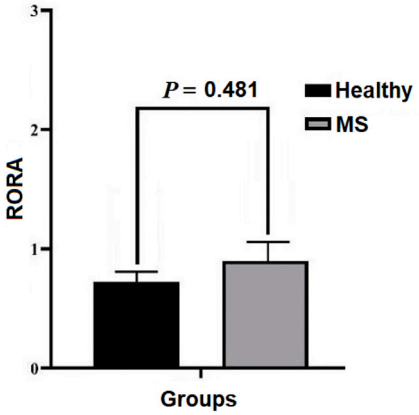


Figure 2: The expression rate of RORA gene amongst the MS patients and healthy individuals.



Demographic charters

Table II shows the demographic charters of the examined MS patients and healthy individuals. As shown, the mean age of the studied MS and healthy population was 61.32 and 60.72 years with a male to female ratio of 18/12 and 14/16, respectively. Statistically significant differences were obtained for the history of alcohol and smoking between MS and healthy population (P <0.05). MS patients had the higher history of smoking and alcohol.

COX5B gene expression

Figure 1 shows the expression rate of *COX5B* gene amongst the MS patients and healthy individuals. Findings showed that *COX5B* gene expression was significantly decreased in MS patients compared to healthy individuals (P = 0.0433).

RORA gene expression

Figure 2 shows the expression rate of *RORA* gene amongst the MS patients and healthy individuals. Findings showed that *RORA* gene expression was increased in MS patients compared to the control group, but it was not significant (P = 0.481).

Discussion

Infectious[29-33] and autoimmune diseases[34] have been considered as the most important causes of morbidity and mortality in the last century. In the present study, two important genetic markers have been determined for MS. Findings revealed that alcohol and smoking histories may affect the occurrence of MS among individuals. This claim was also approved by Hedström et al. (2021) (Sweden)[35], Ivashynka et al. (2019) (Italy)[36], and D'hooghe et al. (2012) (Belgium)[37]. Our findings also showed that sex and age didn't have any relation to the occurrence of MS, which was similar to previous surveys[38, 39]. As *COX5B* gene expression was significantly decreased in MS patients compared to healthy individual, it can introduce as a good marker for the MS diagnosis and further evaluation. Similarly, Safavizadeh et al. (2012)[40]

reported that *COX5B* gene expression is significantly reduced in MS patients compared to control (P <0.05), whereas there was no significant difference in the *COX2* gene expression. Role of the *COX5B* gene in MS has also been determined previously[41].

In despite of the increase in the *RORA* gene expression in MS group compared to the healthy individuals, difference was not statistically significant. Thus, it seems that further researches should perform to obtain the exact role of *RORA* gene in MS occurrence and pathogenicity. *RORA* is proposed to promote Th17 cells differentiation that play a crucial role in many inflammatory diseases, including MS. The gene is also involved in regulation of inflammatory responses and neuronal cell development. In a survey conducted by Eftekharian et al. (2016)[42], the relationship between *RORA* rs11639084 and rs4774388 gene polymorphisms on the individual susceptibility of MS was examined. Their findings revealed that both variants showed significant differences in allele and genotype distributions between the studied groups. Genotypes were risk associated in additive (*P*-value of 0.0003 and odds ratio equal to 1.7 (95% CI: 1.27-2.26)), dominant (*P*-value of <0.0001 and odds ratio equal to 0.55 (95% CI: 0.41-0.73)) and recessive (*P*-value of 0.04 and odds ratio equal to 0.33 (95% CI: (0.12-0.96)) models for rs11639084. However, the rs4774388 genotypes were risk associated in recessive model with a P-value of 0.036 and an odds ratio of 0.62 (95% CI: (0.4-0.97)). Down-regulation of *RORA* gene expression in the blood of MS patients was also reported by Sayad et al (2018)[43].

Conclusion

The present survey is the first report on the assessment of both *COX5B* and *RORA* gene expression in MS patients. As only significant difference was found for the expression rate of *COX5B* gene, its analysis can be effective for diagnosis of MS in individuals. However, several works should perform to obtain the main activity of *RORA* gene in MS pathogenicity.

Interests conflict

The authors declare no conflict of interest.

References

1. Dehkordi FS, Saberian S, Momtaz H. Detection and segregation of Brucella abortus and Brucella melitensis in aborted bovine, ovine, caprine, buffaloes and camelid fetuses by application of conventional and real-time polymerase chain reaction. The Thai Journal of Veterinary Medicine. 2012a;42(1):13.

2. Dehkordi FS, Momtaz H, Doosti A. Application of Real-Time PCR for detection of Aspergillus species in aborted ruminant foetuses. Bulgarian Journal of Veterinary Medicine. 2012b;15(1):30-6.

3. Dehkordi FS. Prevalence study of Coxiella burnetii in aborted ovine and caprine fetuses by evaluation of nested and real-time PCR assays. American Journal of Animal and Veterinary Sciences. 2011a;6(4):180-6.

4. Dehkordi FS, Tirgir F, Valizadeh Y. Effects of Guajol® ointment synthesized from medicinal smoke condensate of jennet feces on burn wound healing on Wistar rat. Veterinary Research Forum. 2017b; 8(3):215.

5. Dehkordi FS, Tavakoli-Far B, Jafariaskari S, Momtaz H, Esmaeilzadeh S, Ranjbar R, Rabiei M. Uropathogenic Escherichia coli in the high vaginal swab samples of fertile and infertile women: virulence factors, O-serogroups, and phenotyping and genotyping characterization of antibiotic resistance. New Microbes and New Infections. 2020;38:100824.

6. Dehkordi FS, Haghighi N, Momtaz H, Rafsanjani MS, Momeni M. Conventional vs real-time PCR for detection of bovine herpes virus type 1 in aborted bovine, buffalo and camel foetuses. Bulgarian Journal of Veterinary Medicine. 2013b;16(2):102-12.

7. Dehkordi FS, Yazdani F, Mozafari J, Valizadeh Y. Virulence factors, serogroups and antimicrobial resistance properties of Escherichia coli strains in fermented dairy products. BMC Research Notes. 2014a;7(1):1-8.

8. Dehkordi FS, Barati S, Momtaz H, Ahari SN, Dehkordi SN. Comparison of shedding, and antibiotic resistance properties of Listeria monocytogenes isolated from milk, feces, urine, and vaginal secretion of bovine, ovine, caprine, buffalo, and camel species in Iran. Jundishapur Journal of Microbiology. 2013a;6(3):284.

9. Ghorbani F, Gheisari E, Dehkordi FS. Genotyping of vacA alleles of Helicobacter pylori strains recovered from some Iranian food items. Tropical Journal of Pharmaceutical Research. 2016 S;15(8):1631-6.

10. Dehkordi FS, Gandomi H, Basti AA, Misaghi A, Rahimi E. Phenotypic and genotypic characterization of antibiotic resistance of methicillin-resistant Staphylococcus aureus isolated from hospital food. Antimicrobial Resistance & Infection Control. 2017a;6(1):1-1.

11. Inojosa H, Schriefer D, Ziemssen T. Clinical outcome measures in multiple sclerosis: a review. Autoimmunity reviews. 2020 May 1;19(5):102512.

12. Trojano M, Amato MP. Progress in multiple sclerosis—from diagnosis to therapy. Nature Reviews Neurology. 2018 Feb;14(2):72-4.

13. Palumbo S, Bosetti F. Alterations of brain eicosanoid synthetic pathway in multiple sclerosis and in animal models of demyelination: role of cyclooxygenase-2. Prostaglandins, Leukotrienes and Essential Fatty Acids. 2013 Oct 1;89(5):273-8.

14. Takeda Y, Kang HS, Lih FB, Jiang H, Blaner WS, Jetten AM. Retinoid acid-related orphan receptor, ROR, participates in diurnal transcriptional regulation of lipid metabolic genes. Nucleic Acids Res. 2014;42(16):10448-59.

15. Eftekharian MM, Noroozi R, Sayad A, Sarrafzadeh S, Toghi M, Azimi T, Komaki A, Mazdeh M, Inoko H, Taheri M, Mirfakhraie R. RAR-related orphan receptor A (RORA): A new susceptibility gene

for multiple sclerosis. Journal of the neurological sciences. 2016 Oct 15;369:259-62.

16. Dehkordi FS. Prevalence study of Bovine viral diarrhea virus by evaluation of antigen capture ELISA and RT-PCR assay in Bovine, Ovine, Caprine, Buffalo and Camel aborted fetuses in Iran. AMB Express. 2011b;1(1):1-6.

17. Dehkordi FS, Parsaei P, Saberian S, Moshkelani S, Hajshafiei P, Hoseini SR, Babaei M, Ghorbani MN. Prevalence study of Theileria annulata by comparison of four diagnostic Techniques in shouthwest Iran. Bulgarian Journal of Veterinary Medicine. 2012c;15(2): 123-130.

