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PREMIOS Y BECAS 2022

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La **Fundació Patronat Científic** convoca los Premios de Investigación ***Mateu Orfila***, ***Damià Carbó*** y ***Metge Matas*** con la finalidad de **premiar la trayectoria de la investigación en Ciencias de la Salud** en nuestra comunidad.

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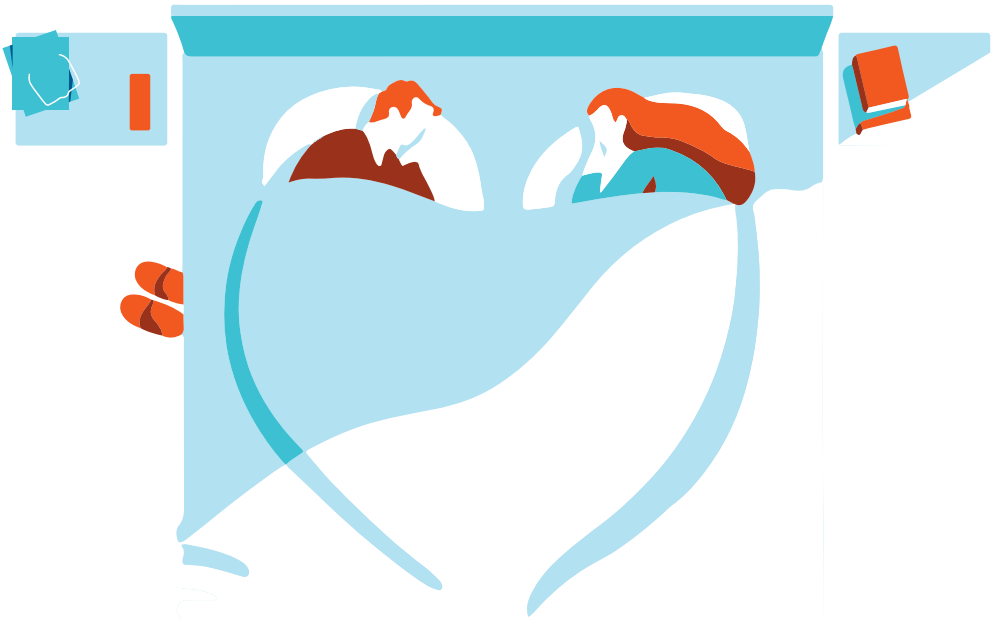
Haz algo grande por tu salud



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EDITORIAL

La psicología del comer

The psychology of eating

Andreu Genestra

Cocinero con una estrella Michelín

Me operaron de una luxación externa y el único recuerdo que tengo al salir de la anestesia es de hambre, mucha hambre. Crema pálida de verduras y carne seca era lo que me esperaba para la primera comida después de 24 horas…

De acuerdo que no va a tener ningún riesgo a nivel bacterias ni a efectos técnicos sanitarios pero… dónde está el valor anímico? Acaso no importa el efecto psicológico de un paciente?

Por qué a los niños pequeños se les da el pescado pasado de cocción? Por qué las comidas no se las sazonamos con especias? Por qué las verduras, el arroz, la pasta no se la servimos al dente?

Son preguntas que desde el prisma culinario no entiendo y me cuestiono siempre.

El cerebro es nuestra fuente procesadora de estímulos, donde a la hora de la alimentación no solo se procesa la ingesta de calorías en nuestro organismo sino que también trabaja el sentido de la vista, el olor, el gusto, la textura y los sonidos que se puedan producir.

Olvidamos una parte muy importante de la experiencia de la alimentación: la felicidad, el sentirnos confortables, sensación de evadirse por un momento y centrarse en uno mismo, la acción que nos permita seguir viviendo y que solemos realizar unas cuantas veces durante el día. Diría que es la meditación más básica que conecta con uno mismo.

Debemos remontar a nuestro primer placer innato; aquel que se nos ofrece al darnos el pecho de una madre, porque no solo es la leche materna que alimenta al recién nacido , es el olor corporal, la textura que el bebe recibe al tocar con las manos el seno o el sonido que aporta el chupar.

Si nos damos cuenta la alimentación no solo contribuye al estómago sino al alma. Cuando cocinamos influimos a nuestro subconsciente con sabores como el picante o el ácido, toques amargos o salados o dulces , que hacen estremecernos.. Las texturas ya sean blandas o gelatinosas, crujientes como el maíz salado o semi espesas, quedan en nuestro recuerdo siempre, todo es importante.

La gastronomía afecta al carácter, a la autoestima y no deja de ser un lenguaje no escrito el cuál identificamos para expresar un territorio, una cultura o una religión. Por qué la evolución no nos lleva a mejorar todos esos estigmas sino que lo empeora? La evolución nos ha llevado a comer de la peor manera que jamás se ha producido un alimento, por ejemplo el pan. No solo lo producimos mal sino que hemos creado una legión de soldados gastronómicos en contra del gluten… Se han preguntado si un pan de harinas ecológicas sin apenas refinar tiene mucho gluten?

Bajo mi humilde mirada como cocinero me da pena cuando sin prescripción médica nos autocensuramos privilegios alimenticios como pueda ser comer carne, pescado, lácteos… El ser humano debería seguir la dieta mediterránea como método preventivo de enfermedades, sin tener que tomar aditivos químicos o homeopáticos en substitución de lo que encontramos en nuestros mercados. Dieta mediterránea significa temporalidad, buenos productos de procedencia cercana y sobretodo en su justa medida.

La globalización nos lleva a consumir productos de todo el mundo, al menos lo creemos. El Aguacate, vegetal que denominamos como sano, su cultivo produce la desertificación de la zona por el alto consumo de agua, mucho más calórico que un filete y que normalmente nunca lo consumimos maduro al venir de la otra parte del mundo. Si la comparásemos con una col, considerada uno de los mejores vegetales, que su cultivo no es agresivo y sus propiedades alimenticias son increíbles? Seguramente me dirán que no es tan apetecible, pero ¿y si se les enseña a que sea apetecible y fácil?

Debemos dedicarle tiempo, no hay otra. Debemos hacer una inversión a nuestra salud y bienestar. Nuestro recetario local cuida de nuestro entorno, nuestra cultura y nuestros sabores… esa herencia transmitida familiarmente que no podemos olvidar.

Recuerden ,no hay que vivir para comer sino comer para vivir… aunque si la comida se convierte en un acto de cuidar la mente, el alma y el estómago nos aporta algo más que simple calorías…

They operated on me for an external dislocation and the only memory I have when I come out of anesthesia is of hunger, very hungry. Pale cream of vegetables and dried meat was what I expected for the first meal after 24 hours…

I agree that it will not have any risk at the bacterial level or for technical sanitary purposes, but… where is the emotional value? Doesn't the psychological effect on a patient matter?

Why are young children given overcooked fish? Why don't we season foods with spices? Why are vegetables, rice and pasta not served *al dente*?

These are questions that from a culinary point of view I do not understand and I always question myself.

The brain is our processing source of stimuli, where at the time of feeding not only is the intake of calories processed in our body but also the sense of sight, smell, taste, texture and sounds that are heard work they can produce.

We forget a very important part of the eating experience: happiness, feeling comfortable, the feeling of escaping for a moment and focusing on oneself, the action that allows us to continue living and that us usually do a few times during the day. I would say that it is the most basic meditation that connects with oneself.

We must go back to our first innate pleasure; the one that is offered to us by giving us a mother's breast, because it is not only the breast milk that feeds the newborn, it is the body odor, the texture that the baby receives when touching the breast with his hands or the sound that the suck.

If we realize food not only contributes to the stomach but also to the soul. When we cook we influence our subconscious with flavors such as spicy or acid, bitter or salty or sweet touches, which make us shudder. The textures, whether soft or gelatinous, crunchy like salted corn or semi thick, always remain in our memory, everything is important.

Gastronomy affects character, self-esteem and is still an unwritten language that we identify to express a territory, a culture or a religion. Why does evolution not lead us to improve all these stigmas but rather worsens them? Evolution has led us to eat in the worst way that food has ever been produced, for example BREAD. Not only do we produce it poorly, but we have created a legion of gastronomic soldiers against gluten. Have you ever wondered if a bread made from organic flour with hardly any refinement has a lot of gluten?

Under my humble gaze as a cook, it pains me to observe how when, without a medical prescription, we self-censor food privileges such as eating meat, fish, dairy products… Human beings should follow the Mediterranean diet as a preventive method for diseases, without having to take chemical additives or homeopathic in substitution of what we find in our markets. Mediterranean diet means temporality, good products from nearby sources and above all in the right measure.

Globalization leads us to consume products from all over the world, at least we think so. Avocado is a vegetable that we consider healthy, but its cultivation produces desertification in the area due to the high water consumption it requires, it is much more caloric than a steak and, moreover, we normally never consume it ripe as it comes from the other part of the world. What if we compared it to a cabbage, which should be considered one of the best vegetables, with a non-aggressive cultivation and incredible nutritional properties? Surely they will tell me that it is not so appetizing, but what if it is taught to be appetizing and easy?

We must dedicate time to it, there is no other. We must make an investment in our health and well-being. Our local cookbook takes care of our environment, our culture and our flavors, that family-transmitted heritage that we cannot forget.

Remember, you don't have to live to eat but eat to live… although if food becomes an act of caring for the mind, soul and stomach, it gives us something more than simple calories…

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ORIGINAL

A systematic review of the literature describing the outcomes of near-peer mentoring and near-peer teaching and learning programs for medical students in Iran

Una revisión sistemática de la literatura que describe los resultados de los programas de tutoría y enseñanza y aprendizaje entre pares para estudiantes de medicina en Irán

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Abstract

Introduction and objective: The complex or peculiar nature of medical studies does not always allow all students to succeed in Iran's academic experiences. The first year of medical studies, for example, is described as stressful and difficult for students. Approaches such as near-peer mentoring and near-peer teaching can be instrumental in supporting students.
Methods: This systematic review aims to analyze the literature describing the outcomes of near-peer mentoring and near-peer teaching and learning programs for medical students in Iran. Scientific databases were explored using keywords such as near-peer mentoring, near-peer teaching, medical students, peer coaching, peer advice, peer guidance, big brothers big sisters mentoring program, peer support and peer counseling, Iran. Out of 17845 studies initially identified, about 14 met the inclusion criteria (programs involving medical students, regardless of the year of study, mentors close to their peers, i.e., in the second year, but not limited to, program located in Iran). The drafting was done according to PRISMA standards.
Results: The results show that there are several outcomes for near-peer mentoring and near-peer teaching. The primary identified outcomes are positive relationships, improving academic support, improving psychosocial support, and developing specific professional skills.
Conclusion: We conclude that near-peer mentoring and near-peer teaching can help students' support and capacity building among medical students in Iran.

Keywords: Near-peer mentoring, near-peer teaching, medical students.

Resumen

Introducción y objetivos: La naturaleza compleja o peculiar de los estudios de medicina no siempre permite a todos los estudiantes tener éxito en las experiencias académicas de Irán. El primer año de los estudios de medicina, por ejemplo, se describe como estresante y difícil para los estudiantes. Enfoques como la tutoría y la enseñanza entre pares pueden ser fundamentales para apoyar a los estudiantes. Esta revisión sistemática tiene como objetivo analizar la literatura que describe los resultados de los programas de tutoría y enseñanza cercana a los pares para estudiantes de medicina en Irán.
Metodología: Se exploraron las bases de datos científicas con palabras clave como near-peer mentoring, near-peer teaching, medical students, peer coaching, peer advice, peer guidance, big brothers big sisters mentoring program, peer support and peer counseling, Iran. De los 17845 estudios identificados inicialmente, unos 14 cumplieron los criterios de inclusión (programas con estudiantes de medicina, independientemente del año de estudio, mentores cercanos a sus pares, es decir, en el segundo año, pero sin limitarse a ellos, programa ubicado en Irán). La redacción se realizó según las normas PRISMA.
Resultados: Los resultados muestran que hay varios trabajos para la tutoría cercana a los pares y la enseñanza cercana a los pares. Los principales resultados identificados son las relaciones positivas, la mejora del apoyo académico, la mejora del apoyo psicosocial y el desarrollo de habilidades profesionales específicas.
Conclusión: Llegamos a la conclusión de que la tutoría entre pares y la enseñanza entre pares pueden contribuir al apoyo y al desarrollo de capacidades de los estudiantes de medicina en Irán.

*Palabras clave:*Tutoría entre pares, enseñanza entre pares, estudiantes de medicina.

Introduction

Peer mentoring is designed to help to matriculate medical students reach their potential through supported matches with other medical students in the second year or above. Many universities worldwide are opting for near-peer mentoring and near-peer teaching and learning programs to help medical students and ensure their success. In their admissions process, several medical schools highlight peer mentoring in the support system that the school offers to their students. Such a program focuses on young minds development, and the peer acts as a role model and provides guidance to the junior students through a relationship based on trust and caring. This type of mentoring or support meets several requirements: the great diversity of students, the impossibility for faculty mentors to provide personalized support to each student, etc. New student support enables new students to deal with students' diversity and the problems resulting[1].

Peer mentoring can be defined as a formal relationship in which a more qualified student provides guidance and support to another student[2]. It is an academic relationship in which a senior learner (a year or more above) provides guidance and support to a new (junior) learner to enable him to navigate their education[3]. Peer education is close to a subset of peer education, in which the "teacher" has experiences approximately "2 to 5" years more than a "student"[4].

The benefits of near-peer mentoring and near-peer teaching have been reported in several studies. Analyzing the literature on near-peer mentoring programs' outcomes, Akinla *et al*. (2018)[3] have identified three primary outcomes: professional and personal development, stress reduction, and ease of transitioning. Previous scientific evidence reports that mentoring helps to reduce stress and makes it easier for first-year medical students to adjust[5].

Previous data attributed beneficial effects to near-peer mentoring and near-peer teaching that deserve to be studied and valued in Iran. This systematic review proposes to analyze literature describing the outcomes of near-peer mentoring and near-peer teaching and learning programs for medical students in Iran. This will also involve; describing the effects of near-peer mentoring schemes and near-peer teaching and learning programs for medical sciences students in Iran's transition phase. Comparison with other countries, identifying similar mentoring programs in medical sciences schools in already published literature, and determining how the evaluation was carried out in such programs. All this will make it possible to decide the factors involved in effective peer mentoring programs and the outcomes' scope in supporting success.

Methodology

The method used to carry out this systematic review was instigated by that used by Akinla *et al*.[3], with several modifications. The PRISMA guidelines are observed strictly throughout the search. The data collection and processing considered four main stages.

Eligibility criteria: The most relevant articles from Iran without regard to the publication year were selected based on the keywords searched, the rigor of the methodology used and the conclusions drawn. The articles were in English or Arabic and the impact factor of the publication journal was also considered. The programs presented in each article concern the first-year medical school student and lasted an average of one year. Evaluations of the programs were done throughout the program or at the end depending on the study.

Information sources: The targeted databases were PubMed, Google Scholar, Embase, SID, Magiran, and Scopus. They were screened from January to February 2021.

Search and study selection: Equations were designed from the keywords to research the databases. PRISMA Flowchart showing search process and study selection are presented in **figure 1**.

Data collection process and data items: Data were extracted from the reports using pre-designed forms. The data collected was considered true. No confirmation was made with the investigators.

Definition of a hierarchy of evidence: To optimize the bibliographic search quality and identify the most relevant articles, the hierarchy of evidence successively considered randomized controlled trials, systematic reviews, quantitative studies, qualitative studies/policy documents, and finally, experts' opinions.

Keywords: Equations were designed from the following keywords to carry out the research (''near-peer mentoring "OR" near-peer teaching") AND " 'medical student' "AND Iran; "near-peer mentoring" AND Iran; "peer coaching" OR "peer advice" OR "peer guidance" OR "big brothers big sisters mentoring program" OR "peer support and peer counseling" AND ''medical student' 'AND Iran etc.

Inclusion criteria:
Inclusion criteria are:
1. programs involving medical students, regardless of the year of study,
2. Mentors should be close to their peers, i.e., in the second year, but not limited to
3. Program located in Iran. No restrictions were made regarding the year in which the study was carried out.

Exclusion criteria:
Exclusion criteria are
1. lack of sufficient detail about the program and its outcomes
2. Duplicate contents in the articles
3. A mentor is close to their peers (faculty mentor…)
4. Mentorship programs inadequately described, i.e., lacking details on structure, objectives, and/or evaluation
5. Programs aimed at recruiting students to particular specialties or field of interests
6. Mentorship program not related to medical student

Analysis and processing of articles: At the end of the process, 14 articles were retained (**figure 1**). Their analysis took into account the recommendations of Lincoln and Guba6. The recurring codes in the articles were used to write the results.

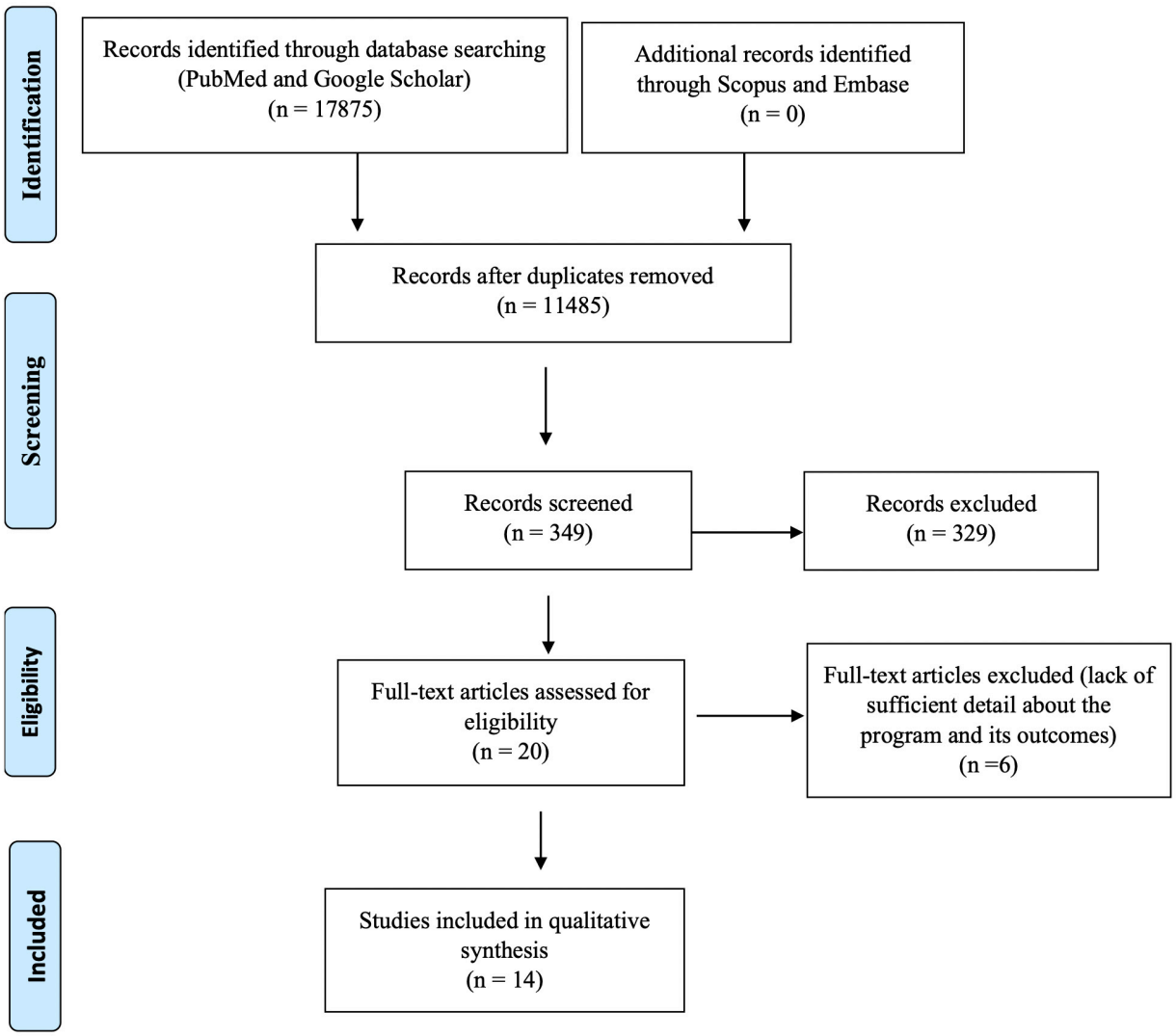
Results

Study selection and characteristics: 14 articles were selected, evaluated for eligibility, and included in the journal from a total of 17875 articles.

Description of each program: The inclusion criteria identified six main programs whose characteristics are summarized in **table I**.

The dual mentoring program from Tehran University of Medical Sciences (TUMS), School of Medicine: In 2011, Tehran University of Medical Sciences (TUMS), School of Medicine launched the dual mentoring program7. One of the particularities of this program was the students' involvement from the beginning. Four volunteer fifth-year medical students received approval from the school administration to organize the program.

Figure 1: PRISMA Flowchart showing search process and study selection.



The actors involved: The actors involved in the program are 12 medical students (as mentors): 6 from the clinical phase and six from the preclinical phase, with a faculty from the school involved in the mentors' supervision.

Characteristics and preparation of the actors: An initial preparation phase trained the mentors in communication techniques and the fundamentals of mentoring. Mentoring pairs were then formed (a clinical mentor linked to a preclinical mentor) and named dual mentoring. Thirty-six mentees were randomly selected from among 150 first-year medical students.

Practical implementation: Mentors and mentees were expected to communicate through the following means: telephone calls (once a week at the beginning to form the mentor-mentee relationship, which was gradually reduced to once every three weeks at the end of the program); e-mail or virtual modalities (including e-mail templates, addressing common first-year student problems and learning concepts and skills); and face-to-face meetings (individually or in groups). Meetings with role models (those who have been successful in junior clinical medical schools) were also part of the program. Due to the likely limitations of the student mentors' consulting abilities in psychology, education, or finance, a referral system was developed to direct recipients to university support or leadership centers, as appropriate. Also, regular weekly inter mentor sessions were organized so that mentors could exchange ideas and share their experiences. To identify the program's reach, impact, and outcome, researchers conducted a study involving all mentors (n=12) and a group of mentees (n=21). Through group discussions, the perceptions of the stakeholders were collected.

Table I: Anthropometric, clinical and analytical characteristics of participants in the study.

N	Program Name	Academic institutions	Launch year	Aim	Actors involved	Characteristics of mentees and mentor	Main outcomes	References
1	dual mentoring program	Tehran University of Medical Sciences (TUMS), School of Medicine	2011	assist the first-year medical students	Mentor, mentee, a faculty member	individual mentee, two students (one in the clinical phase and another in the preclinical phase)	helpful in guiding students on their first-year courses, clinical mentors were effective in shaping the mentees' professional identity and promoting their interests in basic science subjects	[7]
2	mentoring program	Shiraz Medical School	July 2015	assist the first-year medical students	Mentor, mentee, a full academic professor with experiences in medical science	Three mentees assigned to one mentor	adjusting faster to the new conditions significant increase of grade point average	[8]
3	near-peer education	Nursing students of Ilam University of Medical Sciences	2020	determine the effect of two educational methods (Near-Peer and Instructor) on hand hygiene skills learning in nursing students	near-pear and students	the first-year nursing students as a mentee the last year nursing students as near-peer	Developing specific professional (hand hygiene by Nurses students)	[9]
4	Peer Assisted Learning Approach on clinical Self-efficacy of Nursing Students	Islamic Azad University of Tehran Medical Sciences Branch	2016	Evaluate the effect of using Peer Assisted Learning approach on Clinical self-efficacy of nursing students in selected fields of Islamic Azad University of Medical Sciences in Tehran	Peer-assisted learner Nursing students	Peer-assisted learner Assisted nursing students	Increasing clinical self-efficacy of nursing students	[10]
5	Peer mentoring for medical students during the COVID-19 pandemic via a social media platform	3.1.5.Peer mentoring for medical students during the COVID-19 pandemic via a social media platform	2020	Shiraz University of Medical Sciences	Peer mentors mentee	371 undergraduate students (as mentee) were assisted by ten final year students (as peer mentors)	impact in helping students adapt more quickly to the current emergency condition; Participation in this initiative would have been beneficial for their professional development	[11]

Mentoring program from Shiraz Medical School

Actors involved and their characteristics: Fifteen high-caliber medical students (third or fifth semester) with good communication skills were invited to participate in the program as mentors.

Practical implementation: A preparation phase took place to train the new mentors. Workshops were held to build their unique teaching and learning methods, communication, and consultation techniques. Three mentees were placed under the responsibility of a mentor. Good communication between the mentor and mentees was a criterion for selection. An experienced full professor acted as a supervisor.

Evaluation: The program's effectiveness was evaluated at the end of the first year of the study through a questionnaire (containing five questions) addressed to the mentees[8].