18. Dehkordi FS, Haghighi Borujeni MR, Rahimi E, Abdizadeh R. Detection of Toxoplasma gondii in raw caprine, ovine, buffalo, bovine, and camel milk using cell cultivation, cat bioassay, capture ELISA, and PCR methods in Iran. Foodborne Pathogens and Disease. 2013c;10(2):120-5.

19. Dehkordi FS, Khamesipour F, Momeni M. Brucella abortus and Brucella melitensis in Iranian bovine and buffalo semen samples: The first clinical trial on seasonal, Senile and geographical distribution using culture, conventional and real-time polymerase chain reaction assays. Kafkas Univ Vet Fak Dergisi. 2014c;20(6):821-8.

20. Dehkordi FS, Valizadeh Y, Birgani TA, Dehkordi KG. Prevalence study of Brucella melitensis and Brucella abortus in cow's milk using dot enzyme linked immuno sorbent assay and duplex polymerase chain reaction. Journal of Pure and Applied Microbiology. 2014b;8(2):1065-9.

21. Safarpordehkordi F, Yahaghi E, Khodaverdi Darian E. Prevalence of antibiotic resistance in Escherichia coli isolated from poultry meat supply in Isfahan. Iranian Journal of Medical Microbiology. 2014 Aug 10;8(2):41-7.

22. Safarpour Dehkordi F, Hosseini S, Rahimi E, Momeni M, Yahaghi E, Khodaverdi Darian E. Investigate the frequency of virulence genes Vibrio parahaemolyticus isolated from fish, lobsters and crabs caught from Persian Gulf. Iranian Journal of Medical Microbiology. 2014;8(2):1-7.

23. Safavizadeh N, Rahmani SA, Zaefizadeh M. COX5B and COX2 gene expressions in Multiple Sclerosis/Multipl Sklerozda COX5B and COX2 gen ekspresyonu. Journal of Cell and Molecular Biology. 2012;10(2):21.

24. Chauvet C, Bois-Joyeux B, Danan JL. Retinoic acid receptor-related orphan receptor (ROR) α4 is the predominant isoform of the nuclear receptor RORα in the liver and is up-regulated by hypoxia in HepG2 human hepatoma cells. Biochemical Journal. 2002;364(2):449-56.

25. Safarpour Dehkourdi F, Momtaz H, Esmailzade S, Khayyat Khameneie M, Yahaghi E. Detection of virulence factors of Uropathoigenic Escherichia coli isolates from infertile women high vaginal swabs. Iranian Journal of Medical Microbiology. 2014;7(4):1-8.

26. Dehkordi FS, Taghizadeh F. Prevalence and some risk factors associated with brucellosis and leptospirosis in aborted fetuses of ruminant species. Research Opinions in Animal and Veterinary Sciences. 2012;2:275-81.

27. Safarpoor Dehkordi F, Haghighi N. Detection of bovine viral diarrhea virus in bovine and buffalo milk thorough conventional and real-time reverse transcriptase polymerase chain reaction. Research Opinions in Animal and Veterinary Sciences. 2012;2:263-7.

28. Dehkordi FS, Rafsanjani MS. Prevalence study of Coxiella burnetii in aborted fetuses of small ruminants in various partum and seasons in Iran. African Journal of Microbiology Research. 2012 Jul 19;6(27):5594-600.

29. Sheikhshahrokh A, Ranjbar R, Saeidi E, Dehkordi FS, Heiat M, Ghasemi-Dehkordi P, Goodarzi H. Frontier therapeutics and vaccine strategies for sars-cov-2 (COVID-19): A review. Iranian Journal of Public Health. 2020 Oct;49(Suppl 1):18.

30. Nejat S, Momtaz H, Yadegari M, Nejat S, Safarpour Dehkordi F, Khamesipour F. Seasonal, geographical, age and breed distributions of equine viral arteritis in Iran. Kafkas Univ Vet Fak Derg. 2015 Jan 1;21(1):111-6.

31. Rahi A, Kazemeini H, Jafariaskari S, Seif A, Hosseini S, Dehkordi FS. Genotypic and phenotypic-based assessment of antibiotic resistance and profile of staphylococcal cassette chromosome mec in the methicillin-resistant Staphylococcus aureus recovered from raw milk. Infection and drug resistance. 2020;13:273.

32. Ranjbar R, Seif A, Dehkordi FS. Prevalence of antibiotic resistance and distribution of virulence factors in the shiga toxigenic Escherichia coli recovered from hospital food. Jundishapur Journal of Microbiology. 2019;12(5):8.

33. Ranjbar R, Yadollahi Farsani F, Safarpoor Dehkordi F. Antimicrobial resistance and genotyping of vacA, cagA, and iceA alleles of the Helicobacter pylori strains isolated from traditional dairy products. Journal of Food Safety. 2019 Apr;39(2):e12594.

34. Rieckmann P, Boyko A, Centonze D, Elovaara I, Giovannoni G, Havrdová E, Hommes O, Kesselring J, Kobelt G, Langdon D, LeLorier J. Achieving patient engagement in multiple sclerosis: A perspective from the multiple sclerosis in the 21st Century Steering Group. Multiple Sclerosis and Related Disorders. 2015 May 1;4(3):202-18.

35. Hedström AK, Olsson T, Alfredsson L. The increased risk of multiple sclerosis associated with HLA-DRB1* 15: 01 and smoking is modified by alcohol consumption. Scientific reports. 2021 Oct 27;11(1):1-7.

36. Ivashynka A, Copetti M, Naldi P, D'Alfonso S, Leone MA. The impact of lifetime alcohol and cigarette smoking loads on multiple sclerosis severity. Frontiers in neurology. 2019 Aug 13;10:866.

37. D'hooghe MB, Haentjens P, Nagels G, De Keyser J. Alcohol, coffee, fish, smoking and disease progression in multiple sclerosis. European Journal of Neurology. 2012 Apr;19(4):616-24.

38. Harbo HF, Gold R, Tintoré M. Sex and gender issues in multiple sclerosis. Therapeutic advances in neurological disorders. 2013 Jul;6(4):237-48.

39. Bove RM, Healy B, Augustine A, Musallam A, Gholipour T, Chitnis T. Effect of gender on late-onset multiple sclerosis. Multiple Sclerosis Journal. 2012 Oct;18(10):1472-9.

40. Safavizadeh N, Rahmani SA, Zaefizadeh M. COX5B and COX2 gene expressions in Multiple Sclerosis. Journal of Cell and Molecular Biology. 2012 Dec 1;10(2):21.

41. Safavizadeh N, Rahmani SA, Zaefizadeh M. Investigation of cytocrom c oxidase gene subunits expression on the Multiple sclerosis. Indian journal of human genetics. 2013 Jan;19(1):18.

42. Eftekharian MM, Noroozi R, Sayad A, Sarrafzadeh S, Toghi M, Azimi T, Komaki A, Mazdeh M, Inoko H, Taheri M, Mirfakhraie R. RAR-related orphan receptor A (RORA): A new susceptibility gene for multiple sclerosis. Journal of the neurological sciences. 2016 Oct 15;369:259-62.

43. Sayad A, Salmani T, Hemmesi MK, Ganji M, Ghafouri-Fard S, Hatami M, Soudyab M, Taheri M. Down-regulation of RORA gene expression in the blood of multiple sclerosis patients. Human antibodies. 2018 Jan 1;26(4):219-24.

eISSN 2255-0569

ARTÍCULO ESPECIAL

Aproximación diagnóstica a la enfermedad urológica del Papa Inocencio XI. Análisis de la patocronía y re-formulación diagnóstica

Diagnostic approach to the urological disease of Pope Innocent XI. Analysis of pathochrony and diagnostic re-formulation

Antoni Gelabert Mas[1], **Luis Grande**[2]

1. MD, PhD, Hospital del Mar/Universitat Autònoma de Barcelona, Emeritus Chair Urology Dept/Professor of Surgery; Barcelona, Spain
2. MD, PhD, Hospital del Mar/Universitat Autònoma de Barcelona, Emeritus Chair Surg Dept/Professor of Surgery; Barcelona, Spain

Autor correspondencia
Antoni Gelabert Mas
Hospital del Mar/Universitat Autònoma de Barcelona
E-mail: agelabert@psmar.cat

Recibido: 15 - X - 2021
Aceptado: 7 - XII - 2021

doi: 10.3306/AJHS.2022.37.01.166

Resumen

Se realiza una reformulación diagnóstica de la causa de muerte del Papa Inocencio XI a partir de la reinterpretación del informe de la autopsia practicada en 1769 por Giovanni Maria Lancisi, y del dibujo que la acompaña y los conocimientos actuales. Se propone que el Papa Inocencio XI falleció por una insuficiencia renal terminal por Pionefrosis causada por una litiasis coraliforme bilateral en un riñón en herradura.

Palabras clave: Diagnóstico clínico, autopsia; trastorno mineral y óseo asociado a la enfermedad renal crónica, cálculos renales, riñón en herradura.

Abstract

A diagnostic reformulation of the cause of death of Pope Innocent XI is made on the basis of the reinterpretation of the autopsy report performed in 1769 by Giovanni Maria Lancisi and the accompanying drawing and current knowledge.
of the autopsy practiced in 1769 by Giovanni Maria Lancisi, and of the drawing that accompanies it and the current knowledge. It is Pope Innocent XI died of end-stage renal failure due to pyonephrosis caused by a bilateral coralliform lithiasis in a horseshoe kidney. in a horseshoe kidney.

Keywords: clinical diagnosis, autopsy; mineral and bone disorder associated with chronic kidney disease, renal calculi, horseshoe kidney.

Introducción

En la Historia de Medicina se recogen numerosos personajes clave en los que existe una clara influencia entre su enfermedad, su forma de vida y sus decisiones profesionales. La biografía del Papa Inocencio XI, es conocida y estudiada en su vertiente social, política y eclesiástica. Sin embargo, su *pathos*, apenas se ha estudiado y solamente se afirma, de manera muy sucinta, que falleció por las complicaciones de una litiasis renal.

En este trabajo se ha profundizado en la Patocronía del Papa Inocencio XI y se han reformulado los diagnósticos urológicos a la luz de los conocimientos actuales, cribados por el concepto de salud definido por la OMS: *Un estado completo de bienestar físico, mental y social, y no solamente la ausencia de afecciones o enfermedades*[1]. Se sabe que no gozó durante su vida de este concepto de salud y se sospecha que una buena parte, sino todas, las decisiones de gobierno eclesiástico que tomó, que fueron muchas y muy importantes, algunas muy beligerantes, se vieron influenciadas por su frágil estado de salud.

Hace unas décadas, uno de los autores ya publicó una nota en el que se apuntaba esa influencia en el gobierno papal[2]. Ahora se ha revisado y profundizado en este aspecto al disponer de nuevas fuentes de

estudio y haber podido consultar bibliografía específica de su papado en Archivos Episcopales y Bibliotecas Eclesiásticas, incluida la Biblioteca Vaticana, hecho que ha permitido analizar con detalle su *pathos* biográfico. La investigación ha llevado a re-formular un diagnóstico no mencionado ni divulgado históricamente, hasta donde se ha podido constatar, salvo la breve reseña ya citada. Del análisis de los datos investigados se pretende demostrar la robustez del diagnóstico propuesto, y explicar por qué antes nunca ni nadie lo había mencionado. Pese a la minuciosidad de la investigación, no se han podido concretar las razones por las que se realizó la necropsia a este papa, cuando en aquellos años los papas estaban considerados "templo sagrado" y, por tanto, prohibido su profanamiento[3].

Breves apuntes biográficos

El Papa Inocencio XI, de nombre familiar Benedetto Odescalchi (1611-1689), pertenecía a un clan de negociantes acaudalados de Como (Italia) y eligió la carrera eclesiástica, llegando a obispo de Navara. Nunca había viajado fuera de las fronteras de su país, siendo totalmente desconocedor de las relaciones, conflictos e intereses internacionales de la época. De vida austera, principios rígidos, gran integridad moral, se le definió como el Papa de los pobres. Aunque terco en sus relaciones y comunicaciones personales, se le reconocen momentos de duda en los que se dejó influenciar. Por su trayectoria vital y su actuación política, más que un Papa, se le considera un "soberano"[4].

Durante su pontificado mantuvo conflictos constantes. El más significativo y grave fue su enfrentamiento con el rey Luís XIV de Francia, quien, sin disimulo, aspiraba controlar la iglesia francesa, y erigirse en "superior jerárquico". Inocencio XI no podía aceptar ese estatus bajo ningún concepto. El litigio empezó con la pretendida implantación de la *Régale temporelle*, un impuesto que debían pagar al rey las sedes episcopales, mientras estuvieran vacantes, y la *Régale spirituelle*, que permitía al rey nombrar a los obispos y demás cargos eclesiásticos, salvo los curas parroquiales.

El enfrentamiento se enconó de forma radical tras la redacción por parte de Jacques Bénigne Bossuet de la *Declaration des quatre articles*, aprobada por unanimidad en la Asamblea del Clero Francés de 1682. En ella se sustentaba la doctrina del predominio del rey sobre la iglesia católica en Francia, conforme a su concepción absolutista. El rey otorgó derecho de asilo a todas las diócesis bajo su jurisdicción, incluso las situadas en Roma, a lo que se opuso Inocencio XI. Francia desplazó contingentes armados a la cancillería romana y a las diócesis bajo su influencia. El Papa excomulgó, públicamente, al embajador francés y, de forma secreta, al propio rey Luís XIV. Este hecho estuvo a punto de provocar un nuevo cisma en el catolicismo, aunque finalmente se impuso el criterio vaticano[5].

Otro litigio grave lo mantuvo con el presbítero español Miguel de Molinos, famoso predicador y guía espiritual. Molinos se estableció en la iglesia agustina de San Alfonso en Roma donde desarrollaba su actividad apostólica divulgando el *quietismo*. Al principio Inocencio XI compartía esta corriente teológica, pero con el tiempo se apartó de ella y la condenó. Molinos fue atacado por los jesuitas Paolo Segueri y Giovanni Paolo Oliva, quienes propiciaron su detención, junto algunos de sus discípulos, el 18 de julio de 1687. Tras un lento proceso, dificultado por la imposibilidad de conseguir pruebas de sus presuntas desviaciones doctrinales, acabó condenado por un tribunal eclesiástico, a reclusión perpetua. Inocencio XI ratificó la sentencia el 20 de noviembre de 1687 y Molinos murió en la mazmorra el 28 de diciembre de 1696.

El gobierno de Inocencio XI, que así se etiqueta su papado, estuvo hasta el último momento dominado por los elevados ideales de aunar a toda la cristiandad en la liga contra los turcos, su gran lucha contra el enemigo tradicional de Oriente, siendo el alma de la resistencia contra la ola islámica que se avecinaba. Fue el epílogo de la épica de los grandes pontífices de la Reforma que inmortalizaron los siglos XVI y XVII y un personaje clave en la historia de la Iglesia, soportando momentos duros en su pontificado[6].

Notas sobre su salud y agonía terminal

En 1676, a los 65 años, el Papa aún conservaba fuerza y mente activas, aunque un año antes ya había dado los primeros síntomas de afección renal grave, atribuyéndola a su excesiva rigidez en el ayuno y al estrés del cargo, todo ello envuelto en una depresión significativa e insomnio pertinaz que no hacía más que subrayar su declive físico y mental. Con sigilo y cierto secretismo se hacían prematuros pronósticos en vista a un futuro cónclave, pese a que su pontificado duraría trece años más. El primer revés importante en su salud, divulgado públicamente; se señala en el año 1682 cuando tuvo una grave crisis de podagra, que le mantuvo en cama, recluido en sus habitaciones privadas durante bastante tiempo, habitaciones en las que, según manifestaba su servicio personal, hacía un calor insoportable.

De todas formas, superó este acceso agudo y se reincorporó a su actividad diaria. Cuatro años más tarde, los ataques de podagra se hicieron más frecuentes, razón por la que el Papa se vio apartado durante largos períodos del gobierno de la Iglesia. De nuevo, logra sobreponerse y se concibieron nuevas esperanzas, por parte del círculo cardenalicio, sobre

la recuperación total y la prolongación de su "reinado". Fue una simple ilusión ya que al año siguiente, en 1689, una nueva crisis de podagra se complicó con fiebre alta y agravación de su estado general. Un grave fallo renal con edemas generalizados obligó a practicarle incisiones en ambas piernas, según praxis habitual de la época, para disminuir la hinchazón. Durante este episodio el propio Papa previó su fin y se rodeó solamente de sus allegados más íntimos, de su médico de cabecera, el entonces renombrado Giovanni Maria Lancisi, y de su confesor personal.