Near peer teaching on hand hygiene skills learning in nursing students of Ilam University of Medical Sciences: In this case, researchers used a near-peer teaching method to evaluate its impact on learning hand hygiene skills in Ilam University of Medical Sciences nursing students[9].

Actors and preparation: A mentor group comprises five top-scoring final year students with good speaking skills and sufficient teaching proficiency. They are selected and trained.

Practical implementation: Eight first-year students were assigned to a near-peer mentoring. Exercises were performed in 3 sessions of 30 to 45 minutes each over two weeks. The control group was trained by the instructor according to the usual methods of the faculty. All students were evaluated after four weeks of training.

Peer-assisted learning approach on clinical self-efficacy of nursing students at Islamic Azad University of Tehran Medical Sciences Branch: Experimenting with this type of learning led to dividing the subjects (into two case groups and a simple random sampling control group); the control group received conventional methods (by the clinical instructor) and the case groups by peer learning, and received clinical training for three weeks. The data collection tool included psychometric questionnaires to assess self-efficacy in clinical practice with a 4-point Likert scale in 4 domains[10].

Peer mentoring for medical students during the COVID-19 pandemic via a social media platform: To help medical students manage the stress and anxiety associated with universities' temporary closure during the COVID-19 pandemic, a virtual social platform was created with Shiraz University's medical school students. Through this platform, high-level medical students were able to mentor and assist undergraduate medical students. The study involved 371 undergraduate students and ten final-year students as experts (with experienced professors). Discussions focused on managing stress and anxiety and how to organize one's work time during the pandemic.

The evaluation involved the use of a questionnaire to measure the effects of this activity. 71% of early-career medical students felt that the social media platform had a significant impact in helping them adapt more quickly to the current emergency conditions. Participation in this initiative would have been beneficial for their professional development[11].

The effect of peer mentoring program performance on clinical function in second-semester nursing students: For this program 44-second semester nursing students were selected by census and meeting pre-determined inclusion criteria, were randomly assigned into two groups: a control group (21) and an intervention group (23). The control group received clinical instruction using the traditional method and the second group received instruction based on the peer mentoring program. In the intervention group, a 7th-semester mentor was assigned to 5-4 second-semester students. The mentors were to guide and support the younger students[12].

Outcomes

Positive Relationship: Mentors involved in the dual-mentoring of Tehran University of Medical Sciences (TUMS), School of Medicine, felt that mentoring was a reliable, persistent, and systematic relationship[7].

Academic support: Improved academic support is a reported outcome in all identified programs. In dual-mentoring, the mentees felt that the mentors provided them with a great deal of academic support, especially when preparing for exams[7]. A significant increase in average scores was observed in the mentees' scores in the mentoring program of Shiraz Medical School[8].

Psychosocial Support: Psychosocial benefits include increased motivation and hope for mentees and reduced stress in the face of difficulties[7]. The evaluation of Shiraz Medical School's mentoring program showed that 53% of mentees impacted their ability to adapt to new situations[8].

Developing specific Professional skills: The example of Near peer teaching on hand hygiene skills learning in nursing students of Ilam University of Medical

Sciences is illustrative since the study did not focus on a set of academic activities over a year but the development of a specific competency. The results showed that the scores for hand hygiene competency in the Peer group post-test were significantly higher than those before the intervention (P<0.001). Also, scores for hand hygiene competence between post-test "Near-Peer" group were significantly higher than the instructor group (P<0.001)[9]. In the same sense, the peer-assisted learning approach experimented at Islamic Azad University of Tehran Medical Sciences Branch has resulted in increased clinical self-efficacy of nursing students[10].

Increasing the mentors' abilities and social skills: In Peer mentoring for medical students during the COVID-19 pandemic via a social media platform at Shiraz University of Medical Sciences, the activity would have contributed to strengthening the mentors' professional skills as future physicians[11].

Discussion

This systematic review aimed to analyze the literature describing the outcomes of near-peer mentoring and near-peer teaching and learning programs for medical students in Iran. The inclusion criteria identified six main programs, with each of the specific characteristics. In the analysis, we found that the various studies' outcomes are similar, with benefits for both the mentor and the mentees. The primary outcomes are positive relationships, academic support, psychosocial support, developing specific professional skills, and increasing the mentors' abilities and social skills. Several studies have also highlighted such outcomes for medical student's mentoring programs. According to[13], "Clinical mentoring programs help to develop students' clinical skills and can increase interest in under-subscribed specialties." Also, positive mentoring can have a significant influence on specialty choice.

There are many similarities between the programs identified in Iran and some mentoring programs in other countries. Many dissimilarities also exist. Examining these two aspects allows you to draw your conclusions about the prospects for improving programs in Iran. The BigSib student peer mentoring program, for example, has been implemented at Universiti Sains Malaysia medical school to enhance and strengthen the training of medical students in soft skills and professional development. A study reported a percentage of 45.9% of students perceiving the program as a success. It would help develop the interpersonal skills and professionalism of students. It is a kind of platform that puts second-year medical students and first-year medical students in interaction. The BigSibs are a group of second-year medical students selected based on academic performance and attitude. The roles of BigSib are to act as Siblings, Eyes, and Ears for the School, Counselor, Role-model and Trainer (SECRET). As siblings, they are expected to share experiences, support, and help the juniors[14]. Medical Education Unit of University College of Medical Sciences, Delhi, initiated in 2009 a mentorship program in which volunteer teachers mentored first-year medical students. The mentor was responsible for interacting with the new students and providing them with an immediate support network[15]. In 2010, the program's evaluation results led to introducing a new mentoring style based on "near-peers." An older or more competent peer act as a mentor to a younger one. Results from a study designed to gather the perceptions of mentors and mentees of the program showed that mentees liked the impacts of the experience to the point that they, in turn, wanted to be mentors[5].

Medical students generally need the more experienced seniors to guide them[16]. Participants in this study mentioned that the formal mentor-mentee relationship is more effective because of the reciprocal commitment and reliable, accurate, and specific advice from the mentors. Based on the results, dual mentoring was successful because the preclinical mentors were successful in their mission to guide students on their first-year courses and exams. The clinical mentors were effective in establishing the professional identity of the mentees. The system of involving multiple mentors in medical students has been shown to resolve differences between faculty mentors and mentees[17-19].

However, although few studies have demonstrated the effects of mentoring on mentors, those who participated in this program felt that the relationship established with their mentees was very beneficial to them. It increased their personal and social skills but also gave them a sense of satisfaction, which is consistent with the results of other peer mentoring programs[20,21]. From a resource-saving perspective, student-led mentoring programs are proving to be an effective alternative to school-based programs. However, independence from school administrations may result in the loss of some important support systems. Fornari et al. (2014) reported that most schools house their mentoring programs in the office of student affairs and the office of academic affairs without any accountability given to undergraduate medical students[22].

Limitations

As a limitation of this program, the views of mentors and mentees were identified using a qualitative methodology. Analysis of the short- and long-term outcomes of the mentoring program in terms of academic improvement could certainly quantitatively improve understanding of the program. Another limitation is that the mentoring program was established only for first-year medical students, so different results could be obtained from other students.

Conclusions

We conclude that near-peer mentoring and near-peer teaching can help students' support and capacity building among medical students in Iran.

List of Abbreviations

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; TUMS: Tehran University of Medical Sciences; SECRET: School, Counselor, Role-model and Trainer.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors were involved in data curation, formal analysis, investigation, methodology and reviewing and editing the manuscript. All authors have read and approved the manuscript.

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ORIGINAL

Egg White Hydrolysate as a new bioactive food ingredient in the prevention of gastrointestinal effects induced by aluminum exposure in rats

Hidrolizado de clara de huevo como nuevo ingrediente alimentario bioactivo en la prevención de los efectos gastrointestinales inducidos por la exposición al aluminio en ratas

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Abstract

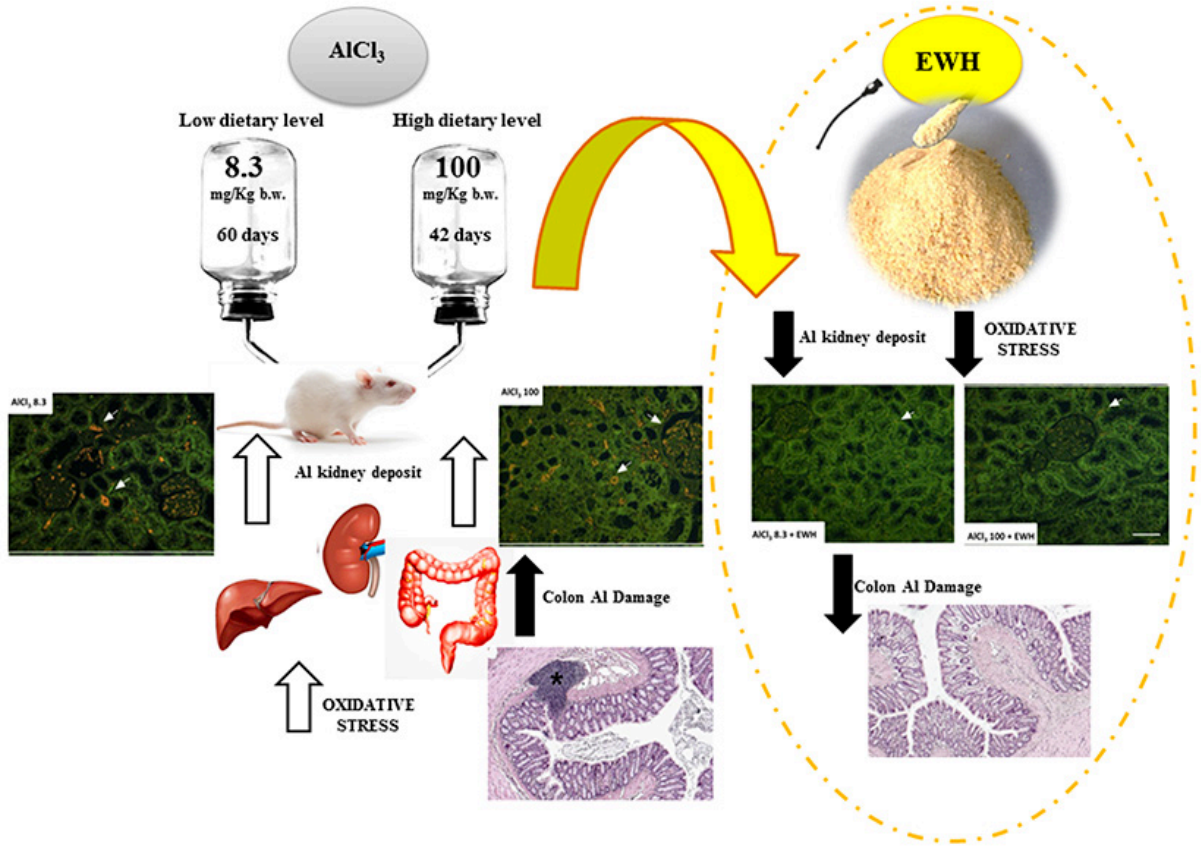
Objective: We investigated the effects of an egg-white hydrolysate (EWH) on the gastrointestinal tract and organs related to aluminum (Al) metabolism after Al exposure at both low and high-human dietary levels.
Methods: Male Wistar rats were orally treated to both low and high dietary doses of Al. Group 1) Aluminum-low dietary level (AlCl3 at 8.3 mg/kg b.w. for 60 days), co-treated or not with EWH (1 g/kg/day); Group 2) Aluminum-high dietary level (AlCl3 at 100 mg/kg b.w. for 42 days), co-treated or not with EWH.
Results: Both Al treatments increased oxidative damage in the liver and kidney. The highest Al dose impaired colon morphology, inducing inflammation and mucosal ulcerations. EWH prevented the raised oxidative stress level and colon damage and seems to reduce the presence of Al at the tissue level.
Conclusions: Our results appoint the EWH as a promisor food ingredient to prevent adverse effects produced by Al exposure in human health.

Keywords: Environmental contaminant, human health, bioactive ingredient, egg-derived peptides.

Resumen

Objetivos: Se investigaron los efectos de un hidrolizado de clara de huevo (EWH) en el tracto gastrointestinal y en los órganos relacionados con el metabolismo del aluminio (Al) tras la exposición a niveles dietéticos bajos y altos de Al.
Metodología: Las ratas Wistar macho fueron tratadas por vía oral con dosis dietéticas bajas y altas de Al. Grupo 1) Nivel dietético bajo de aluminio (AlCl3 a 8,3 mg/kg de peso durante 60 días), tratado o no con EWH (1 g/kg/día); Grupo 2) Nivel dietético alto de aluminio (AlCl3 a 100 mg/kg de peso durante 42 días), tratado o no con EWH.
Resultado: Ambos tratamientos con Al aumentaron el daño oxidativo en el hígado y el riñón. La dosis más alta de Al deterioró la morfología del colon, induciendo inflamación y ulceraciones en la mucosa. El EWH evitó el aumento del nivel de estrés oxidativo y el daño en el colon y parece reducir la presencia de Al a nivel tisular.
Conclusión: Nuestros resultados designan al EWH como un ingrediente alimentario prometedor para prevenir los efectos adversos producidos por la exposición al Al en la salud humana.

Palabras clave: Contaminante ambiental, salud humana, ingrediente bioactivo, péptidos derivados del huevo.



Introduction

Human is continuously exposed to aluminum (Al), a hazardous environmental contaminant without physiological function, and diet is an important route by which humans are exposed to this non-essential metal[1,2]. After reaching the gastrointestinal tract, the absorption and, consequently, distribution and excretion of Al from the human body are under continuous investigation. However, it seems that the bioavailability of Al is dependent on the surrounding gastrointestinal medium[3,4]. Once in the body, Al is deposited in bone and brain[5], kidney[6], liver[7], heart, and in reproductive organs of rats[8] producing deleterious effects.

Al is a toxin; therefore, the increased presence in the body of this metal may have consequences for human health and is linked to the development of hematological disorders[9,10], osteopenia[11], neurological disorders[12], macrophagic myofascitis[13], cardiovascular dysfunction[14], reproductive disorders[15] and breast cancer[16]. However, we still do not understand the real consequences of Al in the body and the predominant toxic mechanism.

Recently, the oxidative and inflammatory actions of Al have been suggested[17,18]. Moreover, pro-oxidant capacity of Al has been recognized and seems to be that a Fenton promotion cycle catalyzed by the formation of the radical Al-superoxide is underlying[19].

Nevertheless, the systemic and long-term effects of Al exposure in human health are not well understood. Recently, by creating an animal model of dietary exposure to Al, we have demonstrated that Al even at a considered low-level of exposure could represent a risk for human health and, more than once, the adverse effects were similar to the observed after a high-dietary level of Al exposure[17].

Considering the burgeoning human exposure to Al, the development of therapies to prevent or minimize these consequences is of great importance. In previous works, the dietary administration of this egg white hydrolysate (EWH) prevented in part the development of memory loss, behavioral impairment and cardiovascular dysfunction observed after Al exposure in rats[20,21]. Moreover, the beneficial effects of EWH against cardiometabolic dysfunction observed in various obesity experimental models[22,23] as well as in the prevention of systemic toxicity induced by heavy metals in rats[24,25] have been

also demonstrated. These effects seem to be associated with the potent anti-inflammatory and antioxidant properties of EWH[26,27,28], which could minimize the impact of the growing environmental presence of Al in the human health. In this regard, the effect of these bioactive peptides produced after an enzymatic treatment of egg white with pepsin for 8h[29], could counteract the toxic consequences of Al exposure.

In this context, the gastrointestinal tract plays an important role in the absorption and metabolism of Al into the body. Therefore, the consequences of Al exposure in the gastrointestinal epithelium and, whether EWH could achieve a protective role on gastrointestinal tract are unknown. In the current study, our purpose was to investigate the effects of Al exposure on the gastrointestinal tract and on other related digestive organs implicated in the Al metabolism, and to elucidate the protective role of EWH on these effects.

Materials and Methods

1. Preparation of Egg White Hydrolysate

EWH was obtained after enzymatic treatment of pasteurized egg white with pepsin for 8h, frozen, and lyophilized until used, as described[22]. The peptide profile and the degree of hydrolysis of EWH were checked by RP-HPLC and some bioactive peptide sequences previously identified were analyzed by HPLC-MS/MS (FRADHPFL, RADHPFL, YAEERYPIL, YRGGLEPINF, ESIINF, RDILNQ, IVF, YQIGL, SALAM, FSL)[29].

2. Animals treatment

Male Wistar rats (90 days-old, 350 ± 10.5 g) were obtained from the Charles River Animal Laboratory (Barcelona, Spain), housed under constant room temperature, humidity, and 12:12h light-dark, with water and food ad libitum. The experiments presented in this study were developed in accordance with the Brazilian Societies of Experimental Biology and the European legislation on the use of experimental animals (EU Directive 2010/63/EU; R.D. 53/2013). This work has Brazilian and Spanish ethical approvals (CEUA, Universidade Federal do Pampa, Brazil - 017/2018; Universidad Rey Juan Carlos, Spain - 39/2014).

Rats were randomized into two groups:

Group 1. Aluminum low dietary level - rats were divided into 4 subgroups (n=8/each) (1a-d) and received once a day for 60 days: a) Control - ultrapure water (Milli-Q, Merck Millipore Corporation. © 2012 EMD Millipore, Billerica, MA); b) Aluminum – Al at 8.3 mg/kg b.w., dose similar to human dietary Al intake[17]; c) Hydrolysate - ultrapure water plus EWH at 1 g/kg by gavage[27]; d) Hydrolysate-Aluminum - Al at 8.3 mg/kg b.w. plus EWH. In Group 1 rats received water and Al in their drinking water for 60 days, to simulate human exposure by diet[17].

Group 2. Aluminum high dietary level - rats were divided into 4 subgroups (n=8/each) (2a-d) and received daily for 42 days: a) Control – ultrapure water; b) Aluminum – Al at 100 mg/kg b.w., dose considered as a super-dietary Al intake[30]; c) Hydrolysate - ultrapure water plus EWH at 1 g/kg by gavage; d) Hydrolysate-Aluminum - Al at 100 mg/kg b.w. plus EWH. In Group 2 rats received Al by gavage and ultrapure water as drinking water for 42 days[30]. The stock solutions of Al (AlCl3.6 H2O at 0.034 M, Group 1; 8.3 mg/kg/b.w. and, 0.331 M, Group 2; 100 mg/kg/b.w.) was prepared in ultrapure water.

The body weights and the consumption of food and liquid intakes were measured once a week. After the exposure period, rats were euthanized, and the kidney, liver, and colon were removed and, being one side processed for imaging analysis and the other prepared for biochemical determinations [homogenized in 50 mM Tris HCl, pH 7.4, (1/10, w/v) centrifuged and, supernatants were frozen at -80°C].

3. Reactive species levels

Reactive oxygen species levels in the liver and kidney were measured by the spectrofluorometric method of[31] with modifications[17]. The fluorescence intensity was recorded for 60 min at 15 min intervals (520 nm emission, 480 nm excitation - SpectraMax M5 Molecular Devices, CA, USA), and the reactive species levels were expressed as units of fluorescence.

4. Lipid peroxidation levels

Lipid peroxidation levels in liver and kidney were determined as malondialdehyde (MDA) levels according to the colorimetric method of[32], with modifications[17]. The lipid peroxidation levels were measured at 532 nm (SpectraMax M5 Molecular Devices, CA, USA) and expressed as nanomoles of MDA per mg of protein.

5. Ferric Reducing/Antioxidant Power Assay

The total antioxidant capacity in the liver and kidney was measured by Ferric Reducing/Antioxidant Power (FRAP) assay, according to[33], with modifications[17]. The FRAP levels in tissues were measured at 593 nm (SpectraMax M5 Molecular Devices, CA, USA), normalized using a dose-response curve of Trolox (50-1000 µM –vitamin E analog) and expressed respected to Trolox equivalents.

6. Histological analysis

The liver, kidney, and colon were histopathological analyzed. For that, tissues were fixed for 2 days in 10% formaldehyde, washed, embedded in paraffin, sectioned at 5 µm, and stained with hematoxylin/eosin. 10 randomly regions of each tissue were blinded evaluated under the 10X objective using a Zeiss Axioskop 2 microscope (Zeiss, Jena, Germany), and the images were analyzed using AxioVision 4.6. A

semi-quantitative scoring system was used to analyze and morphologically classify the colon, following the protocol described by[34]. Briefly, for the morphological classification, it was considered the following features: 1. epithelium damage (vary from 0, normal to 3, severe epithelial lifting), 2. inflammatory cells infiltration (vary from 0, absence to 3, severe infiltration involving the muscle), 3. extent of muscle thickening (vary from 0, normal to 2, severe), 4. edema (vary from 0, no edema to 2, diffuse edema). The results were expressed as a sum of scores for each analyzed feature.

7. Lumogallion staining for the presence of aluminum

The presence of Al was verified in formalin-fixed tissues using the specific lumogallion staining method[12,35]. Briefly, tissues were rehydrated and placed for 45 minutes into either 1 mM lumogallion (TCI Europe N.V. Belgium) buffered in 50 mM PIPES, pH 7.4 or the PIPES-buffer alone for auto-fluorescence analyses. After several washes with PIPES-buffer, slides were rinsed in ultrapure water, mounted using an aqueous mounting medium, and stored at 4ºC overnight before imaging. Tissues were imaged using a Zeiss Axioskop 2 microscope and, the fluorescence intensity calculated with NIH Image J software version 1.46r (http://rsbweb.nih.gov/ij/), using the same imaging parameters.

8. Statistical analysis

Data are expressed as mean ± SEM and analyzed using Graphpad Prism6 (GraphPad Software, Inc., LaJolla, CA, USA). Results were analyzed using two-way ANOVA; when ANOVA showed a significant treatment effect, Bonferroni's post hoc test was used to compare individual means. Values were considered statistically different when $P < 0.05$.

Table I: Effects of EWH on body weight (g), absolute (g or mg) and relative (g/100g or mg/100g) weights of organs and, water and food intake of rats exposure to AlCl3 for 60 days (8.3 mg/kg b.w. *per day* – Group 1), co-treated or not with EWH.

Parameters	Experimental groups			
	Control (n=8)	$AlCl_3$ (n=8)	Hydrolysate (n=8)	Hydrolysate-Aluminum (n=8)
Initial body weight (g)	365.6 ± 10.32	409.7 ± 9.57	385.6 ± 14.71	397.7 ± 8.64
Final body weight (g)	434.1 ± 13.11	468 ± 10.58	467.6 ± 21.03	448.4 ± 13.98
Water intake (ml/day)	36.10 ± 0.80	36.16 ± 0.67	37.73 ± 0.95	35.72 ± 0.38
Food intake (mg/day)	21.46 ± 0.28	22.55 ± 0.38	22.27 ± 0.59	22.26 ± 0.69
Faeces (g)	1.57 ± 0.21	2.48 ± 0.50	1.89 ± 0.41	1.82 ± 0.26
Urine (ml)	24.92 ± 1.41	25.00 ± 3.28	27.25 ± 3.59	19.38 ± 1.98
Liver (g)	11.93 ± 0.50	12.78 ± 0.59	12.18 ± 0.78	11.06 ± 0.56
Liver (g/100g)	2.75 ± 0.13	2.73 ± 0.13	2.59 ± 0.09	2.46 ± 0.06
Kidney (g)	1.15 ± 0.04	1.29 ± 0.08	1.14 ± 0.03	1.19 ± 0.07
Kidney (g/100g)	0.26 ± 0.01	0.58 ± 0.32	0.24 ± 0.01	0.26 ± 0.01
Epididymal fat (g)	11.13 ± 1.20	13.61 ± 1.37	12.98 ± 1.48	11.69 ± 0.75
Brown fat (g)	0.53 ± 0.03	0.51 ± 0.02	0.51 ± 0.05	0.47 ± 0.05
Subcutaneous fat (g)	8.82 ± 0.89	10.34 ± 1.01	11.27 ± 2.01	10.27 ± 0.76
Retroperitoneal fat (g)	12.72 ± 1.38	13.89 ± 1.40	16.61 ± 2.04	13.30 ± 1.28
Tibia height (cm)	3.81 ± 0.12	3.98 ± 0.02	3.98 ± 0.1	3.97 ± 0.08
Soleus (g)	0.13 ± 0.04	0.14 ± 0.01	0.14 ± 0.01	0.12 ± 0.01

Data are expressed as means ± SEM. The relative organ weight was calculated by use of the formula: organ weight/body weight x 100. Units: g: gram, mg: milligram, cm: centimeters, ml: milliliters; 1 way ANOVA (P>0.05).