Tuvo una ligera mejoría a primeros de agosto, momento en el que se le administró el viático y el 10 de agosto pidió la Extremaunción. La mañana siguiente, conservando aún el pleno conocimiento, Leandro Colloredo, cardenal nombrado por el propio Inocencio XI, le da la absolución *in articulo mortis*. Tras una corta agonía que duró unas seis horas, falleció la mañana del 12 de agosto. Todo el orbe sintió su muerte, excepto Francia. A modo de ejemplo, el poeta francés Jean de la Fontaine, le dedicó un poema, no precisamente de alabanza[7]:

Pour nouvelles de l'Italie,
Le pape empire tous les jours.
Expliquez, seigneur, ce discours
Du côté de la maladie;
Car aucun saint-père autrement
Ne doit empirer nullement
Celui-ci véritablement
N'est envers nous ni saint ni père
Nos soins, de l'erreur triomphants
Ne fout qu'augmenter sa colère
Contre l'aîné de ses enfants
Sa santé toujours diminue
L'avenir m'est chose inconnue,
Et je n'en parle qu'a lattons
Mais les gens de delà les monts
Auront bientôt pleuré cet homme
Car il défend les Jeannetons
Chose très nécessaire à Rome

Parece obvio que el Papa, en esa última década, alteró sus costumbres, el trabajo administrativo, sus comidas, las relaciones sociales y su actividad pública, conocedor de su enfermedad crónica y molesto por la alteración morbosa de su existencia que, como diría Laín Entralgo, turbaba su esperanza temporal y espiritual, afectado por su *diselpidia existencial*[8].

Datos histórico-médicos para la reformulación de su diagnóstico

En el tratado de litotomía de Tommaso Alghisi[9] existe una transcripción, se supone que literal, de la autopsia a la que fue sometido el Papa Inocencio XI:

…Intorno poi alle observazioni delle Pietre, dice Egli, *io ne averei molte: ma bella sopra tutte è quella, che fu fatta nella S. Memoria D'INNOCENZIO XI. D'età anni settantanove; nelle cui reni fu aperto un teatro di maraviglie;…questi poi tagliati scopriono a me, che avevo avuto l'onore d'esser suo Medico segreto, la cagione degli antichi dolori de Reni, e del l'orine sanguigne, che S. Santità scaricava qualora faceva moto straordinario;cioé a dire, ci fecero veder due Pietre di tal grandeza, e di sí rara figura, che como portentose…ambedue però occupavano internamente tutta la sostenza de Reni…Da questa rara, e oltremodo bella osservazione si puó dedurre, che la parte necesaria allá separazione dell orina è solamente la pura cotecci glandulare de Reni, la quale nél nostro caso re stó intatta…mentre il rimanente delle Parti Orinarie, Vesica, e su Collo, furono vedute sanissime, con poco liquore orinoso, e senza Pietra…*

Nueva propuesta fisiopatológica, anatomopatológica y diagnóstica

De estos datos parece claro que el Pontífice padecía una enfermedad renal ya que sufría*…antichi dolori de Reni, e de l'orine sanguine…* de lo que se puede inferir que presentaba cólicos nefríticos acompañados de hematuria y muy probablemente episodios febriles por una pielonefritis acompañante. Es de suponer que esta situación clínica debía presentarse con cierta frecuencia, condicionaba su estado anímico y afectaba su rendimiento en la gestión de sus altas responsabilidades. Si este dato se engarza con las reiteradas crisis de podagra, se puede reformular el diagnóstico clínico histórico de esta forma:

1. Cólicos nefríticos complicados con Pielonefritis aguda.

Las últimas décadas de su vida presentó repetidas crisis de podagra que pueden ser atribuidas sin lugar a dudas a una hiperuricemia primaria ya que, por su aspecto físico, enjuto, no se presupone que padeciese un síndrome metabólico. Desde un punto de vista fisiopatológico, a tenor de los conocimientos actuales sobre la hiperuricemia primaria, si ésta no se trata de forma apropiada, su evolución es inexorable hacia la formación de litiasis coraliformes bilaterales.

2. Litiasis coraliforme de ácido úrico

De hecho eso es lo que, de forma muy gráfica, recoge Alghisi de la autopsia realizada por Lancisi al Papa Inocencio XI. En razón de su posición de médico personal del Papa, era obviamente conocedor de los padecimientos y sufrimientos del paciente y cuando abre el retroperitoneo y los riñones se encuentra con *…nelle cui reni fu aperto un teatro di maraviglie…:* unos cálculos coraliformes que reproducen fielmente las cavidades renales donde se alojan y que tenían un considerable tamaño: *…quella del destro era di peso d'once sei;*

e l'altra del sinistro d'onze nove; ambedues però occupavano internamente tutta la sostanza de´ Reni… (**Figura 1**). Años después, Pierre Dionis, en su *Cours d'Operations de Chirurgie*, confirma la relevancia de este hallazgo, al recoger la descripción hecha por Lancisi e incluso encargar un grabado que se incluyó como figura en su tratado (**Figura 2**)[10].

Figure 1: Dibujo de los riñones del Papa Inocencio XI una vez realizada la autopsia (Alghisi, 1708, p XXV-XXVII). Véase la divergencia de los polos superiores, la orientación antero-interna de los cálices, así como las pelvis por delante del hilio renal, aspectos característicos de los riñones en herradura.

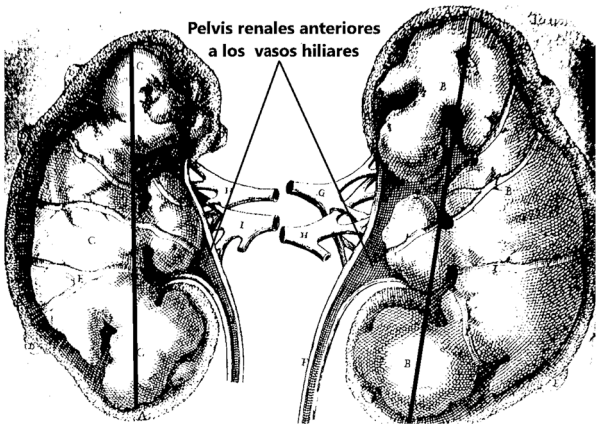


Figure 2: Grabado de los cálculos renales del Papa Inocencio XI. (Dionis, 1750, p. 180-182).

Si se miran con detenimiento los dibujos y se pormenoriza cada una de las palabras de la descripción, a nuestro entender, Lancisi describe, sin ser consciente de ello, una malformación anatómica, un riñón en herradura, de cuya descripción completa y detallada no dispondríamos hasta unos años después.

3. Riñón en herradura

Lancisi manifiesta que ha visto muchos cálculos renales en su vida, pero no aquella visión anatómica: *…io ne averei molte: ma bella sopra tutte è quella….* La imagen le provoca gran impacto, muy probablemente por varios motivos: el primero por la forma de los cálculos ya comentada, pero también por la anatomía y alineación de los riñones, la orientación interna heterotópica de los cálices y la disposición antero interna de las pelvis. Esta observación coincide con la descripción radiológica actual[11]:

> *La urografía intravenosa confirma la disposición en V de los riñones, destacando la rotación anómala de las pelvis, en posición anterior. El dato con mayor valor diagnóstico es, tal vez, el aspecto característico de los cálices inferiores, apuntando a la línea media, superpuestos a la columna vertebral.*

Aunque con anterioridad a la muerte del Papa Inocencio XI, se habían hecho varias descripciones de "riñones monstruosos", alguno de los cuales, a tenor de las descripciones y de los dibujos existentes, hoy no dudaríamos en calificar de riñones en herradura, pero no será hasta Morgani, es decir casi 100 años después de fallecimiento del Papa, cuando se realiza la descripción anatómica definitiva y se intenta establecer una correlación clínico-patológica. En esta tesitura, es muy probable que esas observaciones preliminares hubiesen pasado desapercibidas a Lancisi y Alghisi (de hecho no existe mención alguna en sus trabajos a esas observaciones previas) y, desde luego, es poco plausible que se hubiera reconocido la entidad como un riñón en herradura.

Además de estos hechos anatómicos, hay otras situaciones que podían haber influido en que la descripción no fuera todo lo completa que cabía esperar. Ambos hemi-riñones estaban profundamente alterados por la Pionefrosis calculosa, siendo la sínfisis renal en el caso estudiado, una mínima lámina fibrótica, como el resto del parénquima. En un riñón en herradura este segmento también es parenquimatoso, por lo tanto, esta zona también estaba afectada por la degeneración hidro-pionefrótica, siendo fácilmente interpretable como una membrana de adherencia inflamatoria natural, muy frecuentes en las Pionefrosis calculosas terminales. En estos casos, es muy fácil su sección o ruptura con maniobras de movilización renal, especialmente si el objetivo principal era extraer los dos cálculos individualizados, y mantenerlos como reliquias, como así ha sido. Esta interpretación se basa en las palabras de Lancisi, al abrir y exponer el área renal: *…poichí tagliato l'esterne membrane; enlle oui reno fu aperto…*; porque si no fuese por la forma del conjunto renal y por la forma especial de los cálculos y los riñones pionefrósicos, ¿a qué viene esta visión maravillosa?