Table II: Effects of EWH on body weight (g), absolute (g or mg) and relative (g/100g or mg/100g) weights of organs and, water and food intake of rats exposure to AlCl3 for 42 days (100 mg/kg b.w. *per day* – Group 2), co-treated or not with EWH.

Parameters	Experimental groups			
	Control (n=8)	$AlCl_3$ (n=8)	Hydrolysate (n=8)	Hydrolysate-Aluminum (n=8)
Initial body weight (g)	284.4 ± 12.58	283 ± 9.64	297 ± 9.75	309.5 ± 13.57
Final body weight (g)	386.9 ± 8.59	408.3 ± 12.48	413 ± 7.16	408.5 ± 12.33
Water intake (ml/day)	31.49 ± 1.30	31.78 ± 1.27	32.45 ± 1.72	30.62 ± 0.76
Food intake (mg/day)	20.72 ± 0.56	21.48 ± 0.67	21.91 ± ¬0.81	21.58 ± 0.27
Faeces (g)	2.90 ± 0.20	2.94 ± 0.42	2.21 ± 0.36	2.68 ± 0.32
Urine (ml)	10.96 ± 3.55	17.37 ± 6.07	16.11 ± 5.33	9.87 ± 3.84
Liver (g)	10.54 ± 0.39	11.60 ± 0.41	11.38 ± 0.30	11.43 ± 0.41
Liver (g/100g)	2.73 ± 0.03	2.80 ± 0.09	2.79 ± 0.04	2.80 ± 0.10
Kidney (g)	1.18 ± 0.08	1.17 ± 0.04	1.19 ± 0.02	1.21 ± 0.04
Kidney (g/100g)	0.30 ± 0.02	0.28 ± 0.01	0.29 ± 0.01	0.29 ± 0.01
Epididymal fat (g)	8.00 ± 0.89	9.01 ± 0.45	8.51 ± 0.45	10.70 ± 1.23
Brown fat (g)	0.58 ± 0.03	0.41 ± 0.01	0.53 ± 0.05	0.55 ± 0.03
Subcutaneous fat (g)	9.62 ± 0.95	7.38 ± 0.88	9.39 ± 0.83	9.68 ± 1.40
Retroperitoneal fat (g)	10.03 ± 0.94	10.42 ± 0.66	10.42 ± 1.26	11.61 ± 1.65
Tibia height (cm)	3.75 ± 0.04	3.97 ± 0.04	3.87 ± 0.05	3.90 ± 0.05
Soleus (g)	0.12 ± 0.01	0.13 ± 0.01	0.13 ± 0.01	0.15 ± 0.01

Data are expressed as means ± SEM. The relative organ weight was calculated by use of the formula: organ weight/body weight x 100. Units: g: gram, mg: milligram, cm: centimeters, ml: milliliters; 1 way ANOVA (P>0.05).

Figure 1: Effects of EWH on oxidative stress assays in Al-exposed rats. Reactive oxygen species (ROS), lipid peroxidation and total antioxidant capacity in liver and kidney of rats exposed to AlCl3 at low doses (8.3 mg/kg b.w. for 60 days) co-treated or not with EWH. Results are expressed as mean ± SEM, n=8, * P < 0.05 compared with their corresponding controls, # P < 0.05 compared with AlCl3 group (two-way ANOVA and Bonferroni as post-hoc test).

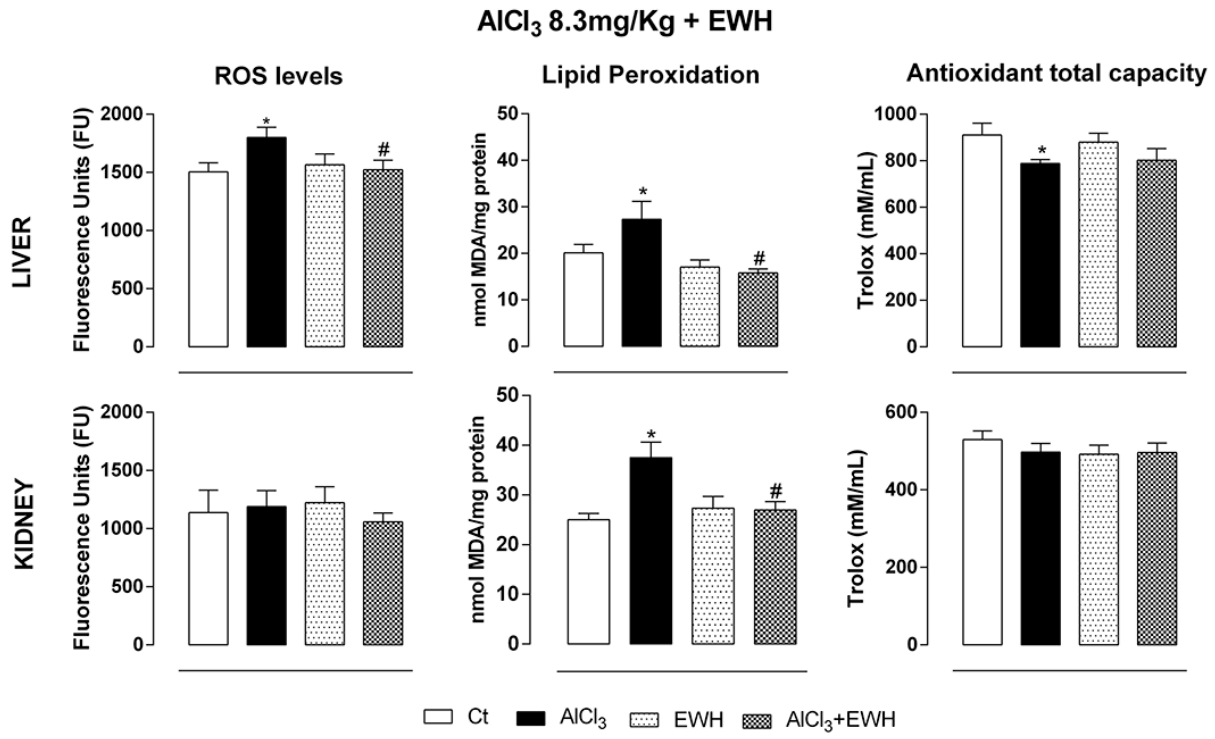


Figure 2: Effects of EWH on oxidative stress assays in Al-exposed rats. Reactive oxygen species (ROS), lipid peroxidation and total antioxidant capacity in liver and kidney of rats exposed to AlCl3 at high doses (100 mg/kg b.w. for 42 days) co-treated or not with EWH. Results are expressed as mean ± SEM, n=8, * P < 0.05 compared with their corresponding controls, # P < 0.05 compared with AlCl3 group (two-way ANOVA and Bonferroni as post-hoc test).

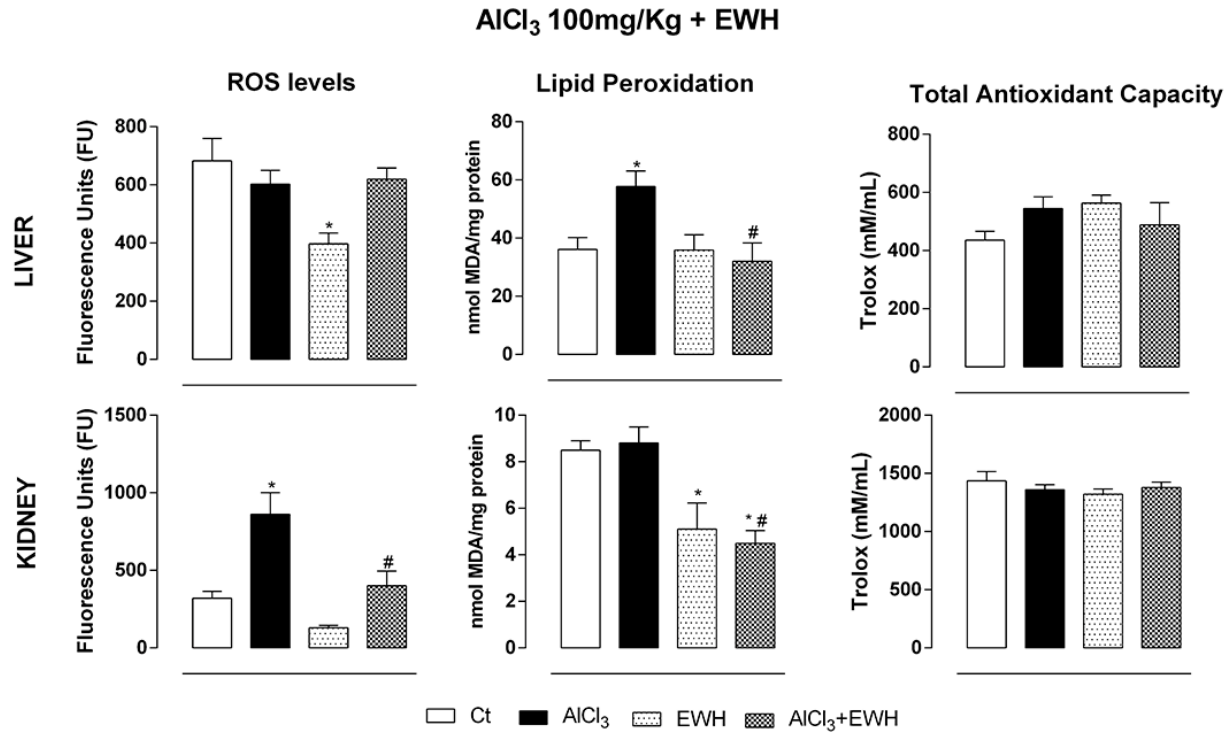


Figure 3: Effect of EWH on liver histology in Al-treated rats. Representative images showing normal histology in all groups: control (Ct), EWH, Al-exposed rats at 8.3 or 100 mg/kg b.w., and Al-exposed rats and co-treated with EWH. Scale bar: 100 µm.

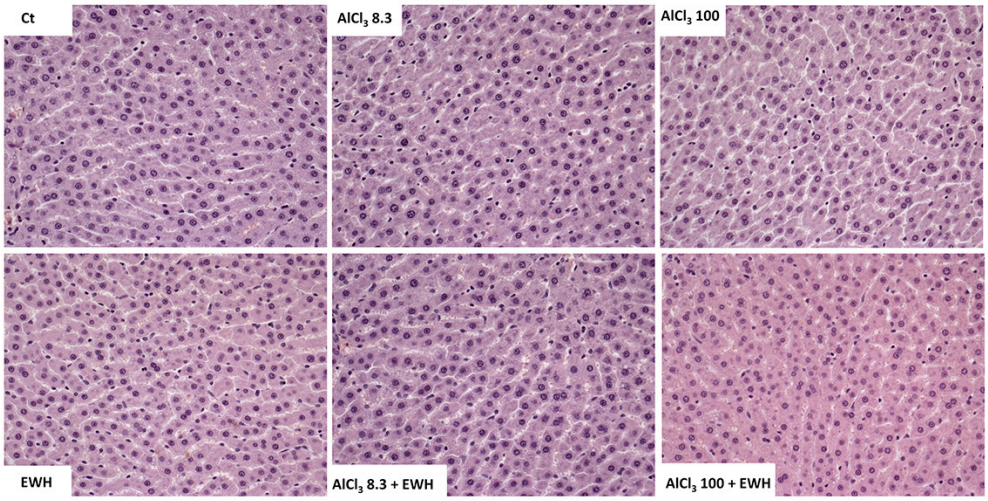


Figure 4: Effect of EWH on kidney histology in Al-treated rats. Representative images showing normal histology in all groups: control (Ct), EWH, Al-exposed rats at 8.3 or 100 mg/kg b.w., and Al-exposed rats and co-treated with EWH. Scale bar: 100 µm.

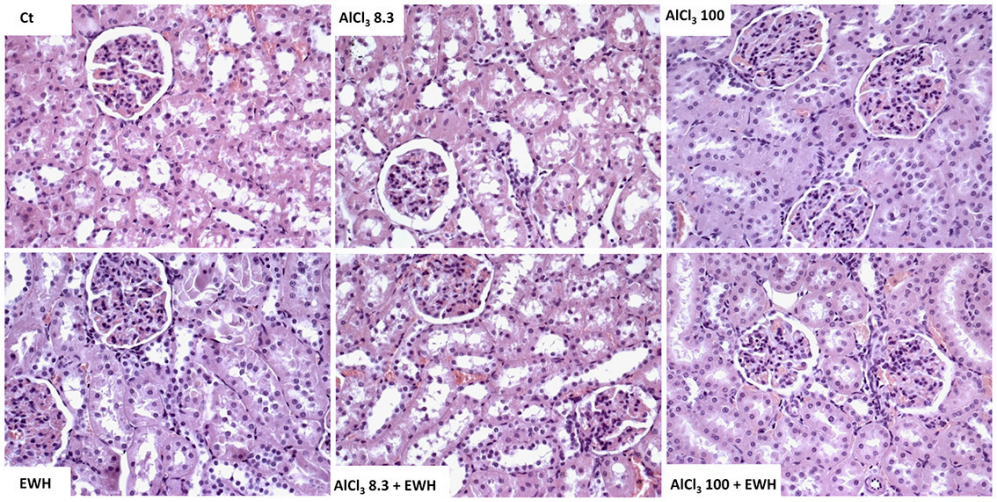


Figure 5: Effect of EWH on colon histology in Al-treated rats. Normal histology in colon of control (Ct) and EWH groups. Colon sections of Al-exposed rats at 100 mg/kg b.w. indicating the presence of epithelial damage and mucosal ulcerations (arrows) and Peyer's patches (*). The co-treatment with EWH prevents the impairment of colon histoarchitecture after Al exposure at 100 mg/kg. Histological damage score after the analysis of the average of 5 fields per rat. Scale bar: 100 µm.

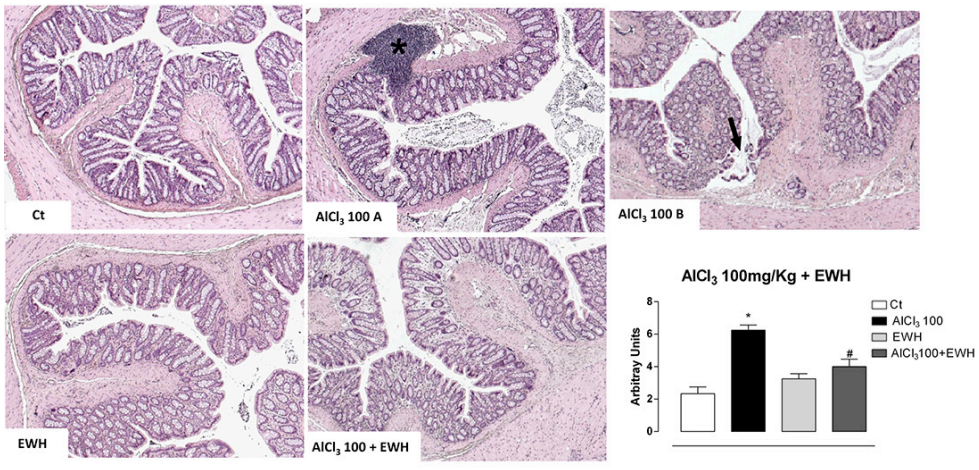


Figure 6: Effect of EWH on the presence of aluminum (orange) in liver. Representative images indicating the presence of Al: lumogallion fluorescence in control (Ct), EWH treated rats and, animals treated with AlCl3 at 8.3 or 100 mg/kg, co-treated or not with EWH. Arrows indicate the presence of aluminum. Fluorescence intensity after the analysis of the average of 6 fields per rat. Scale bar: 50 µm.

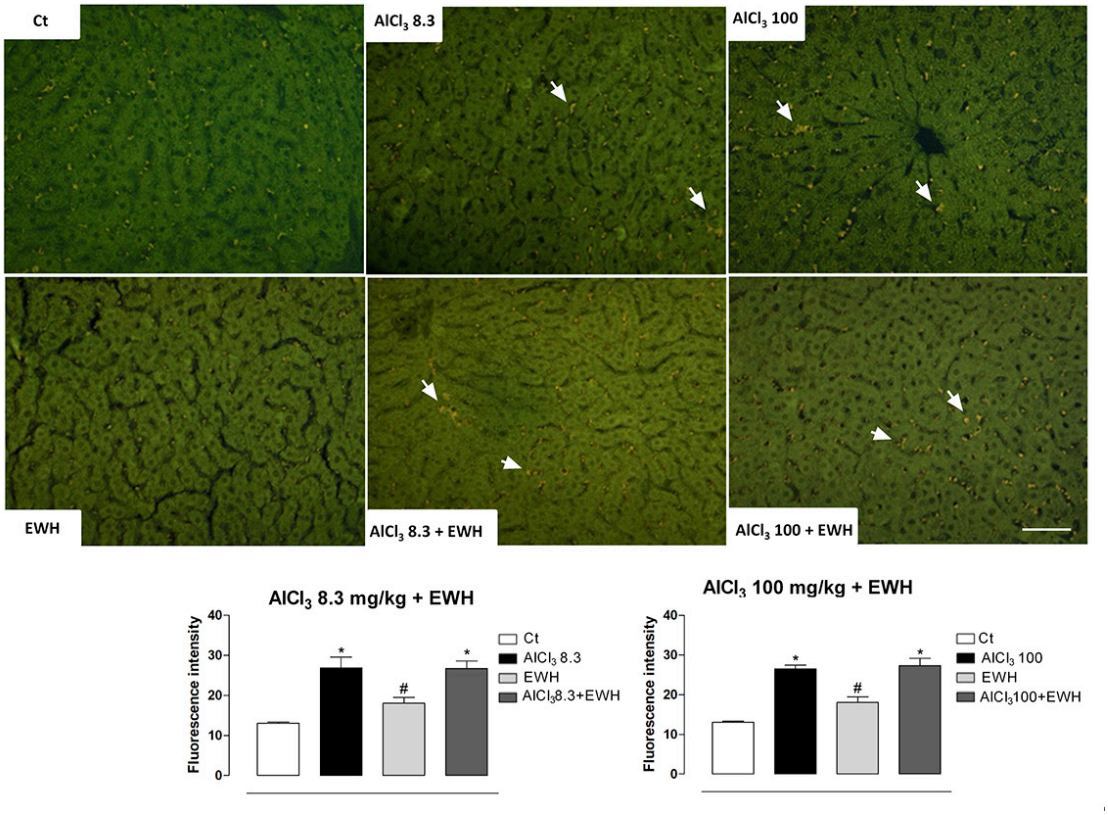
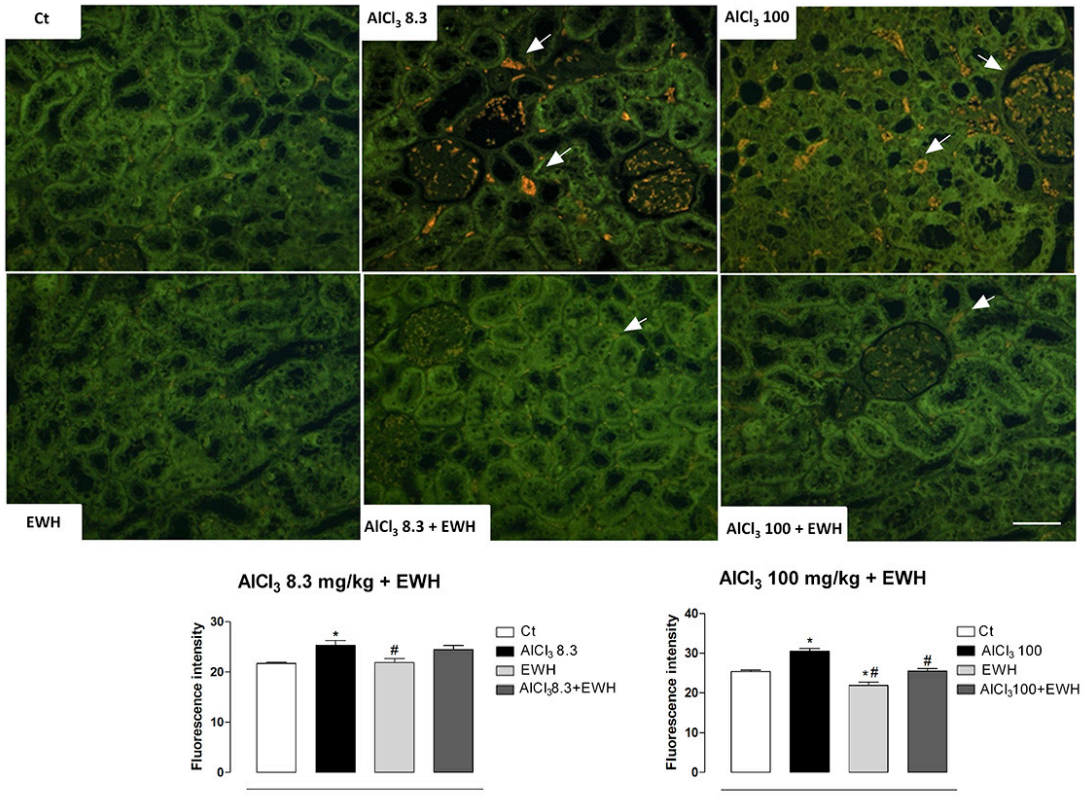


Figure 7: Effect of EWH on the presence of aluminum (orange) in kidney. Representative images indicating the presence of Al: lumogallion fluorescence in control (Ct), EWH treated rats and, animals treated with AlCl3 at 8.3 or 100 mg/kg, co-treated or not with EWH. Arrows indicate the presence of aluminum. Fluorescence intensity after the analysis of the average of 6 fields per rat. Scale bar: 50 µm.



Results

1. Body weight, feed, and fluid consumption

Neither the Al intakes or EWH treatments modified the body and organs weights of rats; the fluid (water or Al) and food consumptions were similar between groups (**Tables I** and **II**).

2. Oxidative stress

Al treatment at low doses of 8.3 mg/kg b.w. raised ROS levels and decreased total antioxidant capacity in the liver and raised lipid peroxidation in both liver and kidney (**Figure 1**). These effects were almost totally prevented by the concomitant oral uptake of EWH (**Figure 1**). Rats treated with Al at the highest dose of 100 mg/kg b.w. showed increased ROS levels in the kidney and lipid peroxidation in the liver, which was prevented by the concomitant intake of EWH (**Figure 2**). Moreover, the dietary supplementation with EWH decreased ROS levels in liver and lipid peroxidation in the kidney of animals not exposed to Al as well as decreased levels of lipid peroxidation in the kidney of animals co-exposed to Al and EWH (**Figure 2**).

3.Histopathology analysis of liver, kidney, and colon

Histology showed normal histoarchitecture of liver and kidney in all experimental groups (**Figures 3** and **4**). On the opposite, Al at a high dietary level strongly impaired the histology of the colon (**Figure 5**). Specifically, Al-induced zonal destruction of epithelium surface and mucosal ulcerations involving submucosa, promoted inflammatory cell infiltrations and the presence of Peyer's patches (**Figure 5**). However, rats that were exposed to both Al and EWH showed colon histology similar to the control and EWH groups (**Figure 5**).

4. Presence of aluminum in liver and kidney

The presence of Al in the liver and kidney was verified by lumogallion and means of fluorescence microscopy. Tissues not incubated with lumogallion showed green autofluorescence (data not shown) and, tissues from control (Ct) and EWH rats showed unspecific fluorescence (**Figures 6** and **7**). Liver and kidney sections from Al-treated rats showed specific bright orange fluorescence when incubated with lumogallion, indicating the presence of Al. Rats in the Al + EWH groups showed weakly orange fluorescence, in which the oral uptake of EWH significantly prevented the presence of Al in the kidney of rats exposed to the highest dose of the metal (**Figures 6** and **7**).

Discussion

Al is everywhere and, besides the efforts to reduce its impact, humans are continuous highly exposed and, a load of Al in the human body, increasing. Oral ingestion is the most important way of human exposure to Al. Therefore, the gastrointestinal tract is the first and primary Al contact pathway, which, when ingested, seems to alter the immune function and microflora permeability[36,37]. Al is a neurotoxin, leading to encephalopathy in renal dialysis patients[38] and appointed as an environmental factor in Alzheimer's Disease[39,40]. Over the past few decades, the involvement of Al in human diseases has considerably increased. Al is now suggested as have a role in human reproductive dysfunction and infertility[41], diabetes mellitus[42], peripheral neuropathy[43], hypertension[44] bone and hematological diseases[9,11]. The human toxic effects of Al depend upon the achievement of a threshold or burden[45].

Our research group have developed an animal model of Al exposure, and we have observed that the equivalent amount of Al ingested by the dietary source is sufficient to induce toxic effects, suggesting the achievement of this "toxic" threshold[17]. Herein, we have demonstrated that beyond the increased oxidative stress in target organs of Al metabolism, Al strongly impairs colon morphology, inducing inflammation, and mucosal ulcerations. Interestingly, these alterations already start in rats exposed to Al at human equivalent dietary level.

Moreover, due to numerous applications and sources, it seems that most of the population are exceeding the maximum limits imposed by regulatory agencies[1,2]. In this sense, strategies and therapies that aim to minimize or prevent the effects of human exposure to numerous environmental contaminants are needed. Food-derived compounds could be an important alternative to maximize the benefits of natural ingredients and seem to be a potential remedy[46,47].

In the current study, we have addressed the effects of dietary supplementation with EWH in rats exposed to human equivalent dietary Al intakes. Our results appoint the EWH as an effective functional food ingredient in the prevention of long-term effects of Al exposure. Specifically, the co-ingestion of EWH was able to prevent colon inflammation and epithelial damages, reduce inflammatory cell infiltrations, and the number of Peyer's patches after Al exposure at a high dietary level and, the increased oxidative damage in liver and kidney of Al-exposed rats. Besides, the ingestion of EWH per se seems to reduce the presence of Al in liver and kidney of control rats not exposed to Al and prevents the increased presence of Al in the kidney of rats exposed to Al at the highest dose, suggesting the putative beneficial effect of a functional food ingredient that could be added to the human diet.

In previous works the potential effects of EWH have been attributed to its antioxidant and anti-inflammatory abilities. The pepsin hydrolysis of egg white releases bioactive peptides with several biological properties[29]. Some

peptide sequences were identified and some of them demonstrated angiotensin-converting enzyme inhibitory activity[29], vascular-relaxing function[48] and/or, antioxidant capacity[26,49] and *in vivo* blood pressure lowering effect[50].

In the present study, rats exposed to both Al and EWH showed reduced oxidative stress in the liver and kidney, and the EWH was able to prevent the increased gastrointestinal inflammation and histopathological damages observed after Al exposure at a super-dietary level. The important inflammation and damage in the colon of Al-treated rats and the efficacy of EWH to prevent may suggest a protective action of these bioactive peptides in the gastrointestinal tract. The gastrointestinal tract is the first site of contact with the oral uptake Al, influencing its bioavailability and absorption[36]. It is known that the surrounding gastrointestinal medium and several dietary compounds can modulate Al absorption. Citrate and other short-chain carboxylic acids such as acetate, oxalate, lactate, malate, tartrate, gluconate, ascorbate, and carbonate seem to increase Al absorption in the gastrointestinal tract and, on the contrary, compounds containing silicone may decrease the absorption of Al facilitating its excretion from the human body[51,52,53].

Recently, by using the intestinal model of Caco-2 cells, it was shown that the intestinal cellular uptake of Al occurs preferably in the particle form[54]. Of interest, our group, by using the same model of differentiated cells, has demonstrated that the EWH released peptides FRADHPFL, RADHP and YPI are susceptible to intestinal transepithelial transport through the monolayer[28]. Therefore, we could also postulate a competition between these small peptides and Al transporters influencing the Al absorption into the small intestinal epithelial cell.

Nevertheless, there are numerous mechanisms and pathways by which EWH could be acting to prevent or minimize the effects of Al that must be extensively studied. In the cardiometabolic disease, the beneficial effects of EWH against metabolic complications in Zucker obese rats were related to changes of gut microbiota, specifically obese rats receiving EWH in drinking water for 12 weeks show microbiota pattern similar to those of the control lean rats[55]. Recently, it was demonstrated the influence of gut microbiota in the Al absorption and systemic effects. The specific probiotic bacteria *L. plantarum* CCFM639 seems to increase fecal Al excretion, decrease intestinal Al absorption and Al accumulation in kidney, liver, and brain, alleviating increased oxidative stress after Al exposure in mice[56,57]. In the current study, EWH was able to reduce the tissular presence of Al in the kidney, and the increased oxidative stress as well as prevent inflammation and colon histopathological damages in rats after Al exposure at a human super dietary level. Therefore, it is also possible to postulate that EWH could interfere and modulate the gut microbiota, which must be further investigated and is the focus of our follow studies.

Conclusion

Our data suggest the use of pepsin EWH as an alternative bioactive food ingredient in the prevention of Al-related complications as an attempt to reduce the impact of the increased human exposure to Al. The EWH supplementation was able to prevent the increased oxidative stress in the liver and kidney, markedly reduced colon histopathological damages and the presence of Al in the kidney of rats exposed to Al at doses that "mimics" high human exposure to this metal. While there are several lines to explain the role of pepsin EWH in the protection against Al toxicity, its antioxidant and anti-inflammatory properties may play an important role. However, it is likely that the underlying mechanisms of egg-derived peptides to reduce the effects of Al are more extensive and must be better understood.

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Author Contributions

Conceptualization: C.S.M., G.A.W., M.M., F.M.P.; Formal analysis: C.S.M., G.A.W., J.A.U.O.; Investigation: C.S.M., J.A.U.O; Methodology: C.S.M., G.A.W., M.M., F.M.P.; Project administration: C.S.M., G.A.W., and M.M.; Writing - original draft: C.S.M., G.A.W., M.M.; Writing - review & Editing: C.S.M., G.A.W., M.M., D.V.V., F.M.P. and J.A.U.O.

All authors have read and approved the final version of the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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ORIGINAL

Investigation of the dynamic system of providing medical services in the hospital for Covid-19 disease patients

Investigación del sistema dinámico de prestación de servicios médicos en el hospital para pacientes con la enfermedad de Covid-19

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Abstract

Introduction and objective: Hospitals are among the social organizations that play a major role in improving the health status of the country and providing health services. The speed of providing health services and the fact that patients do not wait too long to receive these services are among the factors that are considered as the quality of medical services in each hospital. Especially in the current situation, which is very important in hospitals due to coronary heart disease. Therefore, the purpose of this study is to design a dynamic model to study the system of hospital services.
Methods: In this study, first, important and influential factors in the system of providing health services in the hospital were identified through literature review, and after drawing the causal relationships between these factors, the flow accumulation diagram of the system was designed and used using a simulator and a simulator. Was made.
Results and conclusion: results of this study show that hospital management by increasing the number of physicians and increasing the number of hospital beds, can create conditions to improve the quality of health services.

Key words: Dynamic model, health services, hospital, systems dynamics.

Resumen

Introducción y objetivo: Los hospitales se encuentran entre las organizaciones sociales que desempeñan un papel importante en la mejora del estado de salud del país y en la prestación de servicios sanitarios. La rapidez en la prestación de servicios sanitarios y el hecho de que los pacientes no esperen demasiado tiempo para recibir estos servicios son algunos de los factores que se consideran como la calidad de los servicios médicos en cada hospital. Especialmente en la situación actual, que es muy importante en los hospitales debido a las enfermedades coronarias. Por lo tanto, el propósito de este estudio es diseñar un modelo dinámico para estudiar el sistema de servicios hospitalarios.
Metodología: En este estudio, en primer lugar, se identificaron los factores importantes e influyentes en el sistema de prestación de servicios sanitarios en el hospital a través de la revisión de la literatura, y después de dibujar las relaciones causales entre estos factores, se diseñó el diagrama de acumulación de flujo del sistema y se utilizó utilizando un simulador y un simulador. se realizó.
Resultados y conclusión: Los resultados de este estudio muestran que la gestión del hospital, al aumentar el número de médicos y el número de camas del hospital, puede crear condiciones para mejorar la calidad de los servicios sanitarios.

Palabras clave: Modelo dinámico, servicios sanitarios, hospital, dinámica de sistemas.

Introduction

The new coronavirus (Covid-19) is caused by acute respiratory syndrome. The disease was first diagnosed in December 2019 in Hubei Province, Wuhan City, China. On March 11, 2020, the World Health Organization declared the virus a pandemic. According to the latest global statistics of the World Database, as of November 8, 2020, 27 million 327 thousand 404 people in the world have been infected with this virus, of which one million 211 thousand 428 people have died. The economic shock of the Corona outbreak has also led to negative economic effects, including declining sales of many related businesses[1-2]. One of the important concerns of countries is to prevent this disease and predict ways to control and reduce it3-4. The results show that the correct use of the mask and the observance of social distance as well as air flow in spaces and avoidance of closed spaces have a significant effect on reducing the spread of the disease and reducing mortality[5-8].

In this project, corona prediction is investigated with a systems dynamics approach. First, the relationships of important effective variables on the development of the disease are obtained in SPSS software and then the data is analyzed using Vensim software. In the following, by analyzing the sensitivity and providing recommendations, the effect of vaccines to control the conditions of this new crisis will be examined.

Literature review

High quality of services provided in the hospital is related to issues such as patient satisfaction, efficiency and superiority of the organization, but low quality leads to poor service, which in turn leads to higher prevalence of the disease, higher costs and less trust in the health system[4-5].

Zarei et al in a study aimed at comparing the quality of services from the patient's perspective in the emergency department of public and private hospitals under the auspices of Shahid Beheshti University of Medical Sciences in 2015. In this study, 373 discharged patients from 8 public and private hospitals were selected by convenience sampling method. Data were analyzed using descriptive statistics, Mann-Whitney and multivariate regression tests in SPSS software. The results of this study show that the quality of emergency services in private hospitals is better than public hospitals. They stated that the management of the hospitals should pay more attention to the aspects of education before discharge and follow-up treatment, as well as prompt treatment, and by giving educational booklets to the patient during discharge, along with telephone follow-up and reduction. Waiting times increase patient satisfaction by re-engineering care processes.

Bozorgi et al conducted a study to determine the speed of emergency services and related factors in the 5-level triage system in Imam Khomeini Medical Center in Sari. This cross-sectional study was performed in December 2012 at Imam Khomeini Medical Center in Sari. They reviewed medical records and patient triage sheets by completing data collection forms and calculating the speed of action taken for each patient. The number of samples was 365, statistical analysis was performed using SPSS16 statistical software and data were analyzed by chi-square and Anova tests. The results of this study showed that there is a significant relationship between work shift and the time of access to the doctor and services and patient assignment. There was a significant relationship between the patient's level with the time of access to the doctor and services and assignment. In the end, it was found that the time of providing services in the emergency department of Imam Sari Hospital, which uses a 5-level triage system, is short and the speed of providing services is at the desired level.

Identify factors and determine causal relationships

Many variables and factors affect the system that can affect the behavior of the model. Like all economic, social, etc. systems, the health care delivery system is influenced by several factors that are related to each other.

The first step to build a model in the science of system dynamics is to identify important factors and variables affecting the system under study so that based on these variables can determine the model boundary and determine the causal relationships.

Factors affecting the model of this research and interactions and causal relationships between these factors were identified with the help of experts.

Figure 1 shows the causal relationships between the model variables in our study.

After identifying the variables and drawing a causal diagram, the type and nature of the variables should be determined and then the accumulation-flow diagram of the model should be drawn. The list of variables used in the model and their type and nature are given in **table I**.

After determining the type of variables, the accumulation-flow diagram of the model was plotted as shown in **figure 2**.

Figure 1: Causal diagram of medical services delivery system. Accumulation-flow diagram.

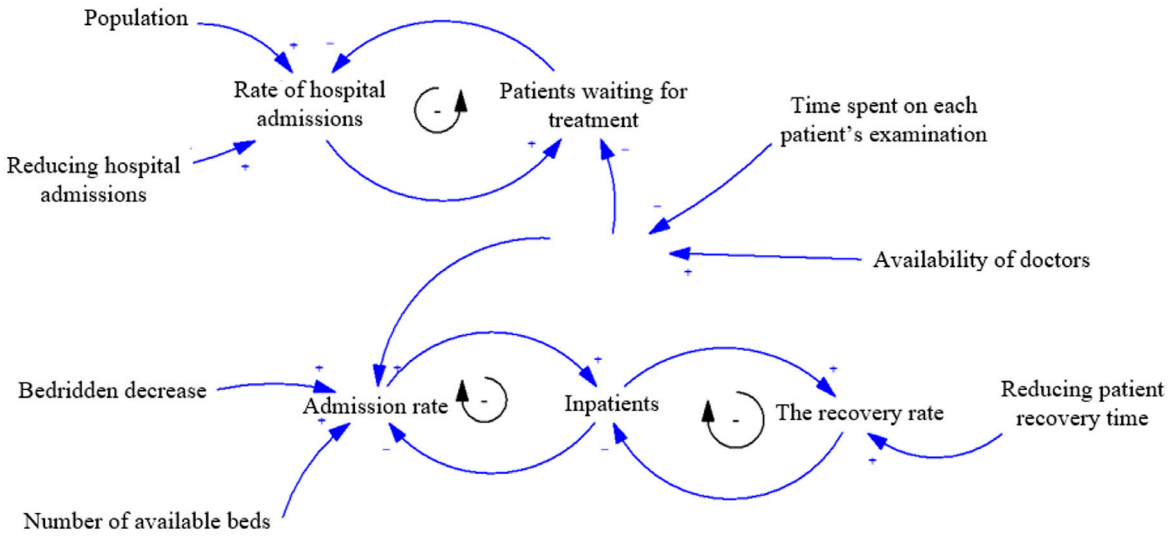


Figure 2: Accumulation-flow diagram of the health care delivery system.

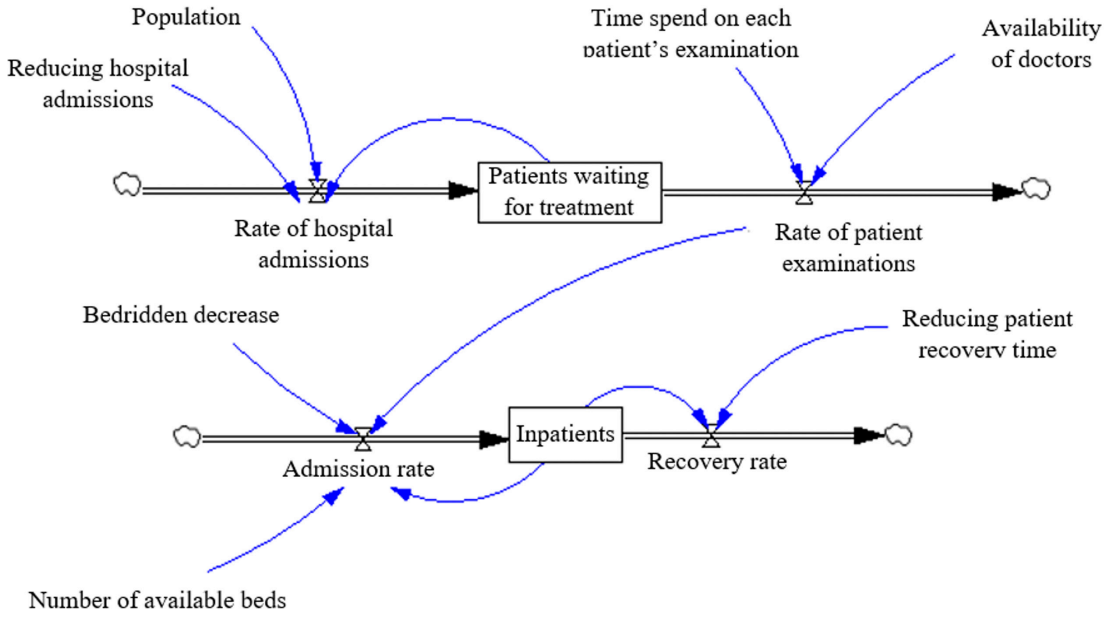


Table I: Variables used in the model.

Name of a variable	Type of variable	The variable's nature	Name of a variable	Type of variable	The variable's nature
Population	Subsidiary	External	Admission rate	Rate	Internal
Rate of hospital admissions	Rate	Internal	Patients waiting for treatment	Accumulation	Internal
Time spend on each patient's examination	Subsidiary	External	Reducing hospital admissions	Subsidiary	External
Availability of doctors	Subsidiary	External	Number of available beds	Subsidiary	external
Reducing patient recovery time	Subsidiary	External	Bedridden decrease	Subsidiary	external
Recovery rate	Rate	Internal	Rate of patient examinations	Rate	Internal
Inpatients	Accumulation	Internal			

Simulation

After drawing the flow accumulation diagram, in order to simulate the model, it is necessary to write a formula that the formulas used in the research model are:
(01) FINAL TIME = 168
Units: Hour
The final time for the simulation.
(02) INITIAL TIME = 0
Units: Hour
The initial time for the simulation.
(03) SAVEPER =
TIME STEP
Units: Hour [0 ,?]
The frequency with which output is stored.
(04) TIME STEP = 1
Units: Hour [0 ,?]
The time step for the simulation.
(05) Inpatients = INTEG (hospitalization rate-recovery rate, 20)
Units: ** undefined **
(06) Patients waiting in the treatment queue = INTEG (Patient examination rate-Patient admission rate, 150)
Units: ** undefined **
(07) Number of beds available = 200
Units: ** undefined **
(08) Number of available physicians = 15
Units: ** undefined **
(09) population = 900000
Units: ** undefined **
(10) Mean examination time per patient = 0.1
Units: ** undefined **
(11) Hospitalization rate = IF THEN ELSE (hospitalized patients> = number of available beds, 0, hospitalization deduction * patient examination rate)
Units: ** undefined **
(12) Recovery rate = Patient recovery fraction * Inpatients
Units: ** undefined **
(13) Patient examination rate = number of available physicians * Average examination time per patient
Units: ** undefined **
(14) Patient admission rate = patients waiting in the treatment queue / (population * patient admission deduction)
Units: ** undefined **
(15) Hospitalization fraction = 0.9
Units: ** undefined **
(16) Patient recovery fraction = 0.001
Units: ** undefined **
(17) Patient admission deduction = 0.001
Units: ** undefined **

……..

After formulating the model, the structure of the model equations should be examined by vensim software. **Figure 3** shows the accuracy of the structure of the equations used in the model.

After confirming the model structure, we simulated the model for a period of 168 hours. The results of model simulation are shown in **figures 4** and **5**.

Figure 3: Shows the accuracy of the structure of the equations used in the model.

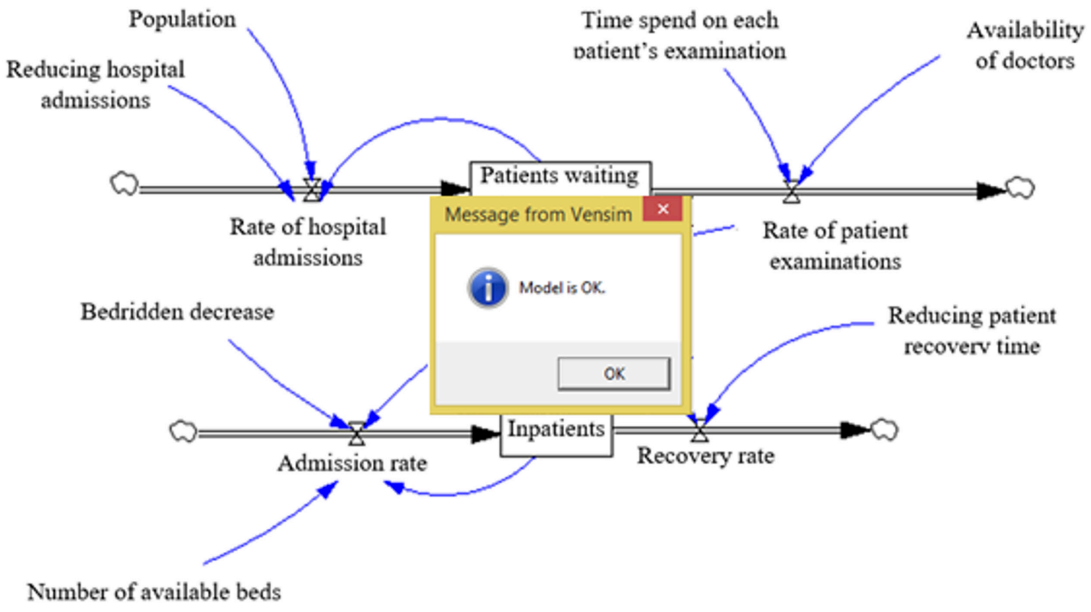


Figure 4: Patients waiting in the treatment queue during the simulation time.

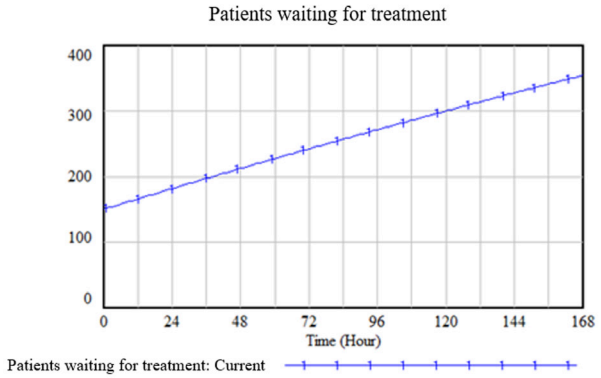
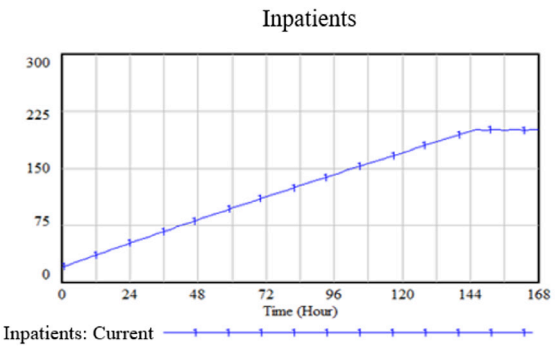


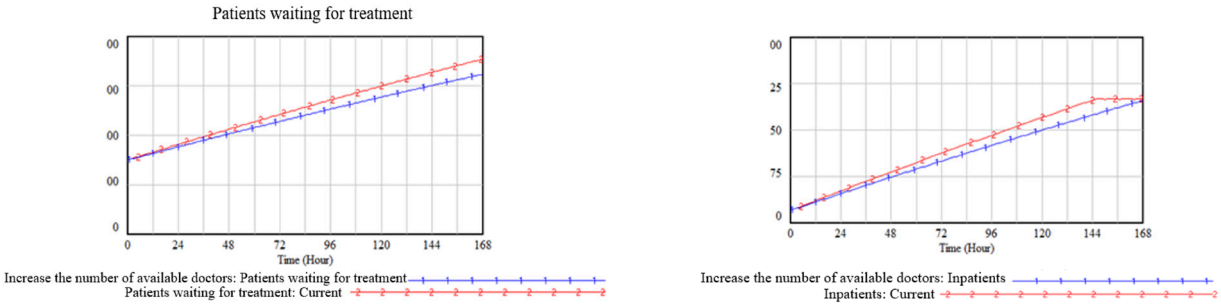
Figure 5: Patients admitted during the simulation time.



Excessively waiting for patients to receive medical services has always been an annoying issue for patients, which will have a negative impact on the quality of service. Therefore, it is necessary to review different policies to reduce patients waiting in the treatment queue.

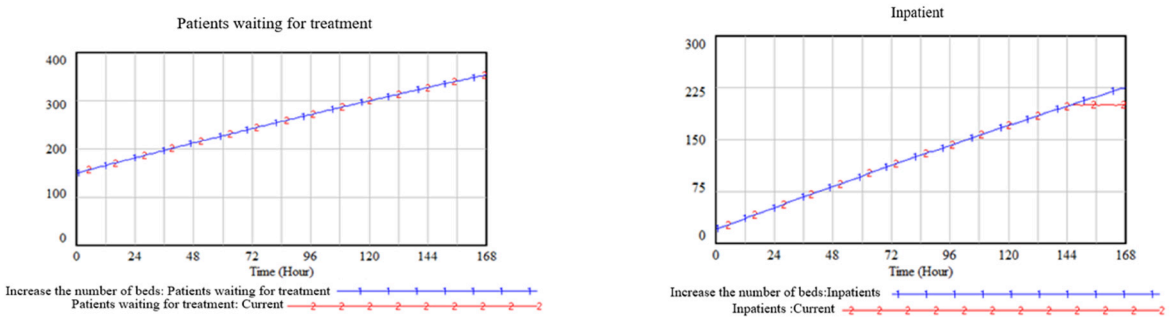
Policy to increase the number of hospital physicians and treatment staff: As the number of hospital physicians increases, the speed of service to patients increases and as a result, the number of people waiting in the treatment queue decreases. The changes to this policy are shown in **figure 6**.

Figure 6: Changes resulting from the implementation of the policy of increasing the number of hospital physicians.



Policies to increase the number of beds: Patients who go to the hospital and are examined by a doctor, are either treated on an outpatient basis and are discharged from the hospital, or need to be admitted if the hospital does not have enough beds. Can accept a new patient for hospitalization and therefore the patient has to go to another medical center or hospital, which can be unpleasant for the patient. Since another factor that affects the quality of medical services is the timely and rapid provision of services to patients and the lack of sufficient beds is a negative factor to determine the quality of the hospital, so increase the number of beds. Hospitals can be an effective measure to improve the speed of providing medical services to patients. **figure 7** shows the changes resulting from this policy.