Otro dato anatómico que apoya la propuesta de un riñón en herradura es la disposición de los vasos renales. En los riñones normales la ramificación no suele darse hasta que los vasos principales penetran en el hilio; en cambio, en los riñones en herradura la ramificación es muy precoz y cada rama se dirige a un segmento de la masa renal. En el caso que nos ocupa, no parece existir esta arteria, que por otra parte no está siempre presente, hecho que podría atribuirse a que el istmo era simplemente una estructura laminar membranosa absolutamente afuncional, con escasa o nula irrigación. Esta atrofia arterial está bien descrita en las pielonefritis.

A la luz de los conocimientos actuales, por las razones clínicas, históricas y anatómicas expuestas creemos estar en condiciones de reconsiderar el diagnóstico del Pontífice Inocencio XI: Insuficiencia renal terminal por riñón en herradura con litiasis coraliforme completa (con toda probabilidad de ácido úrico) y Pionefrosis terminal.

Nota: Se ha solicitado en reiteradas ocasiones a los descendientes de la familia Odescalchi, específicamente a la heredera-primogénita, Maria Pace Odescalchi, que custodia las litiasis coraliformes del Papa Inocencio XI [reliquia en forma de dos urnas que fue expuesta al público el día de la beatificación del Pontífice (7 de octubre de 1957)], documentación gráfica y el posible análisis espectrofotométrico de la mismas. Por una parte, constituirían un documento de gran valor testimonial y, por otra, permitiría conocer la composición química de los cálculos y confirmar esta teoría sin mancillar la reliquia. A día de hoy, no ha accedido a nuestra solicitud.

Agradecimientos: a Josep Mª Martí i Bonet, canónigo de la Catedral de Barcelona y director del Archivo Episcopal de la Diócesis de Barcelona por su orientación histórica y por facilitar el acceso a documentación y bibliografía reservadas.

Conflicto de intereses

Los autores declaran no tener ningún conflicto de intereses.

Bibliografía

1. Organización Mundial de la Salud. Documentos básicos. Ginebra: Organización Mundial de la Salud, 48. ed. 2014. p. 1.

2. Gelabert i Mas, Antoni. El Papa Inocencio XI: Aproximación etiológica a su patología renal. In: Actas del XXVII Congreso Internacional de Historia de la Medicina. Barcelona: 1980. p. 506-510.

3. Hollis, Christopher. El Pontificado. Barcelona: Plaza & Janés, SA, 1965. p. 197-202.

4. Preclin, Edmon; Jarry, Eugene. Luchas políticas. In: Historia de la Iglesia. Agustín Fliche, Victor Martín (eds) Vol. XXI. Valencia: EDICEP, 1. ed,, 1977. p. 22-24.

5. Pastor, Ludovico. En la época de la monarquía absoluta. In: Historia de los Papas Vol. XXX. Barcelona: Gustavo Gili, 1949. p. 9-12.

6. Pastor, Ludovico. En la época de la monarquía absoluta. In: Historia de los Papas Vol. XXXII. Barcelona: Gustavo Gili, 1952. p. 417-425.

7. Fointaine, Jean de la. Oevres completes (Carta del 18 de agosto de 1689 al príncipe de Conti). París: Walckenaer, 1838. p. 666.

8. Laín Entralgo, Pedro. La espera y la esperanza. In: Laín Entralgo, Pedro. Antropología de la esperanza. Barcelona: Ediciones Guadarrama/ Punto Omega. 1978. p. 123-189.

9. Alghisi, Tommaso. Litotomia ovvero del cavar la Pietra. Florencia: Giufeppe Manni, Stamperi, 1708. p. 25-27.

10. Dionis, Pierre. Cour d'operations de chirugie. Paris: D'Houry. 4.ed. 1740. p. 182.

11. Domínguez, Carlos; Serrano, Agustín; Garcia-Ybarra, Fernando. Anomalías congénitas renales de fusión. In: Jiménez-Cruz, Juan Fernando; Rioja-Sanz, Luis Ángel (ed.). Tratado de Urología. Barcelona: Prous Science, 2006. p. 592.

12. Da Carpi, Berengario. Isagoge breves perlucide ac uberrime in anatomiam humani corporis. Bolonia: Benedictum Hectoris, 1522. p. 17.

13. Botallo, Leonardo. De catarrho commentarius. Paris: Apud Bernardum Turifanum, 1564. p. 86.

14. Doldio, Leonardo. Mencionado por Bauhinis, Casparus In: Blasium, Gerhardum. Laurentii Bellini Exercitaciones anatómica de structura et usu renum ut et de gustus organo. Leiden: Joh Arnold Langerack, 1711, p. 215.

15. Cabrol, Barthelemy. Alphabet anatomic. Touron: Claude Michel & Gillaume Linocier, 1594. p. 94.

16. Bartholin, Thomas. Historiarum anatomicarum rariorum. Centuria I et II. La Haya: Adriani Vlacq, 1654. p. 166.

17. Tyson, Edward. A strange conjunction of both kidneys; and a great dilatation of the vena cava. Trans. Roy. Soc. London 1678:12:1038-9

18. Stalpart Vander Wiel, Cornelius. Hondert seltsame aanmerkingen so in de genees- als heel-en sni-konst. Amsterdam: Johan ten Horton, 1681. p. 165.

19. Morgagni, Joan Baptiste. De sedibus et causis morborum per anatomem indagatis. Venecia: Typographia Remondiniana 1761. p. 232.

eISSN 2255-0569

CASE REPORT

Critical pain in the armpit of a 75 year old woman Parsonage-Turner syndrome

Dolor crítico en la axila de una mujer de 75 años. Síndrome de Parsonage-Turner

Ole Buhl-Westermann[1], **Hans A. Eguia**[2]

1. Odense University Hospital, Department of Orthopedic Surgery, Svendborg, Fyn, Denmark.
2. Lægehuset Rudkøbing - General Practice, Rudkøking, Langeland, Denmark.

Corresponding author
Ole Buhl-Westermann
Odense University Hospital, Department of Orthopedic Surgery,
Svendborg, Fyn, Denmark
E-mail: Olebchr@gmail.com

Received: 19 - X - 2021
Accepted: 10 - XII - 2021

doi: 10.3306/AJHS.2022.37.01.171

Abstract

Parsonage-Turner (PT) syndrome is a painful disease with unknown aetiology. It often presents with acute pain in the shoulder, upper arm, the side of the neck and over the scapula. We describe the concurrence of PT in a 75-year-old woman with intense shoulder pain. PT is a diagnose of exclusion after clinical elimination of other frequent diseases and should be considered when the pain in the shoulder is not improved with medical treatment and/or physical therapy.

Keywords: Personage-Turner Syndrome, brachial neuritis, brachial amyotrophy.

Resumen

El síndrome de Parsonage-Turner (PT) es una enfermedad dolorosa de etiología desconocida. A menudo se presenta con dolor agudo en el hombro, la parte superior del brazo, el lado del cuello y sobre la escápula. Describimos la concurrencia de TP en una mujer de 75 años con intenso dolor en el hombro. La TP es un diagnóstico de exclusión tras la eliminación clínica de otras enfermedades frecuentes y debe considerarse cuando el dolor en el hombro no mejora con tratamiento médico y/o fisioterapia.

Palabras clave: Síndrome de Personage-Turner, neuritis braquial, amiotrofia braquial.

We describe the case of a 75-year-old-woman, who has hypercholesterolaemia, hypertension and depression (all well controlled and treated with atorvastatin and enalapril). She was referred to us from her primary care physician, who described her as having intense pain and functional limitation of the right upper limb some weeks after pain started. Symptoms appeared some months ago and were treated initially with oral NSAIDs without significant response. On examination, there was pain with the right arm mobilization and constant pain in the right axillary area with irradiation to the chest. We conducted a neurological examination, which was normal.

There was no damage to the joints and no mass lesion was found in the radiographic examination. Laboratory tests were normal (serum proteins, PCR, anti-DNA, anti-ENAs, ANCAs, ACE levels, immunoglobulins, hepatic and tumour markers, and rheumatoid factor were negative). Other biochemical and blood tests (white/red cell count, sodium, potassium, troponins) and ECG were normal.

A posterior MR scanning showed oedema in supra and infraspinatus muscles. These results were completed with electromyography resulting in an intense denervation pattern. With all these findings and after a meeting with doctors from orthopaedics, neurology, and geriatrics the diagnose of Parsonage-Turner Syndrome was decided.