Figure 7: Changes resulting from the implementation of the policy of increasing the number of hospital beds.



Conclusion

Hospitals are among the social organizations that play a major role in improving the health status of the country and providing health services. The speed of providing health services in Mani and not waiting too long for patients to receive these services are among the factors that are considered as the quality of the level of medical services in each hospital. The results of model simulation and application of different policies show that hospital management by increasing the number of physicians can reduce the waiting time of patients in the treatment queue and lead to patient satisfaction with the quality of medical services. Also, increasing the number of hospital beds increases the capacity of the hospital to accept patients who need to be admitted, and as a result, the probability that the patient needs to be admitted but due to the lack of beds, the hospital will not be able to accept it will be less. This issue also increases patients' satisfaction with the level of quality of medical services.

Conflict of Interest

The authors declare that they have no conflict of interest.

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ORIGINAL

Caracterización clínico epidemiológica de los casos positivos a la COVID-19 en Villa Clara. Marzo-noviembre 2020

Clinical epidemiological characterization of positive cases for COVID-19 in Villa Clara. March-November 2020

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Resumen

La COVID-19 es una nueva enfermedad con una alta morbilidad y mortalidad en el mundo y gran variabilidad clínica en su comportamiento. Con el objetivo de caracterizar variables clínicas y epidemiológicas en los pacientes positivos a la COVID-19 de la provincia de Villa Clara, se realizó un estudio descriptivo de casos clínicos positivos a la prueba de Reacción en Cadena a la Polimerasa de Transcriptasa Reversa en tiempo real de la provincia de Villa Clara (317 pacientes), desde marzo a noviembre de 2020. Se utilizó el registro de pruebas de PCR del Laboratorio Provincial de Microbiología y se revisaron las encuestas epidemiológicas. Predominaron los pacientes del sexo femenino, el grupo de edad de 40 a 59 años y los residentes en el municipio de Santa Clara. La mayoría de los enfermos se encontraban asintomáticos al diagnóstico. Los síntomas de mayor frecuencia resultaron la tos y la fiebre. La Hipertensión arterial y la Diabetes Mellitus fueron las comorbilidades que más acompañaron a la enfermedad.

Key words: SARS-CoV2, COVID-19, características clínicas y epidemiológicas de pacientes.

Abstract

COVID-19 is a new disease with high morbidity and mortality in the world and great clinical variability in its behavior. With the aim of characterizing clinical and epidemiological variables in patients positive for COVID-19 in the province of Villa Clara, a descriptive study of positive clinical cases to the real-time Reverse Transcriptase Polymerase Chain Reaction test was carried out. from the province of Villa Clara (317 patients), from March to November 2020. The registry of PCR tests of the Provincial Laboratory of Microbiology was used and the epidemiological surveys were reviewed. Female patients, the age group from 40 to 59 years and residents in the municipality of Santa Clara prevailed. Most of the patients were asymptomatic at diagnosis. The most frequent symptoms were cough and fever. Arterial hypertension and Diabetes Mellitus were the comorbidities that most accompanied the disease.

Palabras clave: SARS-CoV2, COVID-19, Clinical and epidemiological characteristics of patients.

Introducción

La aparición de la enfermedad COVID-19, abreviatura de "enfermedad por coronavirus 2 del síndrome respiratorio agudo severo (SARS-CoV-2)" en China en diciembre del 2019 y su rápida propagación a otros países, motivó que la Organización Mundial de la Salud (OMS) declarara el brote como una Emergencia de Salud Pública de Importancia Internacional (ESPII) el 30 de enero de 2020 y como una pandemia el 11 de marzo del mismo año[1,2,3].

La enfermedad se caracteriza por una alta tasa de transmisión, período de incubación prolongado, presencia de portadores asintomáticos o con síntomas leves, posible progresión a síndrome de dificultad respiratoria del adulto (SDRA) e incluso la muerte, diseminación viral después del alivio de los síntomas y trasmisión ambiental y fómites[3].

Es una enfermedad sin tratamiento farmacológico específico y con unos mecanismos de transmisibilidad y letalidad poco conocidos. Estas características dificultan la implementación de intervenciones sanitarias por parte de los sistemas de salud. A este escenario se agregan la diversidad de aspectos económicos, sociales y demográficos, y las capacidades de los sistemas de salud para identificar y ofrecer atención médica a las personas afectadas.4

Al 15 de septiembre de 2020, del total de casos confirmados acumulados a nivel global con un total de 29.155.581 casos, incluidas 926.544 defunciones. La proporción más alta de casos, según regiones de la OMS es la siguiente: la región de las Américas acumula 14.903.891 casos, incluidas 513.246 defunciones, lo que representa 51% del total casos confirmados y 55% del total de las defunciones, seguida por las regiones de Asia Sudoriental que representa 19% del total de casos y 10% del total de defunciones (5.565.977 casos, incluidas 94.871 defunciones) y Europea con 17% del total de casos y 25% del total de defunciones (4.873.346 casos, incluidas 226.363 defunciones[2].

El Ministerio de Salud Pública, en su sitio digital oficial, informa que Cuba reporta 5 mil 670 casos confirmados en el país al 30 de septiembre de 2020 y la provincia de Villa Clara, 317 casos que representa un 5,6% del total del país. Con el objetivo de realizar una caracterización clínica y epidemiológica de los casos positivos a la COVID-19 en Villa Clara en el período de marzo-septiembre 2020, se realizó el siguiente trabajo[5].

Materiales y métodos

Se realizó un estudio descriptivo de casos clínicos de los 317 pacientes confirmados positivos a la prueba de RT-PCR (reacción en cadena a la polimerasa de transcriptasa reversa en tiempo real) de la provincia Villa Clara desde el 11 de marzo hasta el 30 de noviembre de 2020, según el registro de pruebas de PCR del Laboratorio Provincial de Microbiología. Se diseñó y empleó una planilla recolectora de datos, los cuales se obtuvieron mediante la revisión de las historias epidemiológicas.

Entre las variables analizadas figuraron la edad, el sexo, el municipio de residencia, la forma de presentación de la enfermedad, los síntomas más frecuentes y las comorbilidades asociadas.

Los datos obtenidos se registraron en una hoja de cálculo del programa Microsoft Excel para luego ser evaluados en el software estadístico SPSS versión 23, lo cual permitió elaborar tablas estadísticas y gráficos y exponer los hallazgos encontrados durante el proceso investigativo. Se resumieron las variables utilizadas a través de la determinación de las frecuencias absoluta y relativa como medidas de resumen, las cuales sirvieron para el análisis y la presentación de los resultados.

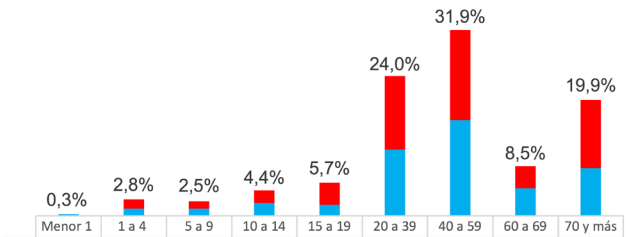
Esta investigación se realizó de acuerdo con las normas éticas para el uso de material y datos humanos, establecidas en la Declaración de Helsinki de la Asamblea Médica Mundial, donde se analizan los principios éticos para las investigaciones médicas en seres humanos.

Resultados

El estudio evidenció un predominio del sexo femenino (52,4%) sobre el masculino (47,6%).

El **gráfico 1** muestra la distribución de pacientes positivos a la prueba de RT-PCR según grupos de edad. Obsérvese el predominio del grupo de 40 a 59 años (31,9%), seguido del de 20 a 39 años (24,0%).

Gráfico 1: Distribución de pacientes positivos a la prueba de RT-PCR según grupos de edad y sexo.



	Menor 1	1 a 4	5 a 9	10 a 14	15 a 19	20 a 39	40 a 59	60 a 69	70 y más
F	0	5	4	7	12	40	49	12	37
M	1	4	4	7	6	36	52	15	26

Fuente: Encuesta epidemiológica.

La distribución de pacientes positivos a la prueba de RT-PCR según municipios de residencia se muestra en el **tabla I** apreciándose que el mayor número de pacientes fue aportado por el municipio de Santa

Tabla I: Distribución de pacientes positivos a la prueba de RT-PCR según municipio de residencia y sexo.

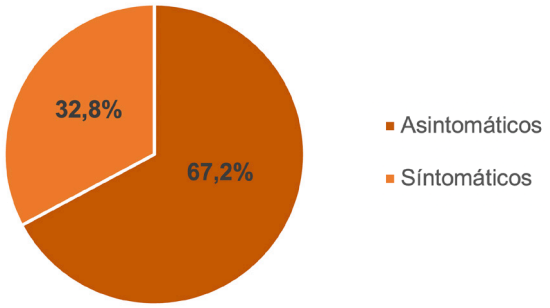
Municipio de residencia	Sexo M	Sexo F	Total	%
Caibarién	7	7	14	4,4
Camajuaní	20	30	50	15,8
Sagua la Grande	2	1	3	0,9
Cifuentes	2	8	10	3,2
Quemado de Güines	1	0	1	0,3
Corralillo	4	3	7	2,2
Encrucijada	0	1	1	0,3
Manicaragua	18	10	28	8,8
Placetas	7	6	13	4,1
Ranchuelo	4	4	8	2,5
Remedios	3	2	5	1,6
Santa Clara	72	84	156	49,2
Santo Domingo	11	10	21	6,6
Total	**151**	**166**	**317**	**100**

Fuente: Encuesta epidemiológica.

Clara (49,2%), seguido por Camajuaní (15,8%) y más alejado Manicaragua (8,8%) pero todos los municipios reportaron casos.

Al mostrar la distribución de pacientes positivos a la prueba de RT-PCR según forma de presentación del cuadro clínico en el **gráfico 2**, se puede apreciar que el diagnóstico se realizó con mayor frecuencia en pacientes asintomáticos (67,2%).

Gráfico 2: Distribución de pacientes positivos a la prueba de RT-PCR según forma de presentación del cuadro clínico.

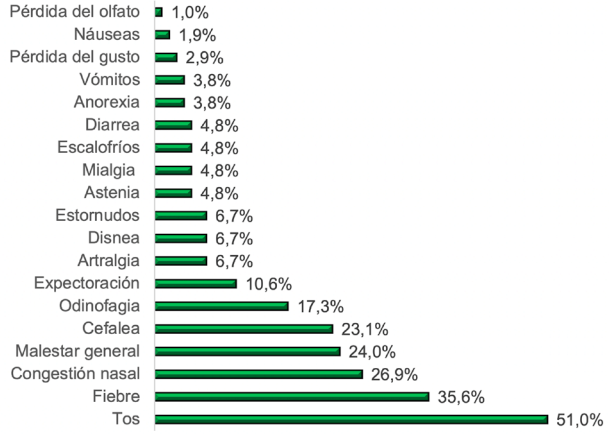


Fuente: Encuesta epidemiológica.

El **gráfico 3** muestra la distribución de pacientes sintomáticos positivos a la prueba de RT-PCR según síntomas más frecuentes. Fue la tos (51,0%) el síntoma más frecuente seguido por la fiebre (35,6%) y la congestión nasal (26,9%).

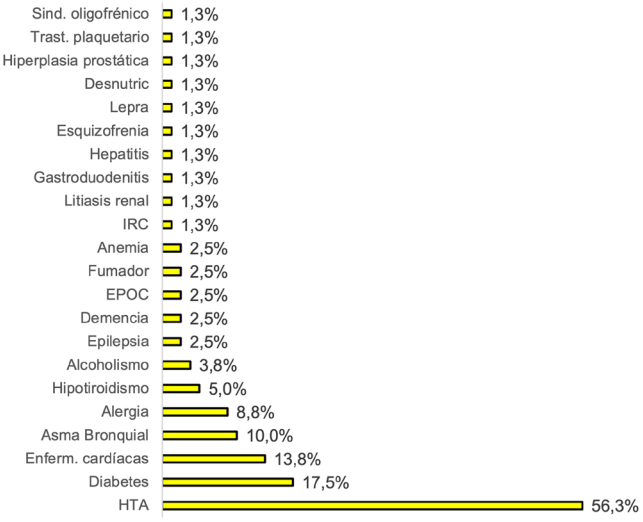
La distribución de pacientes positivos a la prueba de RT-PCR según comorbilidades asociadas aparece en el **gráfico 4** y se aprecia el predominio de la Hipertensión arterial (HTA) como la enfermedad no trasmisible (ENT) más asociada a la COVID-19 (56,3%) seguida por la Diabetes Mellitus (17,5%) y las enfermedades cardíacas (13,8%).

Gráfico 3: Distribución de pacientes positivos a la prueba de RT-PCR según síntomas más frecuentes.



Fuente: Encuesta epidemiológica.

Gráfico 4: Distribución de pacientes positivos a la prueba de RT-PCR según comorbilidades asociadas.



Fuente: Encuesta epidemiológica.

Discusión

Existe gran variedad de casos en el mundo y la prevalencia por sexo de los casos notificados de la COVID-19 varía entre los distintos países del mundo. Estudios realizados en España, Bélgica, Portugal, Holanda y Georgia afirman que no existen diferencias significativas con relación a la distribución de pacientes por sexo. Otros estudios en China, Reino Unido, Perú y Cuba plantean un predominio del sexo masculino[6-12].

El estudio evidenció el predominio del sexo femenino entre los diagnosticados que coincide con los resultados

de Medina-Fuentes G y colaboradores en Camagüey aunque su universo de estudio fue muy reducido. Para Ferrer Castro JE en Santiago de Cuba, sin embargo, existe una mayor incidencia en el sexo masculino; mientras que para Urquiza-Yero Y y colaboradores en Las Tunas es igual para ambos sexos[12-14].

Esta disparidad de resultados dentro del país demuestra la variabilidad del comportamiento de la enfermedad en relación al sexo. Se comparte la opinión de Smtih J quien plantea que la escasez de información por género limita teorizar sobre las probabilidades de asociación entre el sexo y la susceptibilidad al virus. No obstante hay expertos que proponen explicaciones genéticas y hormonales para las diferencias en la susceptibilidad por sexo[15,16].

Existen varios informes que justifican la menor susceptibilidad femenina al contagio; desde los inicios de la pandemia se hablaba de la posible resistencia femenina al virus. Se especula que la poca susceptibilidad de las mujeres a las infecciones virales puede deberse a la protección del cromosoma X extra que presentan en comparación con los hombres[7].

Es oportuno precisar que los resultados se han mostrado en números absolutos y no a través de tendencias, siendo este último tipo de análisis el recomendado en las epidemias, ya que suelen explicar más que las cifras absolutas transversales. Las diferencias antes mostradas en la frecuencia por sexo pueden ser reales o fruto de comparaciones transversales preliminares en diversos estadios de la epidemia[17].

Se comparte el criterio de Urquiza-Yero Y quien plantea que independientemente de las diversas hipótesis planteadas referentes a variables biológicas, existen variables sociales como la responsabilidad social, ejecutada por cada sexo en correspondencia con los patrones culturales y el nivel de igualdad de género existente en una nación, que llevan a que la balanza se incline a un sexo u otro, en dependencia de la exposición al virus que cada uno tenga en relación con la actividad social que desempeña, lo que puede influir en el contagio por la enfermedad[14].

Cuando se analizan los grupos de edades más afectados por la epidemia se evidenció un predominio del grupo de 40 a 59 años seguido del de 20 a 39. Estos resultados son similares a los obtenidos por Cobas Planchez L y colaboradores en La Habana quienes obtuvieron un predominio de los pacientes positivos a la COVID-19 en los mayores de 40 años en un 52,94%. Otras provincias en Cuba muestran un comportamiento diferente, por ejemplo, los resultados obtenidos por Medina-Fuentes G, y colaboradores en Camagüey señalan un predominio de adolescentes y adultos mayores[13,17].

Los autores consideran que estos grupos de edades son los que se han mantenido más activos y con mayor interacción social al permanecer, durante la etapa de más alta transmisibilidad de la enfermedad, cubriendo la satisfacción de las necesidades de la población más vulnerable y, en consecuencia, se mantuvieron más propensos al contagio.

Al hacer referencia al municipio de residencia de los afectados, se puede comprobar que el mayor número perteneció al municipio cabecera que aportó el 57,6% de los casos. Resultados similares obtiene Urquiza-Yero Y y colaboradores en Las Tunas que demostraron mayor frecuencia en los municipios más densamente poblados. Además los autores coinciden con el criterio de estos autores cuando plantean que la densidad poblacional del lugar de residencia es una variable epidemiológica que influye en la propagación del virus unida a la interacción social[14].

En el estudio, el 66,5% de los pacientes se encontraban asintomáticos al momento del diagnóstico. Estudios en Japón, California y en las provincias cubanas de Santiago de Cuba y Las Tunas coinciden con estos resultados; pero para Medina Fuentes y colaboradores en Camagüey fueron los pacientes sintomáticos los más representativos.[12,14,19,20]

Durante las epidemias, los pacientes asintomáticos tienen una gran implicación en el mantenimiento de la transmisión viral en la comunidad, por lo que se debe tener en cuenta este grupo en la cadena de trasmisión de la misma, sobre todo en los casos donde no se ha demostrado la fuente de infección[14,21].

Los autores consideran que la eficacia de las medidas implementadas por el Estado en el Plan para la Prevención y Control del nuevo coronavirus (COVID-19) aprobado, contribuyó a estos resultados pues se han estado realizando estrictos controles de casos con la consecuente búsqueda de todos los posibles contactos de casos positivos[18].

En el variado espectro clínico hallado, fueron la fiebre (41,9%) y la tos (39,5%) los síntomas más frecuentes presentados por los diagnosticados lo cual coincide con la opinión de expertos que consideran la variabilidad en la frecuencia de presentación del cuadro clínico[22].

Resultados similares aparecen en un estudio realizado en la ciudad de Wuhan, China que evidenció que los signos y síntomas importantes de la COVID-19 eran: fiebre (98%), tos seca (76%), disnea (55%), mialgia o fatiga (44%) y linfopenia (63%). Medina Fuentes y colaboradores en Cuba (Camagüey), también encontraron la fiebre como síntoma más frecuentemente presentado (38,4%) aunque seguido de los pacientes asintomáticos y la tos (30,7% respectivamente)[14,23].

Sin embargo para Pan L y colaboradores, al estudiar 204 pacientes en la provincia de Hubei (China), el 50,5% presentó síntomas digestivos, como pérdida del apetito, diarrea, vómitos y dolor abdominal[24].

En el estudio se evidenció que el 31,3% de los enfermos presentó alguna enfermedad crónica no transmisible (ENT) asociada al cuadro clínico, siendo la Hipertensión Arterial (HTA) la más frecuente (56,3%) seguida por la Diabetes Mellitus (17,5%) y las cardiopatías (13,8%).

Estos resultados coinciden con otros estudios realizados en Perú, China y las provincias cubanas de Camagüey y Las Tunas donde la HTA fue la ENT más frecuentemente asociada a la enfermedad en estudio.[10,12,14 y 25]

Diversas publicaciones expresan el papel de los antecedentes clínicos y epidemiológicos en la susceptibilidad, evolución y pronóstico de la enfermedad, dando a conocer que pacientes mayores de 60 años y con comorbilidades asociadas son más propensos al contagio y el desarrollo de formas graves de la enfermedad[12].

Hay autores que plantean que por la patogenia de la COVID-19, los pacientes con HTA y Enfermedad Cerebro vascular sufren afectación miocárdica y lesión vascular, trastornos de la coagulación con formación de trombos y fenómenos embólicos, todo lo cual empeora el curso de estas afecciones, aumenta la tensión arterial, produce arritmias cardiacas, episodios coronarios agudos e insuficiencia cardiaca con choque cardiogénico[26].

Se concluye que en los pacientes diagnosticados con la COVID-19 de la provincia de Villa Clara, han predominado los pacientes del sexo femenino y los del grupo de edad de 40 a 59 años; así como los residentes en el municipio de Santa Clara. La gran mayoría de los enfermos se encontraban asintomáticos al momento del diagnóstico. La tos y la fiebre fueron los síntomas que más frecuencia tuvieron en el cuadro clínico y la Hipertensión arterial y la Diabetes Mellitus fueron las enfermedades no trasmisibles que más acompañaron a la enfermedad.

Compartir las experiencias que se van obteniendo en la práctica, sigue siendo importante para conocer más sobre los patrones de transmisión, las características clínicas y los factores de riesgo de infección de la COVID-19.

Conflicto de intereses

Los autores declaran no tener ningún conflicto de interés.

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ORIGINAL

Study the late gadolinium enhancement (LGE) in patients with heart valvular disorders

Estudiar el realce tardío del gadolinio (LGE) en pacientes con trastornos valvulares del corazón

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Abstract

Background: Various valvular disorders, even severe cases, may be asymptomatic. Studies have found abnormalities in the heart tissue, even in cases that are not currently being treated, by cardiac MRI (CMR) examination, and these findings are used to predict the prognosis of patients undergoing aortic or mitral surgery. Mortality or disability after surgery has been found to be beneficial. Some of these studies have also suggested that Late gadolinium Enhancement (LGE), which is administered by CMR, can also be used as a tool for risk stratification in asymptomatic patients.

Methods: This study was performed as a cross-sectional study on 355 Russian patients. The study population included all patients who underwent CMR during the study period. And their MRI patterns were examined for edema, hyperhemia, and fibrosis. The information required by patients including demographic and demographic characteristics (age and sex) and the variables required by patients were recorded in the patient checklist.

Results: The prevalence of LGE in midmyocardium and subendocardium in LV posterior wall in patients with less than moderate mitral stenosis was significantly higher than others. The pattern of LGE in the septum, which was significantly higher in patients with DCM (dilated cardiomyopathy) and moderate and higher mitral regurgitation, was significantly higher in midmyocardial LGE. Among patients with primary valve involvement, there was no significant difference between patients with involvement between patients with moderate and higher MR and AI, and patients with moderate MR and AI severity below average.

Conclusion: The prevalence of LGE in the midmyocardium and subendocardium in the LV posterior wall was significantly higher in patients with less than moderate mitral stenosis. In addition, midmyocardial LGE was significantly higher in patients with DCM and moderate and higher mitral regurgitation.

Key words: Cardiomyopathy, late gadolinium enhancement (LGE), valvular disorders.

Resumen

Antecedentes: Varios trastornos valvulares, incluso los casos graves, pueden ser asintomáticos. Los estudios han encontrado anomalías en el tejido cardíaco, incluso en los casos que no están siendo tratados actualmente, mediante un examen de resonancia magnética cardíaca (RMC), y estos hallazgos se utilizan para predecir el pronóstico de los pacientes sometidos a cirugía aórtica o mitral. Se ha comprobado que la mortalidad o la discapacidad después de la cirugía son beneficiosas. Algunos de estos estudios también han sugerido que el realce tardío de gadolinio (LGE), que se administra mediante RMC, también puede utilizarse como herramienta para la estratificación del riesgo en pacientes asintomáticos.

Métodos: Este estudio se realizó como un estudio transversal en 355 pacientes rusos. La población del estudio incluyó a todos los pacientes que se sometieron a una RMC durante el período de estudio. Y se examinaron sus patrones de RM para detectar edema, hiperemia y fibrosis. La información requerida por los pacientes, incluidas las características demográficas y de la población (edad y sexo), y las variables requeridas por los pacientes se registraron en la lista de comprobación de los pacientes.

Resultados: La prevalencia del RTG en el miocardio medio y en el subendocardio de la pared posterior del VI en los pacientes con estenosis mitral menos que moderada fue significativamente mayor que en los demás. El patrón de RTG en el septo, que fue significativamente mayor en los pacientes con MCD (miocardiopatía dilatada) y regurgitación mitral moderada y superior, fue significativamente mayor en el RTG en el miocardio medio. Entre los pacientes con afectación valvular primaria, no hubo diferencias significativas entre los pacientes con afectación entre los pacientes con RM e IA moderada y superior, y los pacientes con RM moderada e IA de gravedad inferior a la media.

Conclusiones: La prevalencia del RTG en el miocardio medio y el subendocardio en la pared posterior del VI fue significativamente mayor en los pacientes con estenosis mitral inferior a la moderada. Además, el RTG en el miocardio medio fue significativamente mayor en los pacientes con MCD y regurgitación mitral moderada y superior.

Palabras clave: Miocardiopatía, realce tardío de gadolinio (LGE), trastornos valvulares.

Introduction

Cardiac valvular disorders are an important category of cardiovascular disease. These disorders range from very mild and insignificant cases to severe and life-threatening cases. These diseases in different societies depending on the underlying factors and diseases, the general age of the population, the prevalence of infectious diseases, the prevalence of addiction Injectable and depending on gender can have different prevalence[1,2].