The Parsonage-Turner Syndrome (PTS), also known as brachial neuritis or amyotrophic neuralgia, is a clinical syndrome of infrequent presentation and unknown aetiology. PTS often presents with acute pain in the shoulder, upper arm, the side of the neck and over the scapula. The pain lasts four weeks on average, followed by a rapid multifocal weakness and atrophy of the affected upper limp. The symptoms are often unilateral but can appear as a bilateral condition[1].

PTS is a diagnose of exclusion with an average delay of three to nine months before the diagnosis is made. The incidence of PTS is 1.64 per 100.000 in the United States but is expected to be higher due to the difficulty of recognition. Other conditions, like Rotator Cuff Injury, arthrosis in the shoulder joint or Adhesive Capsulitis, are often considered before the diagnose of PTS is made[1]. Some of the features of PTS compared to other conditions are shown in **table I**:

Table I: Classification of Parsonage-Turner Syndrome and associated conditions (own elaboration)[1,3,4].

	Parsonage-Turner	Traumatic Plexopathy	Rheumatoid Arthritis (RA)
Onset	**Sudden**	**Sudden**	**Slowly progressive**
Sex	**Men > Women (Age 20-69 years)**	**Men > Women (Age 15 – 25 years)**	**Women > Men (age often > 65 years)**
Aetiology	Unknown, but underlying predisposition, susceptibility to mechanical injury and immune-mediated response in the brachial plexus.	Penetrating injuries. Elongation, traction, or compression of the brachial plexus.	An inflammatory cascade of unknown origin, leading to persistent synovial inflammation, damage to the cartilage and underlying bone and extra-articular disease.
Symptoms	Intense pain, which can be difficult to localize (shoulder and proximal part of the upper limb) – 25% bilateral, followed by weakness and muscle atrophy, often in combination with paresthesia and sensory disturbances.	Depending on the involvement of the plexus.	Weak pain, swelling and heat sensation in the fingers, jaw, and neck. Often seen in combination with fatigue, depression, and loss of appetite.
Physical Examination	Muscles commonly affected is the Deltoid, supraspinatus, infraspinatus, serratus ant., biceps and triceps. Nerve affection is seen in isolated nerves or multiple nerves both inside and outside the brachial plexus.	Manual motor testing, range of motion and sensation examination is used to differentiate preganglionic plexopathy from postganglionic plexopathy, (I.e. Involvement of proximal innervated muscles (i.e. rhomboids) suggest preganglionic plexopathy).	Numbers of swollen joints and serology-test (Rheumatoid Factor and ACPA) to meet the ACR/EULAR 2010 criteria.
Electromyography (EMG)	Early EMG is not recommended. EMG after 4-6 weeks shows acute denervation and reduction of motor unit recruitment in a non-myotomal pattern.	Variable axonal plexopathy	Is not used to diagnose/manage RA.
Radiological Findings	Radiographic imaging is often used to exclude other disorders. MR: After 4-5 weeks neurogenic oedema (diffuse hyperintense muscle injury) is seen. Later, atrophy and fatty infiltration are seen.	MR: plexus lesions, compression, and nerve oedema. However, CT myelography is considered the benchmark of radiologic evaluation for nerve root avulsion	Juxta-articular erosions.
Remission	Usually reversible (years)	Unusual without treatment	Unusual
Treatment	NSAIDs/opioids, oral corticoids, and physical therapy.	Physical therapy and/or surgery.	NSAIDs, Corticoids, Disease-modifying Antirheumatic Drugs (DMARDs) and Biological Agents.

There is no specific treatment, that has been proved to reduce the neurologic impairment, nor improves the prognosis of PTS[1]. There have been no randomised control trials and the evidence to support a treatment option is anecdotal. In the acute stage, severe pain is often treated with a combination of NSAIDs and opioids. In one study, 60 mg/day oral prednisone was given in the first week and then tapered to 10 mg per day in the second week, which seems to shorten the duration of symptoms. Antiepileptic medications and tricyclic antidepressants are often used to treat neuropathic pain that often persists after the acute painful attack, however, antiepileptic medications are not as effective at treating the acute severe pain of PTS because of their delayed onset[1,2].

Nonpharmacologic treatments used in the treatment of PTS include physical therapy, osteopathic manipulation, therapeutic modalities, and acupuncture. Despite a proposed role of physical therapy for preventing loss of range of motion and further disability, physical therapy does not seem to speed up recovery. Goals of physical therapy should include maintenance of a range of motion and prevention of loss of function. Depending on the level of pain, range-of-motion exercises for the shoulder may be started immediately[2].

Finally, in some cases, PTS are refractory to conservative pharmacologic and nonpharmacologic treatments. In these cases, surgery is often considered. Surgical procedures for PTS include neurolysis, nerve grafts, and nerve transfers[1].

Interests conflict

The authors declare no conflict of interest.

Patient/ research participant consent

Written informed consent for publication of their clinical details was obtained from the patient.

1. Smith CC, Bevelaqua AC. Challenging pain syndromes: Parsonage-turner syndrome. Phys Med Rehabil Clin N Am. 2014;25(2):265-77.

2. Van Alfen N, Van Engelen BGM, Hughes RAC. Treatment for idiopathic and hereditary neuralgic amyotrophy (brachial neuritis). Cochrane Database Syst Rev. 2009;(3).

3. Noland SS, Bishop AT, Spinner RJ, Shin AY. Adult Traumatic Brachial Plexus Injuries. JAAOS - J Am Acad Orthop Surg [Internet]. 2019;27(19). Available from: https://journals.lww.com/jaaos/Fulltext/2019/10010/Adult_Traumatic_Brachial_Plexus_Injuries.1.aspx

4. Scott DL, Wolfe F, Huizinga TWJ. Rheumatoid arthritis. Lancet [Internet]. 2010 Sep 25;376(9746):1094–108. Available from: https://doi.org/10.1016/S0140-6736(10)60826-4

eISSN 2255-0569

CASE REPORT

Tumor de Células Gigantes originado en la porción anterior de un arco costal. Reporte de un caso y revisión de la literatura

Giant Cell Tumor originating in the anterior portion of a costal arch. Case report and literature review

Rolando González Cabañas[1], Blanca Yiset Garbey Salas[2], Ares Ferran Fernández[3], Jesús Yasoda Endo Milan[4]

1. Hospital Provincial "Ciro Redondo García". Provincia Artemisa. Cuba.
2. Policlínico "Miguel Perera Ortega". Municipio Caimito. Provincia Artemisa. Cuba.
3. Hospital Universitario "Celestino Hernández Robau". Universidad de Ciencias Médicas de Villa Clara. Cuba.
4. Universidad de Ciencias Médicas de Villa Clara. Cuba.

Corresponding author
Jesús Yasoda Endo Milan
Universidad de Ciencias Médicas de Villa Clara. Cuba
E-mail: jesusendo@infomed.sld.cu

Received: 22 - X - 2021
Accepted: 13 - XII - 2021

doi: 10.3306/AJHS.2022.37.01.173

Resumen

El tumor de células gigantes (TCG) es una neoplasia ósea considerada benigna generalmente, aunque localmente agresiva y puede presentar recidivas. Se origina en la epífisis/metáfisis de los huesos largos, su presentación en un arco costal es rara y de ocurrir generalmente se sitúa en la porción posterior, existiendo pocos casos reportados en la porción anterior. Se presenta el caso de una paciente femenina de 40 años de edad con gran masa en el hemi-tórax derecho. Clínicamente aparentaba un tumor profundo de la mama con invasión local de la pared torácica. La detallada evaluación radiográfica reveló una lesión costal con invasión de tejidos blandos. El examen histológico mostró células gigantes. El tumor se extirpó junto con la costilla, el defecto fue reconstruido y la paciente se recuperó sin incidentes. Se concluye que el TCG de las costillas es un caso raro, pero el diagnóstico diferencial de una masa de la pared torácica anterior debe incluirlo.

Palabras clave: Neoplasias óseas, tumor de células gigantes, arcos costales.

Abstract

Giant cell tumor (GCT) is a bone tumor usually considered benign, although locally aggressive and may recur. It originates in the epiphysis / metaphysis of the long bones. Its presentation in a costal arch is rare and if it occurs it is usually located in the posterior portion. There are very few cases reported in the anterior portion of the costal arches. The case of a 40-year-old female patient is presented with large mass in the right hemi-thorax. Clinically it appeared a deep tumor of the breast with local invasion of the thoracic wall. The detailed radiographic evaluation revealed that the mass was a costal lesion with soft tissue invasion. Histological examination of the biopsy sample showed giant cells. The tumor was removed along with the rib. The defect was reconstructed and the patient recovered without incident. It is concluded that it is a case of GCT originating in the anterior arch of a rib with dimensions between the two largest reported in the specialized literature. It is a rare case, but the differential diagnosis of a mass of the anterior chest wall should include GCT of the ribs.