In developing countries, rheumatic fever is still very common, valvular diseases have different prevalence in different groups, for example, at a young age, the main causes are congenital heart disease, while at an older age, it is usually degenerative[3]. Some valvular disorders are also more common in certain groups, such as mitral valve prolapse are more common in women or right heart valve endocarditis and its complications is more common in injecting drug users[3-5]. Valvular disorders, may be asymptomatic even in severe form of them. Previous studies, have found abnormalities in the heart tissue in cardiac Magnetic resonance imaging (MRI) (CMR) even in mild or moderate valvular disease[6]. This findings can be beneficial for predicting the prognosis of patients undergoing aortic or mitral surgery in postoperative mortality or morbidity[7-9]. Some of these studies have also suggested that Late gadolinium Enhancement (LGE) supplied by CMR can also be used as a tool for risk stratification of asymptomatic patients[10].

Due to the wide range of valvular disorders and their high importance in quality of life and also the high accuracy of CMR in examining heart tissue in this study, we decided to investigate late gadolinium enhancement in patients with various valvular disorders.

Materials and methods

Ethics

This survey was ethically approved by the ethical council of research of the Iran University of Medical Sciences, Tehran, Iran (IR.IUMS.FMD.REC.1399.863). In this study, we adhered to all the ethical laws approved by the Ministry of Health at all stages. Also, in this study, no additional cost was imposed on the patient. In publishing the results of this study, the names of patients and participants in the project were not mentioned. In addition, the proposal to carry out this plan was submitted to him for approval by the University Medical Ethics Committee.

Study procedure

This study was a single center, retrospective, cross sectional study. This study designed to compare the differences of LGE pattern in different valvular disease. All patients who underwent cardiac MRI from 2017 February to December 2020 and had valvular disease in the MRI report were included in the study. Exclusions criteria were any sort of congenital heart disease. Three hundred and fifty five patients finally enrolled in this study to be analyzed statistically. 1.5 Tesla MRI technology with identical standards and protocol to all patients. Image acquisition was performed using ECG gated Steady-State Free Precession (SSFP) to multiple planes of the heart (long axis, short axis, 4 chamber, and 3 chamber). Gadolinium was injected via intravenous line with standard dose (0.1 mmol/kg). LGE image using phase-sensitive inversion recovery (PSIR) sequence were captured 10 minutes after gadolinium injection. All volumes and mass measurements were indexed to body surface area. CMR analysis and interpretation, myocardial fibrosis assessment and quantification was performed by a team of cardiovascular imaging cardiologists. Due to the different severity of the Valvular disease, for better data analysis, we classified the patients into two groups with at least moderate severity and patients with lower than moderate valvular disease.

Statistical analysis

Data analysis was performed by SPSS software. For qualitative variables, frequency and frequency are calculated, and for quantitative variables, mean and standard deviation are calculated. Chi-square test was used to test the hypotheses.

Results

In this study, a total of 355 patients were included. demographic data and severity of various valvular disorders and their causes can be seen in **tables I, II** and **III**.

The Late gadolinium Enhancement (LGE) pattern can be seen in in **table IV**.

Table I: Demographic characters of the studied population.

Demographic data 1	Mean	Std. Deviation	Minimum	Maximum
Age	39.91	19.534	1	84
LVEF	39.3524	16.05875	4.00	78.00
RVEF	45.0606	13.00391	1.00	74.00

Table II: Demographic characters of the studied population.

Demographic data		Frequency	Percent
Rhythm	Sinus	317	89.3
	Atrial fibrillation	26	7.3
	Atrial flutter/tachycardia	4	1.1
	Paced rhythm	8	2.3
History of prior surgery	No History	316	89.0
	Once	38	10.7
	2 and more	1	.3
CAD history	No	281	79.2
	History of PCI or CABG or MI or Angiography confirmed CAD	74	20.8
Gender	Male	230	64.8
	Female	125	35.2

Table III: Frequency of valvular disease by etiology.

Valvular disease		Frequency	Percent
Etiology of Valvular disease overall (diagnosis)	Primary	37	10.4
	DCM	83	23.4
	ICMP	72	20.3
	HCM	42	11.8
	Myocarditis	105	29.6
	NCLV	2	.6
	ARVC	7	2.0
	RCM	4	1.1
	CP	2	.6
	Cancer	1	.3
MR Severity	No MR	134	37.7
	Mild or trivial	110	31.0
	Mild to moderate	21	5.9
	At least moderate / moderate	55	15.5
	Moderate to severe	10	2.8
	Severe/very severe	25	7.0
	Total	355	100.0
MR Etiology	No MR	135	38.0
	Prolaptic	18	5.1
	Rheumatic	19	5.4
	Functional (HF/Ischemia)	183	51.5
MS severity	No MS	347	97.7
	Mild	2	.6
	Moderate/at least moderate	2	.6
	Moderate to severe /severe	3	.8
AI severity	No AI	280	78.9
	Mild or trivial	53	14.9
	Mild to moderate	2	.6
	At least moderate / moderate	12	3.4
	Moderate to severe	3	.8
	Severe/very severe	5	1.4
AI etiology	No AI	314	88.5
	Prolaptic	3	.8
	Rheumatic	10	2.8
	Bicuspid	7	2.0
	Degenerative	21	5.9
AS severity	No AS	348	98.0
	Mild	2	.6
	Moderate/at least moderate	1	.3
	Moderate to severe/severe	4	1.1
TR severity	No TR	251	70.7
	Mild or trivial	68	19.2
	Mild to moderate	2	.6
	At least moderate/moderate	16	4.5
	Moderate to severe	3	.8
	Severe/very severe	15	4.2
TR etiology	No TR	251	70.7
	Proleptic	6	1.7
	Rheumatic	4	1.1
	Functional	94	26.5
PI Severity	No PI	351	98.9
	Mild or trivial	2	.6
	At least moderate/moderate	2	.6
PI Etiology	Normal	353	99.4
	Proleptic	1	.3
	functional	1	.3

LGE pattern in different valvular disorders among patients with at least moderate severity of valvular disorders and patients with lower than moderate valvular disease, none of the patterns were significantly different between the two groups except one case. The prevalence of LGE in midmyocardium and subendocardium in LV posterior wall in patients with less than moderate mitral stenosis was significantly higher than others (P-Value <0.001).

Among patients, only three patients with concurrent MR and AS were evaluated for significant valvular disorders (moderate and higher). Also, only 3% of patients (11 patients) had MR and AI simultaneously.

Table IV: Late gadolinium Enhancement (LGE) pattern.

LGE pattern		Frequency	Percent
LV anterior wall	No LGE	265	74.6
	Midmyocardial LGE	14	3.9
	Subepicardial LGE	11	3.1
	Subendocardial LGE	15	4.2
	Transmural LGE	44	12.4
	Edema	5	1.4
	Hyperemia	1	.3
LV Lateral wall	Normal	248	69.9
	Midmyocardial LGE	17	4.8
	Subepicardial LGE	50	14.1
	Subendocardial LGE	13	3.7
	Transmural LGE	22	6.2
	Edema	5	1.4
LV Inferior wall	Normal	246	69.3
	Midmyocardial LGE	24	6.8
	Subepicardial LGE	38	10.7
	Subendocardial LGE	13	3.7
	Transmural LGE	29	8.2
	Edema	4	1.1
	Hyperemia	1	.3
LV Post wall	Normal	336	94.6
	Midmyocardial LGE	3	.8
	Subepicardial LGE	11	3.1
	Subendocardial LGE	3	.8
	Transmural LGE	1	.3
	Hyperemia	1	.3
Septum	Normal	221	62.3
	Midmyocardial LGE	85	23.9
	Subepicardial LGE	19	5.4
	Subendocardial LGE	14	3.9
	Transmural LGE	11	3.1
	Edema	3	.8
	Hyperemia	2	.6
RV free wall	Normal	347	97.7
	LGE	8	2.3

Among primary myocardial diseases, three of the most common diseases among our patients (DCM, HCM and ICMP) were analyze for difference of LGE pattern in different severity of valvular disease. We only compare different LGE pattern in patents with MR due to the very low prevalence of other valvular disorders in these patients. Statistical analysis showed no significant differences between the two groups of study, except for the LGE pattern in the septum in patient with DCM, which was significantly higher in patients with moderate and higher MR in midmyocardial LGE. (P-Value: 0.001).

When we compare patients with primary valvular involvement with these three groups (Primary myocardial disease), the LGE pattern is significantly different (P-Value <0.001) in all part of LV and RV. Except in LV Posterior wall. (P-Value: 0.5)and in RV free wall. (P-Value: 0.054) And when we compare the LGE pattern in myocarditis patients with these three groups of cardiomyopathies, The LGE pattern is significantly different (P-Value <0.001) in all part of LV and RV. except in RV free wall. (P-Value: 0.44) But when we compare patients with primary valve involvement with patients with myocarditis in terms of LGE pattern, the difference is significant only in the lateral, inferior and septal walls.

Among patients with primary valve involvement, there was no significant difference between patients with moderate and higher MR and patients with less than

moderate MR intensity. The same was true of aortic valve insufficiency. Due to the low prevalence of other valvular disorders, comparison between them was omitted. And also due to the low prevalence of valvular disorders in patients with myocarditis, the comparison between this cases was omitted.

Discussion

Late gadolinium enhancement is a technique used in cardiac MRI for cardiac tissue characterization, in particular, the assessment of regional scar formation and myocardial fibrosis. Late gadolinium enhancement is based on the shortening of T1 and different regional distribution patterns of gadolinium-based contrast agents within the extracellular space of the myocardium. It also depends on varying uptake and washout patterns within the normal myocardium and those different disease processes. This is depicted by applying an inversion pulse to null the inherent signal of the myocardium after a certain amount of time[11].

In this study, we examined the valvular disorders and the prevalence of LGE in different parts of the LV and RV wall. This issue has not been done with such details and precision in a study that was completely new in its kind.
In different valvular disorders among patients with at least moderate valvular disease and patients with lower valvular disease, none of the patterns showed a significant difference between the two groups of study, except the prevalence of LGE in the midmyocardium and subendocardium in LV posterior wall who was significantly higher in patients with lower mitral stenosis (P-Value <0.001).

Due to the very low prevalence of concurrent valvular disorders, it was not possible to investigate LGE pattern in pressure overload and volume overload or their combination.

In the study of the effect of valvular disorders on the LGE pattern in patients with cardiomyopathy, only in DCM patients midmyocardial LGE in the septum was significantly higher in patients with moderate and higher MR. In comparison of patients with primary valvular involvement with these three groups of cardiomyopathy, the LGE pattern was significantly different from these three groups in all cases. Except in LV Posterior wall. Also, in comparing the LGE pattern in patients with myocarditis and these three groups of cardiomyopathies, the LGE pattern is significantly different from these three groups in all cases, except in RV free wall. But the difference in patints with primary valvular involvement and myocarditis, only was in the lateral, inferior and septal walls LGE.

Hypertrophic cardiomyopathy (HCM) is the most common genetic disease of the heart. HCM is characterized by a wide range of clinical expression, ranging from asymptomatic mutation carriers to sudden cardiac death as the first manifestation of the disease. Over 1000 mutations have been identified, classically in genes encoding sarcomeric proteins. Noninvasive imaging is central to the diagnosis of HCM and cardiovascular magnetic resonance (CMR) is increasingly used to characterize morphologic, functional and tissue abnormalities associated with HCM. The early and overt phenotypic expression of disease that may be identified by CMR is reviewed. Diastolic dysfunction may be an early marker of the disease, present in mutation carriers prior to the development of left ventricular hypertrophy (LVH). Late gadolinium enhancement by CMR is present in approximately 60% of HCM patients with LVH and may provide novel information regarding risk stratification in HCM. It is likely that integrating genetic advances with enhanced phenotypic characterization of HCM with novel CMR techniques will importantly improve our understanding of this complex disease[12-14].

Conclusion

The prevalence of LGE in the midmyocardium and subendocardium in the LV posterior wall was significantly higher in patients with less than moderate mitral stenosis than others. In addition, midmyocardial septal LGE was significantly higher in patients with moderate and higher MR in DCM patients.

Conflict of Interest

The authors declare that they have no conflict of interest.

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ORIGINAL

The relationship between saliva and the prevalence of tooth decay: A mini review

La relación entre la saliva y la prevalencia de la caries dental: Una mini revisión

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Abstract

Saliva plays a significant role in maintaining oral health, helping to build and maintain the health of soft and hard tissues. When saliva flow is reduced, oral health problems such as dental caries and oral infections can develop. As a biological fluid whose main constituents are proteins and electrolytes, saliva can be a suitable, inexpensive, affordable and non-invasive diagnostic tool in the diagnosis of oral infections. By conducting a proteomic study on saliva, one can accurately understand all salivary protein compounds, their role in human health, the function of each of the protein compounds, and the nature of different isomètres of enzymes in saliva. In this study, after classifying and presenting a summary of the results of research on the role of saliva in the diagnosis and evaluation of oral diseases, especially tooth decay, it has been attempted to discuss the importance of salivary secretion proteins so that the reader can find valuable information on the relationship between saliva and the prevalence of tooth decay.

Key words: Saliva, proteomics, biomarkers, salivary leak proteins, tooth decays.

Resumen

La saliva desempeña un papel importante en el mantenimiento de la salud bucodental, ya que ayuda a construir y mantener la salud de los tejidos blandos y duros. Cuando el flujo de saliva se reduce, pueden surgir problemas de salud bucal como la caries dental y las infecciones orales. Como fluido biológico cuyos principales constituyentes son las proteínas y los electrolitos, la saliva puede ser una herramienta de diagnóstico adecuada, barata, asequible y no invasiva en el diagnóstico de las infecciones orales. Al realizar un estudio proteómico de la saliva, se pueden comprender con precisión todos los compuestos proteicos salivales, su papel en la salud humana, la función de cada uno de los compuestos proteicos y la naturaleza de los diferentes isómeros de enzimas en la saliva. En este estudio, después de clasificar y presentar un resumen de los resultados de las investigaciones sobre el papel de la saliva en el diagnóstico y la evaluación de las enfermedades bucodentales, especialmente la caries, se ha intentado discutir la importancia de las proteínas de secreción salival para que el lector pueda encontrar información valiosa sobre la relación entre la saliva y la prevalencia de la caries.

Palabras clave: Saliva, proteómica, biomarcadores, proteínas de secreción salival, caries dentales.

Introduction

Dentists are looking for a suitable diagnostic tool that is preferably non-invasive so that they can diagnose caries, determine the status of periodontal disease, monitor patients' response to treatment, and estimate how sensitive individuals are to the progression of possible future dental disease. Thus, the role of saliva in the diagnosis of diseases was first introduced by the National Institute of Dental and Craniofacial Research (NIDCR)[1].

This complex oral fluid consists of the secretions of three pairs of main and secondary salivary glands of mucosa. In the second definition, saliva is an extracellular fluid produced and secreted by the salivary glands of the mouth. Salivary secretions are automatically controlled by mechanical and neurological factors. Parasympathetic nerves lead to watery salivary secretions and sympathetic nerves lead to salivary protein secretions[2].

Saliva is an exocrine solution consisting of 99% water. The remaining 1% consists of a variety of electrolytes and proteins. These components combined are responsible for the various functions attributed to saliva[3,4].

Saliva is formed primarily (approximately 90%) from the secretions of the three paired major salivary glands, the submandibular (around 65%), parotid (around 20%) and sublingual (around 5-7%)[5,6]. These glands are controlled by the autonomic nervous system, while minor glands (labial, lingual, buccal and palatine), distributed around the oral cavity, produce the remaining saliva (<10%)[7].

At rest, without exogenous or pharmacological stimulation, there is a small, continuous salivary flow, an unstimulated secretion, present in the form of a film that covers, moisturizes, and lubricates the oral tissues[8]. This flow of saliva at rest is in the region of 0.4–0.5mL/minute in healthy subjects[9].

Stimulated saliva is produced in response to a mechanical, gustatory, olfactory, or pharmacological stimulus, contributing to around 40-50% of daily salivary production[10]. The Salivary Flow (SF) index is a parameter allowing stimulated and unstimulated saliva flow to be classified as normal, low or very low (hyposalivation). In adults, normal total stimulated SF ranges 1-3 mL/minute, low ranges 0.7-1.0 mL/minute, while hyposalivation is characterized by a stimulated SF <0.7mL/minute[10,11].

Saliva also contains calcium and phosphate ions, which are useful for repairing damaged parts of the tooth and reversing the decay process.

Scientists' research indicates that mother's saliva boosts the baby's immune system, so that food pre-chewing acquaints the baby's body with pathogenic pathogens in the mother's saliva, causing the body to produce antibiotics and preparing the baby's immune system[12].

An introduction to Proteomics

Saliva consists of gingival cervical fluid, mucosal transudates, nasal and bronchial expectorated secretions, blood and serum derivatives of oral ulcers, bacteria, bacterial products, viruses and fungi, fallen epithelial cells and other cellular compounds and food leftovers[13].

By studying the proteomics of human saliva, we reach four types of salivary secretion proteins including proline-rich proteins, statins, cystatins, histatins[14].

The purpose of proteomic studies on human saliva are as follow:

Finding all salivary protein compounds, their role in human health, learning about the function of each protein compound and identification of different isomètres of enzymes in saliva[15-17].

Salivary secretion proteins play a significant role against tooth decay. Now, using Nano-proteomics, the concentration, quantity and quality of substances in saliva can be accurately determined. The term proteome was first coined and used in 1994 by Mark Wilkins. In his definition, a proteome refers to the complete set of proteins expressed at a particular moment in a cell. Today, however, the level of this definition has extended from the cell to the organ tissue of the organism. The study of proteomes is the subject of proteomics[18,19].

Biomarkers

Numerous researchers have attempted to show the relationship between saliva and the prevalence of caries, since the most important advantages of saliva is its being cheap, availability, and easy and non-invasive sampling.

In addition, various markers such as hormonal, microbiological, immunological, pharmacological and oncological markers can be found in saliva and compared with its serum concentration[20]. Since the concentration of these markers is lower in saliva than that of blood, it may distort clinical diagnosis through saliva. However, new methods of diagnosis have been designed to solve this problem[21].

Thus, salivary proteins and peptides are easily identified by biochemical methods such as liquid chromatography, gel electrophoresis, capillary electrophoresis, immunoassay and Lectin probe analysis, and they are used as diagnostic biomarkers[22].
Biomarkers play a diagnostic role in detecting oral infections in saliva.

Biomarkers are actually specific molecules that exist in the body and given their unique properties, they can be used by pharmacological or physiological assays as a tool to predict a complication and measure the progression of a disease and its treatment effects[23].

Tooth decay (caries)

Studies show that measuring the concentration of specific oligosaccharides in saliva and specific changes in salivary proteome are used to diagnose tooth decay[24]. As the amount of proline-rich proteins PRP3, PRPI histatin 1 and statins in saliva increases, tooth decay does not occur and a decrease in these proteins causes tooth decay[25]. Moreover, increasing the number of microorganisms

such as *Streptococcus mutanus* and lactobacilli in saliva causes tooth decay[26].

Studies show that healthy human saliva contains certain peptides, such as histatin, which help heal wounds and caries. In addition to its antibacterial properties, histatin protein increases cell contact and transport, as well as the angiogenesis process. The process of angiogenesis is a physiological process in which new blood vessels grow from existing blood vessels. Proline protein has a unique structure because it is the only protein-producing amino acid with a secondary amine. It not only helps make proteins but also acts as a catalyst in many organic reactions. The main properties and role of proline include helping collagen, regenerating cartilage, forming connective tissue, repairing skin damages and wounds, improving intestinal lining, and repairing joints[27].

Proline is converted to hydroxycine and hydroxyproline to help collagen. One of the reasons why proline is important in the body is that it, along with the amino acid glycine, is involved in collagen synthesis[28].

Collagen is the most abundant protein in the human body and is a major component of connective tissue in the body. Proline is an amino acid that is very similar to an amino acid. It is an unnecessary amino acid because the human body can synthesize it spontaneously, unlike certain amino acids that enter the body through the diet. However, glonamate can be used to produce proline. Foods high in proline protein include bone extract, source of proline for animal products such as meat, liver, chicken, fish and eggs[29].

Decreased salivary secretion, decreased salivary pH, decreased salivary buffering, increased total protein and total antioxidants in saliva, decreased total calcium in saliva cause tooth decay in children[30].

Tooth decay is one of the most common chronic infectious diseases in childhood, and various studies show that its effective factors are: *Streptococcus mutans* and Lactobacilli. *Streptococcus mutans* is an acidogenic and to some extent an aciduric bacterium and the main etiological factor in human dental caries, whose high accumulation in dental plaque is an important factor in caries[31].

Now, since the decrease in saliva flow, decrease in buffering capacity, and increase in the number of *Streptococcus mutans* and lactobacilli in saliva are usually associated with an increase in the incidence of tooth decay[32], in health conditions, there is no association between salivation and tooth decay[33]. But when the amount of salivary secretion drops below the minimum, the rate of tooth decay increases. The feeling of dryness in one's mouth, called xerostomia (dry mouth), is seen in salivary gland disorders, systemic disorders, pharmacotherapy, radiation therapy, and old age[34].

In severe cases of xerostomia, saliva is observed with low pH and low buffering capacity, increased concentration of total protein, albumin and sodium, decreased ratio of amylase to protein, increased concentration of lactulose bacilli[35].

Carbonic acid buffer, bicarbonate, acts when saliva flow rate increases.

Phosphate buffer plays an important role when saliva flow is very low.

At pHs above 6, saliva reaches its highest phosphate saturation due to hydroxyapatite. When the pH drops below the critical level of 5.5, hydroxyapatite begins to dissolve, releasing phosphates in an attempt to restore the pH balance.

The mouth is often exposed to foods whose pH is lower than that of saliva and can cause tooth enamel to dissolve[36].

In addition, it has been indicated that the formation of heterotype complexes between salivary molecules, such as high molecular weight mucin glycoprotein, amylase, histatin one, protein one rich in acidic proline and statin are associated with plaque formation and dental caries[37].

Table I: Methods for identifying proteins in saliva.

Proteins	Methods of detection
Cystatins	HPLC-ESIMS
Proline	RP-HPLC-ESIMS-MALDI-TOFMS
AStatrine	Proteomic method
Histatin	Mass fingerprinting method

Proteins involved in salivary defense function are[38]:

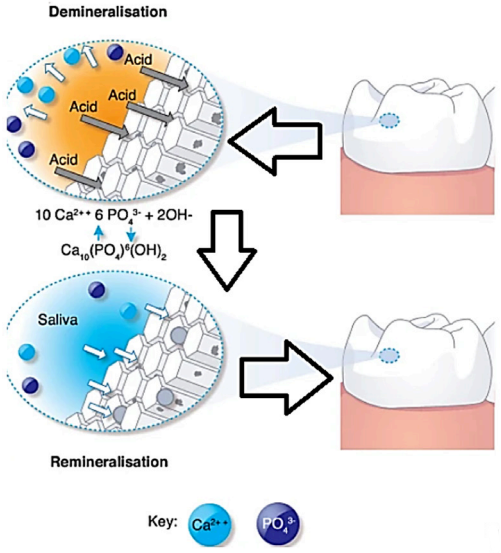
- Immunoglobulins include: IgA, lysozyme, mucins
- Antimicrobial peptides or alarmins
- Catalysidin
- Defensins
- Adrenomedullin
- Histatin: secreted by parotid and submandibular glands.
- Lactoferrin Calprotectin: A protein containing calcium and zinc.

In addition to moderating microbial factors and encouraging preventive dietary behaviors a core goal in caries prevention is promoting the natural protective mechanisms of saliva[39].

The pH of dental plaque is a key factor in the balance between acid demineralization of the teeth and the remineralization of the initial caries lesion. Plaque pH falls each time acid accumulates in the plaque due to bacterial acid production following the consumption of fermentable carbohydrates –mainly sugars– in foods and drinks. Conversely, plaque pH rises when the acids are washed away or neutralized by saliva, which contains the important buffer, bicarbonate[40].

In healthy teeth, the loss of minerals is balanced by the reparative mechanisms of saliva. This equilibrium can be depicted chemically by the equation overleaf opposite (**Figure 1**)[41].

Figure 1: The process of tooth remineralization[41].



When the saliva pH or the plaque pH is below a 'critical value' of about 5.5, the saliva or plaque becomes unsaturated with respect to tooth mineral[42]. As a result, tooth enamel can begin to dissolve. However, when the pH is above this value, the saliva and plaque are supersaturated with respect to tooth mineral. The calcium and phosphate ions in saliva then start to repair any damaged mineral crystals in the enamel – the process of remineralization[43].

Thus, acidic conditions contribute to bringing phosphate and hydroxyl ions below saturation levels, allowing the solid hydroxyapatite crystals of the tooth mineral to dissolve. If above saturation levels, the chemical reaction will move towards remineralization and any damaged crystals will be repaired by the acquisition of ions from the solution[44].

Stimulation of saliva flow results in an increase in the washing out of acids (and sugars), and also an increase in the amount and concentration of bicarbonate buffer and of remineralising ions[45].

Conclusion

From what stated above, one can understand the importance of salivary secretion proteins as methods for identifying and examining oral diseases, especially tooth decay. This calls for conductin further studies in this area. Therefore, since the introduction of liposomes as carriers of proteins in the 1960s and their proposal for the treatment of diseases, it is recommended to use nanotechnology and biocompatible nanomaterials with optimal mechanical properties as restorers and pharmacists in dentistry.

Conflict of Interest

The authors declare that they have no conflict of interest.

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ORIGINAL

Relationship of maxillary anterior teeth and some facial landmarks

Relación de los dientes maxilares anteriores y algunos puntos de referencia faciales

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Abstract

Background/Purpose: The size and shape of teeth is very important and should be beautiful and in harmony with the face components. This study aims to determine the association between the facial features and dimensions of the upper teeth in Iranian population.

Materials and methods: 160 students were selected, (80 male and 80 female), in this cross- sectional survey. Dental and facial dimensions were measured and recorded.Infrmation were analyzed utilizing SPSS 21, and independent t-test and Pearson correlation coefficient.

Results: A direct and significant relationship was observed between the upper central epicocronal height, face length (r=0.314, P<0.001) and mouth width (r=0.166, P=0.036). Also, a direct significant correlation was observed between the upper central mesiodistal width and face length (r=0.244, p=0.002). A direct relationship was observed between the upper anterior arch environment and face length (r=0.415, P<0.001), mouth width (r=0.168, P=0.034), intercanthal distance (r=0.291, P<0.001) and bizygomatic width (r=0.165, P=0.037), which was statistically significant.

Conclusion: Although there are different methods for estimating the teeth size, due to the relationship between some dimensions of the head, face and teeth, these dimensions of the head and face can be used to estimate the dimensions of teeth but most of the available information of facial and dental dimensions and their proportions is related to the other country's statistics, whose population is definitely different from the Iranian population and that there is no complete related information in dental reference books so by use of this study results this method can be used by Iranian dentists.

Key words: Anterior tooth dimensions, facial markers, beauty.

Resumen

Antecedentes/objetivo: El tamaño y la forma de los dientes son muy importantes y deben ser bellos y estar en armonía con los componentes de la cara. Este estudio pretende determinar la asociación entre los rasgos faciales y las dimensiones de los dientes superiores en la población iraní.

Materiales y métodos: En este estudio transversal se seleccionaron 160 estudiantes (80 hombres y 80 mujeres). Se midieron y registraron las dimensiones dentales y faciales, y se analizó la información con el programa SPSS 21, una prueba t independiente y el coeficiente de correlación de Pearson.

Resultados: Se observó una relación directa y significativa entre la altura epicocronal central superior, la longitud de la cara (r=0,314, P<0,001) y la anchura de la boca (r=0,166, P=0,036). Asimismo, se observó una correlación directa y significativa entre la anchura mesiodistal central superior y la longitud de la cara (r=0,244, p=0,002). Se observó una relación directa entre el entorno de la arcada anterior superior y la longitud de la cara (r=0,415, P<0,001), la anchura de la boca (r=0,168, P=0,034), la distancia intercantal (r=0,291, P<0,001) y la anchura bizigomática (r=0,165, P=0,037), que fue estadísticamente significativa.

Conclusiones: Aunque hay diferentes métodos para estimar el tamaño de los dientes, debido a la relación entre algunas dimensiones de la cabeza, la cara y los dientes, estas dimensiones de la cabeza y la cara se pueden utilizar para estimar las dimensiones de los dientes, pero la mayor parte de la información disponible de las dimensiones faciales y dentales y sus proporciones está relacionada con las estadísticas de otros países, cuya población es definitivamente diferente de la población iraní y que no hay información completa relacionada en los libros de referencia dentales por lo que mediante el uso de los resultados de este estudio este método puede ser utilizado por los dentistas iraníes.

Palabras clave: Dimensiones de los dientes anteriores, marcadores faciales, belleza.

Introduction

When anterior teeth are lost for any reason, their replacement by prosthetic and orthodontic treatments is essential in terms of beauty and function. In this case, creating enough space by orthodontic treatment for prosthetic treatments is an important issue. The size and shape of the anterior teeth has played a crucial role the beauty and function of the mouth and face. Therefore, several methods have been introduced to choose the measure of the teeth[1-5]. The appearance of the face created by denture reconstruction is very important for prosthodontists and their patients. Facial beauty is one of the most common reasons why patients seek to replace their missing anterior teeth. On the other hand, one of the reasons for the failure of prosthetic reconstruction is the great importance of beauty in this treatment. One of the most difficult clinical steps in the process of making a proper denture is the determination and substitution of anterior maxillary teeth in lacking of records before tooth extraction. The absence of these records can cause patient dissatisfaction with the beauty of dentures made[6-9]. The size of the upper anterior teeth is necessary to optimize the beauty of the teeth and face, and also their location, shape, and color increase the beauty of the smile. The size, position, shape, and color of the upper anterior teeth are essential for the beauty of the teeth and face, and also these parameters increase the beauty of the smile, so these parameters are of particular importance for the reconstruction of the anterior teeth, although in some cases these parameters are not recorded before tooth extraction[10,11]. Anthropological measurements, including width between two canine tips, bizygomatic width, the distance between two pupils, the distance between interalar, the distance between two canthus, and other anatomical structures are also of great importance for the reconstruction of the anterior tooth[8,9,12].

There are limited scientific criteria in dentistry texts that can provide a general and definitive guide to determine and define the appropriate tooth size. To choose the size of the anterior tooth, in addition to the need for general knowledge, the physical and biological factors related to each patient must also be considered[9,13,14]. One of the critical factors for providing beauty and attractiveness is the proportion, size, shape, and arrangement of the upper anterior teeth, especially the upper central tooth.

The average width of the maxillary central incisor is estimated to be one-sixteenth of the bizygomatic width. The total width of the 6 upper anterior teeth is less than one-third of the bizygomatic width[15-17]. The length of the teeth is determined by the space between the remaining ridges. When there is enough space between the ridges, using longer teeth will decrease the visibility of the prosthetic base and increase the beauty. According to studies, there is a relationship between the size of the face and the height of the crown of the upper central tooth. The height of the upper central tooth is one-sixteenth of the distance between the forehead protrusion and below the chin[17,18]. In general, the information and standards available in the field of selection of upper anterior teeth have been obtained from the Caucasian population and probably do not match the existing population in Iran[8]. Providing the basis for identifying the average racial dimensions of each population, makes it possible to make changes in existing dental generators to provide beauty. Due to the lack of such information in Kerman province, this survey was conducted to determine the association between the dimensions of upper anterior teeth and facial features.

Materials and methods

In this cross-sectional study, size of sample was estimated at least 160 people based on the previous study[6] at the level of 0.05 alpha and power of 80% test . In this study, all 160 students in dental school of Kerman University of Medical Sciences were selected. Inclusion criteria included students in dental school of Kerman University of Medical Sciences students with an age range of 18 to 23 years. The students with any hyperplasia or gingivitis, gingival resorption, gingival surgery, previous reconstructive interventions, diastema, traumatic injury or previous occlusal wear associated with Anterior teeth, malocclusion, or previous orthodontic treatment were excluded. Completed informed consent was gotten from each student. This survey was supervised and affirmed by the Student Research Committee of Kerman University of Medical Sciences (1397-203).

The measured dental dimensions included the mesiodistial width of the upper right central tooth, the epicocronal height length of the upper right central tooth, and the arch circumference from the distal of upper right canine to the distal of upper left one. The dimensions were measured with a digitate caliper with an precision of 0.01 mm. To evaluate the circumference of the arch, a floss was passed through the distal of canines and matched to the arch, and then marked in the contacts area and measured outside the mouth. Dimensions of the face include maximum bizygomatic width (the distance between the outermost points on the zygomatic arches on both sides), the distance between the inner canthus of the eyes, the distance between the corners of the mouth at rest (mouth width), the distance between the two nasal fins (nasal width) and the interval between two points gnathion and nasion (face length). These dimensions were measured directly by a digital caliper while the patient was sitting upright with no head restraints and looking away. To obtain accurate results, each evaluation was performed three times and its average was recorded as the final number. All these measurements were performed by a dentist.

The observations was analyzed by independent t-test, and the relationship between indicators was investigated by Pearson correlation coefficient test. The significance level in this study was considered 0.05.

Result

In this study, 160 participants were studied, (80 male, and 80 female). The mean of all upper anterior teeth dimensions except central mesiodistal width in men was significantly higher than female participants. Although the central mesiodistal width index was higher in male participants, but the results showed no significant difference between groups. Also, men showed significantly more facial dimensions compared with female participants (**Table I**).

A significant and direct relationship was observed between the upper central epicocronal height, face length (r=0.314, P<0.001) and the mouth width(r=0.166, P=0.036), which was statistically significant. also, the relationship between upper central epicocronal height, facial length (r=0.380, P=0.001) and bizygomatic width (r=0.229, P=0.041) was statistically insignificant. in female participants relationship between the upper central epicocronal height with nasal width (r= -0.221, p=0.049) was reverse and insignificant. (**Table II**).

A linear and direct correlation was observed between the upper central mesiodistal width and face length(r=0.244, p=0.002). In male participants, the relationship between upper central mesiodistal width and face length (r=0.390, P<0.001) was direct and significant. (**Table II**).

A linear and direct significant relationship was observed between the upper anterior arch environment and face length (r=0.415, P<0.001), mouth width (r=0.168, P=0.034), internal canthus distance (r=0.291, P<0.001) and bizygomatic width (r=0.165, P=0.037). In male participants, a linear and significant direct relationship between the circumference of the upper anterior arch and the face length (r=0.547, P<0.001) and intercanthal distance (r=0.341, P=0.002). (**Table II**).

Among male and female participants, the mean ratios of the anterior arch to the nose width, the circumference of the anterior arch to the mouth width, the upper central mesiodistal width to the nose width, the upper central mesiodistal width to the mouth width, the interval from the internal canthus to the nose width, the distance from the internal canthus to the mouth width showed a statistically significant difference. But other ratios did not show significant differences (**Table III**).

Table I: The average dimensions difference between the upper anterior teeth and facial indices based on gender.

Dimension	Male		Female		P
	Mean	SD	Mean	SD	
Upper anterior arch circumference	52.0	3.3	50.8	2.4	0.011
Upper central epicocronal height	9.8	1.0	9.4	1.2	0.013
Upper central mesiodistal width	8.1	0.9	7.8	0.9	0.120
Face length	124.0	6.0	116.9	5.0	<0.001
Nasal width	30.2	3.5	27.2	2.9	<0.001
Mouth width	49.8	3.4	44.5	3.0	<0.001
Intercanthal distance	30.7	3.1	29.6	2.7	0.026
Bizygomatic distance	117.2	5.2	112.1	5.7	<0.001

Table II: Relationship between dental dimensions and facial indicators.

	Face length		Nose width		Mouth width		Intercanthal distance		Bizygomatic distance	
	r	p	r	p	r	p	r	p	r	p
Upper central epicocronal height	0.31	<0.001	0.00	0.959	0.17	0.036	0.03	0.694	0.09	0.271
Upper central epicocronal height (male)	0.38	0.001	0.02	0.853	0.04	0.723	0.13	0.246	0.23	0.041
Upper central epicocronal height (female)	0.13	0.243	-0.22	0.049	0.07	0.543	-0.13	0.243	-0.17	0.140
Upper central mesiodistal width	0.24	0.002	0.02	0.761	0.06	0.434	0.05	0.555	0.04	0.594
Upper central mesiodistal width (Male)	0.39	<0.001	0.07	0.560	-0.04	0.732	0.14	0.214	0.17	0.174
Upper central mesiodistal width (Female)	0.02	0.865	-0.14	0.219	0.00	0.984	-0.10	0.400	-0.17	0.123
Upper anterior arch circumference	0.42	<0.001	0.11	0.154	0.17	0.034	0.29	<0.001	0.17	0.140
Upper anterior arch circumference (male)	0.55	<0.001	-0.07	0.544	-0.02	0.850	0.34	0.002	0.14	0.037
Upper anterior arch circumference (female)	0.09	0.455	0.20	0.070	0.17	0.130	0.15	0.186	0.03	0.203

Table III: Differences in the mean ratios under study by gender.

Ratios	Male		Female		Total		P
	Mean	SD	Mean	SD	Mean	SD	
Upper central epicocronal height to face length	0.08	0.01	0.08	0.01	0.07	0.01	0.370
Upper anterior arch environment to upper central mesiodistal width	6.50	0.61	6.56	0.73	6.52	0.67	0.610
Upper anterior arch circumference to the nose width	1.75	0.23	1.89	0.20	1.81	0.22	<0.001
Upper anterior arch circumference to the mouth width	1.05	0.10	1.15	0.09	1.09	0.10	<0.001
Upper anterior arch circumference to intercanthal distance	1.71	0.18	1.73	0.17	1.71	0.17	0.470
Upper anterior arch circumference to bizygomatic distance	0.44	0.03	0.45	0.03	0.44	0.03	0.051
Upper central mesiodistal width to nasal width	0.27	0.04	0.29	0.05	0.28	0.04	0.003
Upper central mesiodistal width to mouth width	0.16	0.02	0.18	0.02	0.16	0.02	<0.001
Upper central mesiodistal width to intercanthal distance	0.27	0.04	0.27	0.04	0.26	0.03	0.730
Upper central mesiodistal width to bizygomatic distance	0.07	0.01	0.07	0.01	0.06	0.01	0.330
Intercanthal distance to the nose width	1.03	0.14	1.09	0.11	1.06	0.13	0.001
Intercanthal distance to the mouth width	0.62	0.07	0.67	0.06	0.64	0.06	<0.001
Intercanthal distance to bizygomatic distance	0.26	0.03	0.26	0.03	0.26	0.02	0.510

Discussion

Beauty is one of the most important reasons for participants to seek prosthetic treatments. Also, smile is affected personal attractiveness and has a great role in the person's own mood and his social impact[19-21]. Having a beautiful smile directly depends on the condition of the teeth, gums and how they fit with the composition of the face[9,22,23]. The correct choice of the six anterior teeth in terms of size, shape and color are major factors of successful Prosthetic treatment. The harmony of face dimensions, such as the corners of the lips, the filtrum, and the distance between the two nasal fins are more prominent in complete denture treatment. The correct choice is to access to the best dentolabial harmony and the appearance of the face[13,24-26]. This choice is especially difficult when no information is available from the patient's natural teeth[27]. Hayden has been suggested to investigate the correct size of the anterior teeth[28,29]. However, the ratios expressed in different studies are not the same, and the most similarity in the results is related to the ratio between the nose width and the width of the six anterior teeth[30]. Many efforts have been made to investigate the approach to suppose the width of these teeth and the beauty obtained[2,3,9,12,31,32]. In this study, the indices of upper anterior Arch circumference, upper central epicocronal height, upper central mesiodistal width, face length, nasal width, mouth width, internal canthus distance and bizygomatic width between the two sexes were measured. The results showed that the mean of all anterior teeth dimension indices except central mesiodistal width in men was significantly higher than female participants. Although the central mesiodistal width index was higher in male participants, but this difference was not significant. Facial landmarks were also significantly higher in men than female participants.

Based on our results, the relationship between upper central mesiodistal width and gender was not statistically significant. Also, the correlation between the upper central mesiodistal width and the bizygomatic width, the distance between the inner canthus, the mouth and nose width was not statistically significant, but the correlation between the upper central mesiodistal width and the face length was statistically significant. It was further found that the ratio of upper central mesiodistal width to nasal width was 0.28, central mesiodistal width to mouth width was 0.16, upper central mesiodistal width to internal canthus distance was 0.26 and upper central mesiodistal width to bizygomatic width was 0.6. All measured ratios except upper central mesiodistal width to bizygomatic width showed a significant difference between females and males. This ratio was higher in women than men. In Ibrahimagic study, the width of the central tooth was 1.5 mm smaller than similar samples of Western Europeans (average width 7 mm); While in British men, the rate is 8.65, in Chinese society 8.85 and in Africa 9.9 mm[33]. In Lavere study, the average length of the upper central tooth was 8.66 in men and 8.19 in women, and It was a total of 8.46 mm. In some sources, the average length of the right maxillary central tooth is 10.5 mm, and the width of the central maxillary tooth is 8.5 mm[25]. Our results showed that the e width of the right maxillary central tooth was 8.55 mm, which agreed with the results of previous researches. In the Keng study, about 42.8% of the subjects had a central width greater than 9.5 mm, indicating the larger size of teeth[34].

The width of the central maxillary tooth in men and women in this study is similar to the findings of a number of other studies. For example, Pak nahad studied the average mesiodistal width of the central incisor of 100 students of Shahid Beheshti Dental School and 8.58 mm reported for men and 8.23 mm for women[35]. On the Iranian population, the mean obtained in this study was 8.7 mm in men and 8.4 mm in women[35]. Further research, Oshaq et al. Obtained an overall average of 8.4, which is close to the results of this study[14]. These results are different from Memarian and Rostamkhany et al[27, 36]. In the first study, the average width of the upper central tooth in a population of 100 participants referred to Tehran Dental School in the age range of 20-30 years was 8.9 in females and 9.1 in males. The next study was on a population of 100 people who were all men. The age range was 17-37 years; the average was 8.9 for this tooth. This difference can be related to the inequality of the number of samples in terms of gender in these two studies. Owsen et al., by measuring the width of the anterior maxillary teeth in various ethnicities, concluded that despite racial differences, men's teeth are always wider than females[37]. Gillen et al. found that men have wider and longer teeth than women He showed that the difference in the measure of the central teeth and the canine in the two sexes is significant[38]. This case is comparable with the result obtained in the study of Hasanreisoglu et al.[13].

In the present study, the Pearson correlation coefficient test shows that there is no strong relation between interzygomatic distance and the mesiodistal width of the upper central incisor. These results are similar to the findings of Scandrett et al.[39]. In Hasanreisoglu et al.'s study, no relationship was found in men[13]. This will lead to wider teeth selection for the patient. Because the ratio obtained is approximately equal to 1:13; however, the ratio obtained in this study has been confirmed in some studies[24]. In Rawat et al. study, the width of the central maxillary teeth to the bizygomatic width follows a ratio of 1:16[40]. The result of their study on the relationship between the bizygomatic width and the central tooth in two sexes is similar to the present study. However, in our study, the ratio of bizygomatic widthto the width of the maxillary central tooth differed from the normal value, which was also statistically significant. It can be due to the different statistical samples. Their study was conducted in India and the present study was conducted in a population from southern Iran.

In this study, the significant relationship observed between tooth length and gender. Also, the correlation between the upper central length and bizygomatic width, the distance between the inner canthus, and the nose width was not statistically significant, but the correlation between the upper central the face length and the mouth width was statistically significant. There was no significant gender difference in Central epicocronl height. Consistent with the results of the present study in Sadeghi et al.'s 2010 study, no relationship was found between gender and tooth size. In this study, the length of teeth was 9.45 mm in men and 9.16 mm in women[41]. In their study, as in the present study, the length and width of teeth were slightly higher in men than in women. In a 2014 study by Radia et al., The relation between upper central and interzygomatic width was 1:15.56 (1:15.57 in men and 1:15.37 in women) and the relationship between upper central epicocronal height and face height has been achieved 1:17.93(1:17.97 in men and 1:17.89in women)[42].

The intercanthal distance in the present study was 30.14 mm. In the study of Lotfi et al., The average distance between the inner canthos was 32.28 mm (7 m), and Abdullah et al. findings[44] also stated that the average distance of internal canthus was 32 mm, which was very close to the present study. Our finding were lower than the results of Murphy et al.[26], who suggested an average intercantal distance of 33.9 mm, but higher than the results obtained by Freihofer[45]. The ratio between the four measurements of the anterior teeth of the maxilla and the distance of the internal canthus in all samples was very close to the results obtained by Al wazzan et al.[43].

The results showed that the central mesiodistal width to the medial canthus distance was equal to 0.26 and this ratio did not show a significant difference in two genders. Similar to the results of the present study, the width of the central tooth to the distance of the internal canthus in the study of Lotfi et al[46]. Was equal to 0.266, which was calculated in the study of Alwazzan et al.[43] 0.267. In general, it should be noted that the differences between the results of the this study with other may be attributable to genetic variation as well as existing differences, in addition to breeding differences, related to differences in measurement methods. In the reconstruction and replacement of anterior teeth, despite the possibility of using different indicators to select teeth with dimensions close to reality, it should be noted that these indicators should not be the sole owner of the selected teeth. Because people's perceptions of beauty are different and individual and social factors affect it[47]. Therefore, in addition to using the basic principles to make the right choices, social, racial and individual differences of each person should be considered to increase participants' satisfaction with their smiles[48].

One of our limitations is that it is uni-center due to the fact that the dimensions of the teeth are different in different ethnicities; it is better to study the information about students in several provinces in future studies. It is suggested that by collecting the results of other similar studies conducted in Iran and conducting a comprehensive analysis, an effective step be taken in presenting the norms of Iranian society and producing teeth with appropriate dimensions.

Conclusion

Although there are various techniques for estimating the teeth size, due to the relationship between some dimensions of the head, face and teeth, these dimensions of the head and face can be used to estimate the dimensions of teeth but most of the available information of facial and dental dimensions and their proportions is related to the other country's statistics, whose population is definitely different from the Iranian population and that there is no complete related information in dental reference books so by use of this study results this method can be used by Iranian dentists.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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ORIGINAL

Study the antimicrobial effects of *Zataria multiflora*-based mouthwash on the microbial community of dental plaques isolated from children: A candidate of novel plant-based mouthwash

Estudio de los efectos antimicrobianos del enjuague bucal a base de Zataria multiflora sobre la comunidad microbiana de placas dentales aisladas de niños: Un candidato a enjuague bucal novedoso a base de plantas

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Abstract

Background: *Zataria multiflora* is a medicinal plant with high antimicrobial effects. It is mainly used as an oral specie in food. The present survey was aimed to assess the antimicrobial effects of *Z. multiflora*-based mouthwash on the microbial community of dental plaques.

Methods: Two-hundred dental plaque samples were collected from individuals. Culture technique was used to assess their microbial contamination. *Z. multiflora* was collected and use in a base of mouthwash in 1% concentration. Antimicrobial effects of *Z. multiflora*-based mouthwash was examined against isolated bacteria and compared to antibiotic agents using the disk diffusion. Minimum inhibitory concentration of *Z. multiflora*-based mouthwash was also studied against isolated bacteria.

Results: *Streptococcus mutans* (19%), *Enterobacter cloacea* (17.50%), and *Staphylococcus aureus* (15%) were the most commonly identified bacteria amongst the dental plaque samples. *H. pylori* (8%) had the lowest prevalence. The mean ranges of the diameter of the growth inhibition zones were 5.71±0.92 (*S. aureus* against tetracycline) to 15.68±0.55 (*S. mutans* against azithromycin) mm. *Z. multiflora* mouthwash (1%) harbored the highest antimicrobial effects against *S. mujtans* (15.33±0.81 mm), and *S. aureus* (12.01±1.10 mm), while showed the lowest against *E. coli* (8.38±0.46 mm) and *E. cloacea* (10.52±0.84 mm). The lowest MIC levels were obtained for *S. mutans* (2 mg/ml). The highest MIC level was found for *E. cloacea* (8 mg/ml). The MIC levels of *Z. multiflora* mouthwash against *E. coli* and *H. pylori* bacteria were higher than examined concentrations.

Conclusion: *Z. multiflora*-based mouthwash may be a useful herbal-based mouthwash against bacteria in dental plaque samples.

Key words: *Zataria multiflora*, mouthwash, antimicrobial effects, dental plaques.

Resumen

Antecedentes: *Zataria multiflora* es una planta medicinal con altos efectos antimicrobianos. Se utiliza principalmente como especie oral en la alimentación. El presente estudio tenía como objetivo evaluar los efectos antimicrobianos de un enjuague bucal a base de *Z. multiflora* sobre la comunidad microbiana de las placas dentales.

Métodos: Se recogieron doscientas muestras de placa dental de individuos. Se utilizó una técnica de cultivo para evaluar su contaminación microbiana. Se recogió *Z. multiflora* y se utilizó en una base de enjuague bucal en una concentración del 1%. Se examinaron los efectos antimicrobianos del enjuague bucal a base de *Z. multiflora* contra las bacterias aisladas y se compararon con los agentes antibióticos mediante la difusión en disco. También se estudió la concentración mínima inhibitoria del enjuague bucal a base de *Z. multiflora* frente a bacterias aisladas.