Keywords: Bone neoplasms, giant cell tumors, ribs.

Introducción

El tumor de células gigantes (TCG) del hueso representa alrededor de 5% de todos los tumores óseos. Es un tumor considerado generalmente benigno con un comportamiento local agresivo[1]. Generalmente surgen en la región epifisaria de las extremidades. Su ubicación sub-articular típica y su alto riesgo de recurrencia pueden asociarse con una morbilidad significativa. Los huesos largos son los que más frecuentemente se ven afectados, especialmente alrededor de la rodilla[2]. Aunque benigno, rara vez puede hacer metástasis, especialmente en los pulmones.

Su aparición en las costillas es inusual[3]. Cuando aparecen en un arco costal, por lo general, se encuentran en su porción posterior (epífisis de la cabeza y el tubérculo), y su presentación anterior es muy rara4. Los TCG de la porción anterior de un arco costal, en las proximidades de los senos pueden presentar problemas de diagnóstico y terapéuticos. En este artículo se presenta un caso con TCG localizado en la porción anterior de un arco costal y se revisan los casos similares publicados en la literatura especializada.

Presentación de caso

Mujer boliviana de 40 años, consulta con la queja principal de una masa que se agranda lentamente justo debajo de su mama derecha durante el último año. El único síntoma asociado fue dolor ocasional leve y sensación de opresión de inicio reciente. Clínicamente, la tumoración era de aproximadamente 20×15 cm, de consistencia dura e indolora, abombando la pared anterior del hemitórax derecho (**Figura 1**). Los márgenes eran imprecisos y la superficie era lisa con piel suprayacente de características normales.

Las radiografías de tórax (vistas frontal y lateral) mostraron una lesión radiopaca, con densidad de partes blandas, en región anterior del hemitórax derecho con amputación de la porción anterior del tercer arco costal (**Figura 2**). La tomografía computarizada del tórax (**Figura 3**) reveló una masa tumoral sólida, no-homogénea, con densidad mayoritaria de partes blandas (40 UH de densidad media) y áreas relativamente hipodensas (20 UH de densidad media) sugestivas de necrosis o degeneración quística. También "mineralización intratumoral" dada por múltiples calcificaciones ramificadas. Dicha tumoración sustituye totalmente el cartílago y la porción anterior del 3er arco costal derecho y se extiende mayoritariamente a una situación intratorácica (mediastinal), pero extrapulmonar. Anteriormente desplaza al músculo pectoral adyacente por detrás de la mama sin infiltrarlo. Posteriormente comprime los tres lóbulos del pulmón derecho. Medialmente desplaza ligeramente el corazón a la izquierda haciendo contacto con las cavidades derechas sin infiltrarlas ni condicionar derrame pericárdico. Sus dimensiones son: 16 cm de extensión céfalo-caudal; 15 cm de diámetro transverso y 13 cm de diámetro AP. Derrame pleural derecho de densidad agua homogénea y espesor de 15 mm con disposición gravitacional.

Figure 1: Tumoración que abomba la pared anterior del hemi-tórax derecho. La piel suprayacente se muestra de características normales.

El tumor se extirpó junto con la costilla. El defecto fue reconstruido y la paciente se recuperó sin incidentes. La histopatología informó una gran masa lobular que encierra la costilla y mide 16 cm de diámetro máximo. La sección de corte mostró áreas de necrosis, hemorragia y una sensación arenosa.

El examen microscópico reflejó una gran cantidad de células gigantes multinucleadas dispersas sobre el parénquima. El estroma contenía células fusiformes vesiculares con núcleos. Había grandes áreas de hemorragia y necrosis. Se realizó una impresión final de un tumor de células gigantes de grado III de la costilla.

Figure 2: Las radiografías de tórax (vistas frontal (A) y lateral (B)) mostraron una lesión radiopaca, con densidad de partes blandas, en región anterior del hemitórax derecho con amputación de la porción anterior del tercer arco costal.

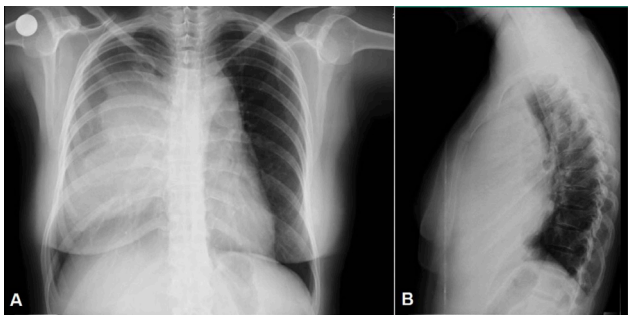
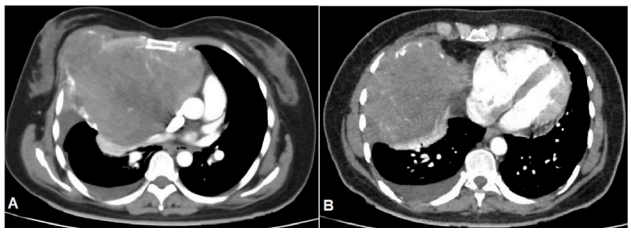


Figure 3: Cortes axiales de TC del tórax, a nivel de la mama (A) y a nivel del corazón (B). Muestran masa sólida, no-homogénea, con densidad mayoritaria de partes blandas y áreas relativamente hipodensas sugestivas de necrosis o degeneración quística. También "mineralización intratumoral" dada por múltiples calcificaciones ramificadas. Sustituye totalmente el cartílago y la porción anterior del 3er arco costal derecho; parece originarse en este sitio y extenderse mayoritariamente a una situación intra-torácica (mediastinal), pero extra-pulmonar. Anteriormente desplaza al músculo pectoral adyacente por detrás de la mama sin infiltrarlo. Posteriormente comprime los tres lóbulos del pulmón derecho. Medialmente desplaza ligeramente el corazón a la izquierda haciendo contacto con las cavidades derechas sin infiltrarlas ni condicionar derrame pericárdico. También es evidente el derrame pleural derecho de densidad agua homogénea.



Discusión

Los tumores de células gigantes del hueso representan el 5% de todos los tumores óseos primarios[5]. La mayoría (85%) ocurre en los huesos largos, y aproximadamente el 50% se encuentran alrededor de la articulación de la rodilla. Muchas series grandes han reportado una incidencia de alrededor del 1% en las costillas. Microscópicamente, los dos componentes básicos de los TCG benignos son el estroma y las células gigantes multinucleadas; las células del estroma son mononucleares y pueden

tener forma de huso, ovoide o redonda, mientras que las células gigantes multinucleadas pueden ser tan grandes que los numerosos núcleos son casi incontables.

La frecuencia de las células gigantes multinucleadas es variable y probablemente depende del patrón estromal. Las variantes de los TCG incluyen condroblastoma, fibroma condromixoide, quiste óseo aneurismático y tumor "marrón" de hiperparatiroidismo. En la presentación de un TCG en un arco costal el diagnóstico diferencial incluye al quiste óseo simple. Es más probable que estos últimos se formen en la parte anterior de las costillas, mientras que los TCG se localizan principalmente en la epífisis del hueso (es decir, la cabeza y el tubérculo de las costillas). Solo el 3% de los TCG se desarrollan en los esqueletos inmaduros que distinguen a estos pacientes de aquellos con quistes óseos aneurismáticos, en los que el tumor se produce al máximo antes de la fusión epifisaria.

Los tumores de células gigantes son tumores localmente agresivos y se presentan con los signos y síntomas de dolor, hinchazón y limitación del movimiento alrededor de una articulación[6]. En el caso que se describe, la paciente presentó una masa retro-mamaria de crecimiento lento durante un período de 1 a 2 años, y el dolor ocasional comenzó cerca de su momento de presentación. Esta presentación retrasada probablemente contribuyó al tamaño del tumor extremadamente grande encontrado en el momento de la resección quirúrgica. Si bien se han reportado múltiples casos de TCG que se originan en la costilla, las dimensiones encontradas en la TC de este caso parece ser el segundo más grande hasta la fecha (**Tabla I**).

Table I: Casos publicados de tumor de células gigantes originados en la porción anterior de un arco costal.

Autor(*)	Arco costal	Tamaño (cm)
Riddle et al. [12]	5to anterior	5.0 x 5.0 4.5
Sakao et al. [2]	5to anterior	5.8 x 5.2
Sakao et al. [2]	2do anterior	7.6 x 6.0
Tavecchio et al. [13]	11no completo	7.6 x 6.0
Shin et al. [14]	2do anterior	8.0 × 6.5 × 6.0
Sakao et al. [2]	2do anterior	9.0 × 7.0 × 5.0
Al-Otaibi et al. [15]	9no anterior	9.5 × 6.5 × 3.0
Sakao et al. [2]	4to anterior	10.0 × 7.0 × 5.0
Sakao et al. [2]	3ro anterior	11.0 × 12.0 × 13.0
Dehghan et al. [16]	4to anterior	12.5 × 10.5 × 5.7
Briccoli et al. [17]	9no anterior/posterior	13.0 × 11.0 × 2.5
Sakao et al. [2]	4to anterior	15.0 × 7.5 × 5.5
Cordeiro et al. [18]	5to anterior	25.0 × 17.0
Sharma et al. [19]	7ma anterior	28.0 x 24.0
Semionov et al. [20]	8vo anterior	5.4 cm
Heo et al. [21]	6to anterior	6.0 × 4.5 × 4.5

Los métodos actuales disponibles para tratar el TCG incluyen legrado con o sin el uso de alcohol, nitrógeno líquido, fenol o metil macrilato o injerto óseo, y la resección quirúrgica completa del segmento afectado del hueso[7]. La escisión es deseable ya que el 10% de los TCG en las costillas sufren una transformación maligna, mientras que la radioterapia no se recomienda ya que la mayoría de las transformaciones malignas están relacionadas con la radioterapia previa. Por lo tanto, la escisión en bloque es un tratamiento apropiado, y la supervivencia libre de enfermedad es directamente proporcional al margen de resección negativo[8]. Hay que añadir que recientemente la FDA ha aprobado el Pexidartinib (TURALIO™) como un novedoso medicamento administrado por vía oral[9].

Debido a la recurrencia tardía y la transformación maligna[10], se justifica un seguimiento prolongado, aunque actualmente los datos de biología molecular permiten hacer un pronóstico más certero[11]. El diagnóstico diferencial del tumor TCG maligno de hueso debe también incluir el osteosarcoma telangectásico y el osteosarcoma rico en células gigantes[12]. La malignidad primaria en el TCG es extremadamente inusual, pero es muy difícil de distinguir y debe tenerse presente en el diagnóstico diferencial[13]. La transformación maligna tardía, aunque rara, puede ocurrir con un pronóstico muy pobre.

Conclusiones

Presentamos el caso de una paciente con un tumor de células gigantes ubicado en la cara anterior de un arco costal con dimensiones entre las dos más grandes reportadas en la literatura especializada. El presente caso ilustra el hecho de que los tumores de células gigantes de la pared torácica anterior pueden confundirse con masas mamarias. La biopsia central con aguja fina o guiada por imagen sería diagnóstica si se obtiene una muestra adecuada. Los autores creen que el diagnóstico diferencial de una masa de la pared torácica anterior debe incluir TCG de las costillas.

Conflicto de intereses

Los autores declaran no tener ningún conflicto de intereses.

Bibliografía

1. Mohaidat ZM, Al-Jamal HZ, Bany-Khalaf AM, Radaideh AM, Audat ZA. Giant cell tumor of bone: Unusual features of a rare tumor. Rare Tumors. 2019 Sep 25;11:2036361319878894.

2. Sharma A, Armstrong AE. Giant cell tumor of rib arising anteriorly as a large inframammary mass: a case report and review of the literature. Case Rep Med. 2012;2012:850509.

3. Suarez Conejero AM, Pérez González R, Otero Morales JM, Cruillas Miranda S, Moret Hernández Y, Ferreiro Granda AM. Tumores pardos en paciente con hiperparatiroidismo secundario en hemodiálisis. Presentación de caso. Revista Habanera de Ciencias Médicas 2015;14(1): 118-26.

4. Gupta V, Mittal R. Giant cell tumor of rib--rare location on the anterior aspect. Arch Orthop Trauma Surg. 2000;120(3-4):231-2.

5. Liede A, Hernandez RK, Tang ET, Li C, Bennett B, Wong SS, Jandial D. Epidemiology of benign giant cell tumor of bone in the Chinese population. J Bone Oncol. 2018 Jul 26;12:96-100.

6. He H, Zeng H, Luo W, Liu Y, Zhang C, Liu Q. Surgical Treatment Options for Giant Cell Tumors of Bone Around the Knee Joint: Extended Curettage or Segmental Resection?. Front Oncol. 2019;9:946.

7. Valladares-Vijil LD , Silva-Cárcamo H, Armando-Domínguez R.. Tumor de células gigantes de hueso: diagnóstico incidental en una paciente con artralgia de larga evolución. Archivos de Medicina 2015; 11(4): 1

8. Wiratnaya IGE. Wide margin excision followed by tibialisation of fibula and ankle arthrodesis as novel surgical technique in giant cell tumor patient. J Clin Orthop Trauma. 2019 Sep-Oct;10(5):1004-7.

9. Lamb YN. Pexidartinib: First Approval. Drugs 2019;79:1805-12

10. Movahedinia S, Shooshtarizadeh T, Mostafavi H. Secondary Malignant Transformation of Giant Cell Tumor of Bone: Is It a Fate?. Iran J Pathol. 2019;14(2):165-174.

11. Maros ME, Schnaidt S, Balla P, Kelemen Z, Sapi Z, Szendroi M, Laszlo T, Forsyth R, Picci P, Krenacs T. In situ cell cycle analysis in giant cell tumor of bone reveals patients with elevated risk of reduced progression-free survival. Bone. 2019 Oct;127:188-98.

12. Subramanian S, Viswanathan VK. Lytic Bone Lesions. 2021 Aug 25. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. PMID: 30969659.

13. Palmerini E, Picci P, Reichardt P, Downey G. Malignancy in Giant Cell Tumor of Bone: A Review of the Literature. Technol Cancer Res Treat. 2019 Jan 1;18:1533033819840000.

www.ramib.org

Junta Directiva de la Reial Acadèmia de Medicina de les Illes Balears

President Macià Tomàs Salvà
Vicepresident Ángel Arturo López González
Secretari General Antonio Cañellas Trobat
Vicesecretari Sebastian Crespí Rotger
Tresorer Joan Besalduch Vidal
Bibliotecària Antonia Barceló Bennasar

Acadèmics d'honor

2003 - Excm. Sr. Santiago Grisolia García, Premi Príncep d'Astúries
2007 - Excm. Sr. Ciril Rozman, Premi Jaime I

Acadèmics numeraris

M. I. Sra. Juana M. Román Piñana
M. I. Sr. Josep Tomàs Monserrat
M. I. Sr. Bartomeu Anguera Sansó
M. I. Sr. Bartomeu Nadal Moncadas
M. I. Sr. Alfonso Ballesteros Fernández
M. I. Sr. Ferran Tolosa i Cabaní
Excm. Sr. Macià Tomàs Salvà
M. I. Sra. Joana M. Sureda Trujillo
M. I. Sr. Joan Buades Reinés
M. I. Sr. José L. Olea Vallejo
M. I. Sr. Pere Riutord Sbert
M. I. Sr. Joan Besalduch Vidal
M. I. Sr. Fèlix Grases Freixedas
M. I. Sr. Antoni Cañellas Trobat
M. I. Sr. Josep Francesc Forteza Albertí
M. I. Sr. Jordi Ibáñez Juvé
M. I. Sr. Joan March Noguera
M. I. Sr. Ángel Arturo López González
M. I. Sra. Pilar Roca Salom
M. I. Sr. Javier Cortés Bordoy
M. I. Sr. Lluís Masmiquel Comas
M. I. Sr. Sebastià Crespí Rotger
M. I. Sra. Antònia Barceló Bennassar
M. I. Sr. Javier Garau Alemany
M. I. Sr. Jordi Reina Prieto
M. I. Sr. Joan M. Benejam Gual
M. I. Sr. Claudio Rubén Mirasso Santos
M. I. Sr. Josep Mª Vicens Gómez

Acadèmics supernumeraris

M.I. Sr. Àlvar Agustí García-Navarro
M.I. Sra. Marta Emma Couce Matovelle

Acadèmics emèrits

M.I. Sr. Arnau Casellas Bernat

www.ramib.org

Protectors de la Reial Acadèmia

Banca March
Conselleria de Presidència
ASISA
Conselleria de Salut
Col·legi Oficial de Metges de les Illes Balears
Fundació Patronat Científic del Col·legi de Metges de les Illes Balears

Benefactors de la Reial Acadèmia

Salut i Força

Patrocinadors de la Reial Acadèmia

Clínica Rotger
Metges Rosselló
Grup Hospitalari Quirónsalud
Col·legi Oficial d'Infermeria de les Illes Balears
Associació Espanyola contra el Càncer a les Illes Balears
Col·legi Oficial de Farmacèutics de Balears
Escola Universitària ADEMA

ACADEMIC JOURNAL
OF HEALTH SCIENCES
MEDICINA BALEAR

www.medicinabalear.org