Resultados: *Streptococcus mutans* (19%), *Enterobacter cloacea* (17,50%) y *Staphylococcus aureus* (15%) fueron las bacterias más comúnmente identificadas entre las muestras de placa dental. *H. pylori* (8%) tuvo la menor prevalencia. Los rangos medios del diámetro de las zonas de inhibición del crecimiento fueron de 5,71±0,92 (*S. aureus* frente a la tetraciclina) a 15,68±0,55 (*S. mutans* frente a la azitromicina) mm. El enjuague bucal de *Z. multiflora* (1%) albergó los mayores efectos antimicrobianos contra *S. mujtans* (15,33±0,81 mm), y *S. aureus* (12,01±1,10 mm), mientras que mostró los más bajos contra *E. coli* (8,38±0,46 mm) y *E. cloacea* (10,52±0,84 mm). Los niveles de MIC más bajos se obtuvieron para *S. mutans* (2 mg/ml). El nivel de CIM más alto se encontró para *E. cloacea* (8 mg/ml). Los niveles de CIM de *Z. multiflora* contra las bacterias *E. coli* y *H. pylori* fueron superiores a las concentraciones examinadas.

Conclusión: El enjuague bucal a base de *Z. multiflora* puede ser un útil colutorio a base de plantas contra las bacterias presentes en las muestras de placa dental.

Palabras clave: *Zataria multiflora*, enjuague bucal, efectos antimicrobianos, placas dentales.

Introduction

Dental plaque is the name given to the aggregations of bacteria and their products which accumulate on the tooth surface[1]. When plaque accumulates on the crowns of teeth the natural, smooth, shiny appearance of the enamel is lost and a dull, matt effect is produced[2]. As it builds up, masses of plaque become more readily visible to the naked eye[3]. Additionally, dental plaque bacteria can be a dangerous sources of infections for other parts of the body, such as gastrointestinal tract, head, neck, and nasopharynx[4].

In direct smears, the early plaque is dominated by cocci and rods, most of which are Gram-positive. In the mature plaque (after about 7 days) the percentage of cocci in the plaque decreases rapidly and filaments and rods constitute about 50% of organisms in plaque[5]. Studies revealed that *Streptococcus mutans*, *Enterobacter cloacea, Staphylococcus aureus, Klebsiella pneumonia, Helicobacter pylori,* and *Escherichia coli*, are the most important and frequent bacterial species isolated from the oral cavity and dental plaque samples, globally[6,7].

Several antimicrobial choices are available for the infections of the oral cavity. However, bacterial isolates of the dental plaque samples harbored severe resistance toward commonly used antimicrobial agents, particularly aminogylocides, tetracyclines, penicillins, cephalosporins, and quinolones[8]. Thus, studying the profile and pattern of antibiotic resistance amongst bacterial isolates of dental plaques as novel reservoirs of bacteria seems essential.

Zataria multiflora (*Z. multiflora*) is a herbal plant belonging to the Laminaceae family. It grows in Iran, Pakistan and Afghanistan and is known as Avishan Shirazi in Iran. The main components of the essential oil of this plant include phenolic compounds such as carvacrol, thymol and eugenol[9]. This plant is known as potential antimicrobial agents and mainly used as a spice in different foodstuffs[10]. Edible nature of this plant make it possible to use it in several types of oral drugs, particularly herbal mouthwash[11].

This study was aimed to assess the antimicrobial effects of *Z. multiflora*-based mouthwash on the microbial community of dental plaques as a novel candidate of plant-based mouthwash in vitro condition.

Materials and methods

Samples and inclusion criteria

A total of 200 children referred to the dentistry clinics for routine check-ups were assessed in this survey. All children with dental plaque samples were included in this survey. Dental plaque presence is the prominent inclusion factor. All children who had received antimicrobial options or antibacterial mouthwashes three months before the experiment were excluded from the research. Dental plaque sample was taken from the gingival crevice at the most profound pocket reading and removed from the clinical site using a sterile universal curette. The curette tip was inserted into the depths of the crevice/pocket, moved coronally while in contact with the tooth surface to remove both sub and supragingival plaque.

Preparation of plant materials

Z. multiflora was purchased from traditional groceries. A total of 3500 grams of *Z. multiflora* was used to create an ethanol extract. It was cleaned, dried at room temperature for 24 hours, and processed in a blender until its texture became smooth. To obtain the extract from the processed *Z. multiflora*, 2000 ml of a 96% ethanol solution was used, and this process was repeated thrice. The initial extract was filtered and evaporated at temperatures ranging from 50 to 60 °C to obtain a 100% pure *Z. multiflora* extract. The pure extract was weighed, stored in a sealed glass container, and subsequently placed in a desiccator before being used as mouthwash.

Mouthwash formulation

As much as 100 ml of mouthwash was produced for each formulation with *Z. multiflora* extract as the active substance. The formulations of *Z. multiflora* mouthwash according to **table I**. Propylene glycol was included in the *Z. multiflora* extract and placed in a glass beaker. It was then raised to 60 °C, stirred with a magnetic stirrer at 300 rpm and Tween 80, and sorbitol and aquadest were added. Benzoic acid and sodium benzoate were dissolved in aquadest and added to the solution and stirred with a magnetic stirrer until homogeneous. Subsequently, 100 ml of the sorbitol and aquadest ad was stirred until the solution became clear, and Oleum menthae piperitae was added.

Table I: Formulation of Z. multiflora mouthwash.

Components	Frequency (%)
Z. multiflora ethanolic extract	1
Propylene glycol	25
Tween 80	5
Oleum menthe piperitae	0.25
Benzoate acid	0.1
Sodium benzoate	1
Sorbitol 70%	15
Aquadest	100

Quality assessment of Z. multiflora mouthwash

Organoleptic, acidity, stability, weight mass, viscosity, irritation, and contact time of *Z. multiflora* mouthwash were assessed using the method described previously[12].

Isolation of bacteria from the dental plaque samples

The dental plaque sample from each child was cultured into a sterile tube containing 5% sheep blood agar, chocolate agar and a selective medium and transported to the microbiology laboratory. All media were incubated at 37°C and 42 °C for 24 to 48 h. after Gram staining and

microscopy, different biochemical tests were performed to identify bacterial strains. The basic biochemical tests used to identify bacterial strains includes Starch Test, Simon Citrate, Oxidase, Catalase, Voges Proskauer, Urease, Indole, Methyl Red and Coagulase Test. Analytical Profile Index (API 20E) (BioMeriouxVitek, Inc., MO, USA) system was used to identify bacteria[13].

Antibacterial effects of mouthwash against isolated bacteria

The simple disk diffusion method was used to assess the antimicrobial effects of synthesized mouthwash. For this purpose, isolated bacteria were cultured on Muller Hinton agar media. A total of 1000 µl of 1% *Z. multiflora* mouthwash were poured into the blank disk and located at the surface of each media. For comparison, penicillin (10 µg/disk), tetracycline (30 µg/disk), azithromycin (15 µg/disk), gentamicin (10 µg/disk), and ampicillin (10 µg/disk) (Oxoid, UK) antibiotic disks were accompanies. All guidelines were performed according to the Clinical and laboratory standard institute (CLSI)[14-16]. The Minimum Inhibitory Concentration (MIC) of synthetic *Z. multiflora* mouthwash was also assessed. For this purpose, 1, 2, 4, and 8 mg/ml concentration of mouthwash were prepared and the MIC value was determined using the previously described method[17].

Statistical analysis

Collected data were transferred to the Microsoft Office Excel software and arranged well. Then, they were statistically analyzed using the SPSS software and chi-square and analysis of variance tests (ANOVA). $P<0.05$ was consider z significant level[18-22].

Results

Table II shows the distribution of bacteria strains isolated from dental plaque samples. As shown, *S. mutans* (19%), *E. cloacea* (17.50%), and *S. aureus* (15%) were the most commonly identified bacteria amongst the dental plaque samples. *H. pylori* (8%) had the lowest prevalence amongst the examined dental plaque samples. Statistically significant difference was obtained between the distribution of different bacteria ($P<0.05$).

Table III shows the dimeter of the growth inhibition zone of bacteria against synthetic mouthwash compare to antimicrobial agents. The mean ranges of the diameter of the growth inhibition zones were 5.71±0.92 (*S. aureus* against tetracycline) to 15.68±0.55 (S. mutans against azithromycin) mm. *Z. multiflora* mouthwash (1%) harbored the highest antimicrobial effects against *S. mujtans* (15.33±0.81 mm), and *S. aureus* (12.01±1.10 mm), while showed the lowest against *E. coli* (8.38±0.46 mm) and *E. cloacea* (10.52±0.84 mm). Statistically significant differences were obtained between the diameter of the growth inhibition zone of bacteria treated with different antimicrobial agents ($P<0.05$).

Table IV shows the MIC values of *Z. multiflora* mouthwash against different isolated bacteria. Findings showed that the lowest MIC levels were obtained for *S. mutans* (2 mg/ml). The highest MIC level was found for *E. cloacea* (8 mg/ml). The MIC levels of *Z. multiflora* mouthwash against *E. coli* and *H. pylori* bacteria were higher than examined concentrations (non detected).

Table II: Distribution of bacteria strains isolated from dental plaque samples.

Samples	N. collected	Distribution of bacteria (%)				
		S. aureus	*S. mutans*	*E. cloacea*	*E. coli*	*H. pylori*
Dental plaques	200	30 (15)	38 (19)	35 (17.50)	20 (10)	16 (8)

Table III: Dimeter of the growth inhibition zone of bacteria against synthetic mouthwash compare to antimicrobial agents.

Tested antimicrobial agents	Diameter of the growth inhibition zone of bacteria (mm)				
	S. aureus	*S. mutans*	*E. cloacea*	*E. coli*	*H. pylori*
Z. multiflora mouthwash (1%)	12.01±1.10 [a*]	15.33±0.81 [a]	10.52±0.84 [a]	8.38±0.46 [b]	10.57±0.61 [a]
Penicillin	8.63±0.34 [b]	9.66±0.23 [c]	10.14±0.22 [a]	8.15±0.51 [b]	10.33±0.35 [a]
Tetracycline	5.71±0.92 [c]	6.61±0.28 [d]	8.17±0.37 [b]	8.81±0.36 [b]	8.66±0.25 [a]
Azithromycin	13.24±0.95 [a]	15.68±0.55 [a]	11.43±0.52 [a]	10.93±0.44 [a]	9.90±0.60 [a]
Gentamicin	6.03±0.32 [c]	11.82±0.39 [b]	11.97±0.93 [a]	8.55±0.81 [b]	9.93±0.65 [a]
Ampicillin	7.15±0.41 [c]	10.17±0.16 [c]	10.08±0.09 [a]	9.72±0.74 ab	9.71±0.69 [a]

*Dissimilar small letters in each column show significant statistical differences ($P<0.05$).

Table IV: MIC values of *Z. multiflora* mouthwash against different isolated bacteria.

Treatment	MIC (mg/ml)				
	S. aureus	*S. mutans*	*E. cloacea*	*E. coli*	*H. pylori*
Z. multiflora mouthwash	4	2	8	ND*	ND

*Non detected.

Discussion

Infections may cause several life-threating diseases globally[23-38]. In this regard, medical plants and traditional medicine act as healing sciences[39]. In this study, *Z. multiflora*-based mouthwash was used as an antimicrobial agent on bacteria isolated from dental plaque samples. Total distribution of *S. aureus, S. mutans, E. cloacea, E. coli,* and *H. pylori* amongst the examined dental plaque samples was 15%, 19%, 17.50%, 10%, and 8%, respectively.

An Indian survey[40] revealed that Streptococcus spp. was the most commonly detected bacteria (51.00%), followed by E. coli (19.00%) and Veillonella spp. (19.00%). A research on United Kingdome[41] showed that *Tannerella forsythensis* (65.00%), *Porphyromonas gingivalis* (49.00%), and *Actinobacillus actinomycetemcomitans* (55.00%) were the most commonly detected pathogens isolated from dental plaque samples. Similarly in Korea[42], *Streptococcus, Corynebacterium, Neisseria*, and *Fusobacterium* were the most commonly detected bacterial strains in dental plaque samples. Brazilian survey[43] showed that the predominant species in all 600 samples included *Corynebacterium diphtheriae, Enterococcus faecalis, S. aureus, Acinetobacter baumannii, P. aeruginosa*, and *E. coli* were predominant bacterial pathogens in the dental plaque samples of children with chronic periodontitis.

Findings of the current research revealed that *Z. multiflora*-based mouthwash had the highest antimicrobial effects on *S. mutans* and *S. aureus*. The main reason for the lower antimicrobial effects of the mouthwash against other bacteria is that they were Gram-negative and have Lipopolysaccharide (LPS) in their cell walls which inhibit the penetration of essential oils and herbal extracts. Aghili et al. (2015)[44] reported that the *Z. multiflora* extract had the higher antimicrobial effects on experimentally contaminated orthodontic elastomeric ligatures compared to chlorhexidine mouthwash. Milho et al. (2021)[45] stated that the essential oils of Cymbopogon citratus (DC.) Stapf and Lippia alba (Mill.) seem to be the most promising in fighting microbial biofilm in *S. mutans*, given their high capacity to reduce biofilm at low concentrations. Significant effects of herbal mouthwash against pathogenic bacteria recovered from the dental plaques have similarly been reported by Tusi et al. (2020) (Iran)[46] and Pedrazzi et al. (2015) (Brazil)[47].

Conclusion

According to the high antimicrobial effects of the *Z. multiflora*-based mouthwash compared to antimicrobial agents even in low concentrations, its application as a novel and herbal-based mouthwash particularly against Gram-positive bacteria responsible for dental plaque formation has been recommended. However, some additional surveys should perform to assess other effects of *Z. multiflora*-based mouthwash on the oral cavity.

Conflict of Interest

The authors declare that they have no conflict of interest.

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ORIGINAL

Relationship between healthy habits and sociodemographic variables in the values of different atherogenic indices

Relación entre hábitos saludables y variables sociodemográficas en los valores de diferentes índices aterogénicos

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Abstract

Introduction: Atherosclerosis is the pathological lesion responsible for most cardiovascular diseases.
Methods: A descriptive, cross-sectional study was carried out in 1.457 Spanish workers to assess the effect of healthy habits (physical exercise determined with the IPAQ questionnaire, Mediterranean diet, and tobacco consumption) and sociodemographic variables (age, sex, and social class) on the values of different atherogenic indices.
Results: The mean values and the prevalence of altered values in all the atherogenic indices analyzed were lower the higher the level of physical activity and also the greater the adherence to the Mediterranean diet. In men there was a greater risk of presenting elevated values in all atherogenic indices, whereas the highest social class only increased this risk in some indices.
Conclusion: Healthy habits such as physical exercise and the Mediterranean diet improve atherogenic indices and reduce the risk of presenting arteriosclerosis.

Key words: Atherogenic index, mediterranean diet, physical activity, social class.

Resumen

Introducción/Objetivo: La aterosclerosis es la lesión patológica responsable de la mayoría de las enfermedades cardiovasculares. El objetivo es determinar la influencia de la dieta mediterránea y la actividad física sobre los valores de diferentes índices aterogénicos.
Métodos: Se realizó un estudio descriptivo y transversal en 1.457 trabajadores españoles para evaluar el efecto de los hábitos saludables (ejercicio físico determinado con el cuestionario IPAQ, dieta mediterránea y consumo de tabaco) y las variables sociodemográficas (edad, sexo y clase social) sobre los valores de diferentes índices aterogénicos.
Resultados: Los valores medios y la prevalencia de valores alterados en todos los índices aterogénicos analizados fueron menores cuanto mayor fue el nivel de actividad física y también la adherencia a la dieta mediterránea. En los hombres hubo un mayor riesgo de presentar valores elevados en todos los índices aterogénicos, mientras que la clase social más alta sólo aumentó este riesgo en algunos índices.
Conclusiones: Los hábitos saludables como el ejercicio físico y la dieta mediterránea mejoran los índices aterogénicos y reducen el riesgo de presentar arteriosclerosis

Palabras clave: Índice aterogénico, dieta mediterránea, actividad física, clase social.

Introduction

Atherosclerosis is the anatomopathological process underlying most cardiovascular diseases, in which accumulations of lipids, monocytes, and T lymphocytes are observed in the intima, causing migration and proliferation of smooth muscle cells, and the elaboration of collagen. Atherosclerotic disease, which begins in the first decade of life, is relatively benign and slowly progressive, remaining asymptomatic until there is a significant reduction in the vascular lumen, an abrupt occlusion, or thrombotic complications. Like most diseases whose prevalence increases with age, it is a complex pathology that depends on the interaction of genetic and environmental factors[1,2]. The combination of an unhealthy diet and low physical activity are the main risk factors for arteriosclerosis[3,4]. The two parameters most associated with cardiovascular disease, both strongly correlated with each other, are the proportion of calories in the diet, –supplied by saturated fatty acids– and blood cholesterol levels[5-7]. For this reason, international organizations consider that 30 minutes of moderate physical activity a day and diets in which the percentage of lipids is less than 30% are essential to reduce the risk of developing cardiovascular disease[8].

Although the multifactorial origin of arteriosclerosis is known, it is also recognized that almost half the risk of developing cardiovascular disease is related to the lipid metabolism[9]. In the search for a greater degree of prediction of cardiovascular disease, the need arose to develop different instruments to better assess it, and atherogenic indices are framed in this context. These indices provide important information on risk factors that are difficult to quantify by classical systematic analyses and are a better reflection of the clinical and metabolic interactions of lipid fractions. We believe that lipoprotein indices have been little used in cardiovascular prevention although they can provide valuable information on risk assessment. Their use as important predictors of cardiovascular risk is based on a large number of epidemiological studies that have shown that these indices have a higher correlation with cardiovascular disease and, as such, are better predictors of cardiovascular disease than simple lipid parameters[10-12]. Therefore, in an attempt to improve the degree of knowledge of these tools, the main objective of the present study was to determine the influence of certain hygienic habits, such as tobacco consumption, diet, and physical exercise, on the values of different atherogenic indices in the Spanish Mediterranean population.

Material and methods

A retrospective, cross-sectional study was performed in 1584 Spanish workers from different productive sectors in the period between January 2017 and December 2017. One hundred and tweny-seven workers were excluded (69 for not accepting to participate and 58 for being under 18 years old), leaving 1457 workers finally included in the study, 718 women (mean age 43.30 years) and 739 men (mean age 46.02 years). The workers were selected from among those who attended periodic occupational medical check-ups.

Inclusion criteria

- Aged between 18 and 67 years.
- Being an active worker.
- Belonging to one of the companies collaborating in the study.
- Accepting to participate 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 and hip girth were measured in both cases 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. For the former, the tape measure was placed parallel to the ground at the level of the last floating rib; and for the latter, horizontally at the level of the hip.

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[13]:

Total cholesterol/HDL-c index: low risk: < 5 in men and < 4.5 in women; moderate risk: between 5 and 9 in men and between 4.5 and 7 in women; and high risk: > 9 in men and > 7 in women. 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.

CHOLINDEX=LDL-C-HDL-C (Triglycerides<400 mg/dL), LDL-C-HDL-C + 1/5 of Triglycerides (Triglycerides ≥ 400 mg/dL)[14].

Cholindex is considered high at 80 and above.

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.

Social class was obtained from the 2011 National Classification of Occupations (CNO-11) based on the proposal made by the Spanish Society of Epidemiology[15]. We chose the classification in 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 was assessed using the questionnaire on adherence to the Mediterranean diet[16] which contains 14 questions with values of 0 or 1 point each. Values below 9 indicate low adherence and above 9 indicate good adherence.

Physical activity was assessed with the International Physical Activity Questionnaire (IPAQ)[17], a self-administered questionnaire consisting of seven questions that assesses the physical activity performed in daily life in the previous seven days.

Results

Table I shows the values of the anthropometric, clinical, analytical, sociodemographic, and healthy habit variables of the population studied, where it can be observed that the values were more unfavorable, except for total cholesterol and tobacco consumption, among men.

All the atherogenic indices analyzed showed a decrease in the mean values as the level of physical activity increased, and this situation appeared in both women and men, as shown in **table II**.

Something similar to that observed with physical activity was seen with the Mediterranean diet, in that people, both men and women, who presented high scores in the questionnaire on adherence to the Mediterranean diet would present better values in all the atherogenic indices. The complete data are shown in **table III**.

The prevalence of altered values of all the atherogenic indices decreased as the level of physical exercise increased; this situation was seen in both men and women. (see **table IV**).

The prevalence of elevated values of the atherogenic indices also demonstrated better results in people with a high adherence to the Mediterranean diet, as shown in **table V**.

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
Glycemia (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	

Sex, physical activity, and Mediterranean diet were the only variables to show an influence in all the scales analyzed. Of these, the one showing the greatest influence was age, with odds ratios ranging from 1.64 (95% CI 1.32-2.06) for high non-HDL/HDL cholesterol to 6.04 (95% CI 4.26-8.58) for high triglycerides/HDL. Age only revealed an influence for high non-HDL/HDL cholesterol. All results are presented in **table VI**.

Table II: Mean values of the different atherogenic index 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
Cholesterol/HDL-c	3.65 (0.91)	3.18 (0.76)	2.92 (0.65)	<0.0001	4.36 (1.14)	3.94 (1.05)	3.60 (0.90)	<0.0001
LDL-c/HDL-c	2.25 (0.75)	1.87 (0.65)	1.64 (0.58)	<0.0001	2.65 (0.89)	2.35 (0.86)	2.16 (0.74)	<0.0001
Triglycerides/HDL-c	1.97 (1.63)	1.50 (0.96)	1.36 (0.89)	<0.0001	3.50 (2.85)	2.79 (2.36)	2.23 (1.82)	<0.0001
HDL-c/LDL-c+VLDL-c	0.42 (0.16)	0.51 (0.18)	0.58 (0.20)	<0.0001	0.33 (0.12)	0.39 (0.17)	0.44 (0.18)	<0.0001
Cholesterol-HDL-c	140.64 (31.22)	124.63 (29.07)	115.50 (27.10)	<0.0001	144.45 (31.84)	136.12 (33.82)	126.76 (28.84)	<0.0001
Triglycerides/LDL-c	0.87 (0.51)	0.81 (0.39)	0.77 (0.56)	<0.0001	1.53 (2.83)	1.38 (2.82)	1.03 (0.72)	<0.0001
Cholesterol no HDL-c/HDL-c	0.71 (0.07)	0.67 (0.07)	0.64 (0.08)	<0.0001	0.76 (0.06)	0.73 (0.08)	0.70 (0.08)	<0.0001
Cholindex	64.52 (33.22)	46.94 (30.87)	35.83 (31.19)	<0.0001	70.70 (31.84)	62.03 (35.55)	55.12 (35.77)	<0.0001

Table III: Mean values of the different atherogenic index 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
Cholesterol/HDL-c	3.29 (0.84)	3.18 (0.79)	<0.0001	4.02 (1.07)	3.73 (1.00)	<0.0001
LDL-c/HDL-c	1.95 (0.70)	1.87 (0.69)	<0.0001	2.42 (0.86)	2.23 (0.80)	<0.0001
Triglycerides/HDL-c	1.69 (1.25)	1.51 (1.10)	<0.0001	2.93 (2.55)	2.44 (2.00)	<0.0001
HDL-c/LDL-c+VLDL-c	0.50 (0.19)	0.52 (0.19)	<0.0001	0.38 (0.15)	0.42 (0.18)	<0.0001
Cholesterol-HDL-c	126.21 (30.61)	125.63 (30.32)	<0.0001	135.62 (33.01)	131.61 (30.91)	<0.0001
Triglycerides/LDL-c	0.87 (0.50)	0.82 (0.46)	<0.0001	1.41 (2.97)	1.11 (0.89)	<0.0001
Cholesterol no HDL-c/HDL-c	0.68 (0.08)	0.67 (0.08)	<0.0001	0.73 (0.07)	0.71 (0.08)	<0.0001
Cholindex	49.44 (32.48)	47.12 (33.52)	<0.0001	63.32 (34.44)	58.08 (36.15)	<0.0001

Table IV: Prevalence of altered values in the different atherogenic index 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	
	Percentage	Percentage	Percentage	p-value	Percentage	Percentage	Percentage	p-value
Cholesterol/HDL-c moderate	14.71	6.96	2.46	<0.0001	27.66	13.01	7.60	<0.0001
Cholesterol/HDL-c high	0.59	0.00	0.00		0.00	0.00	0.00	
LDL-c/HDL-c high	15.88	6.96	2.46	<0.0001	34.04	24.10	13.67	<0.0001
Triglycerides/HDL-c high	10.59	6.38	3.45	<0.0001	41.13	31.97	20.06	<0.0001
Cholesterol no HDL-c/HDL-c high	62.35	42.32	28.57	<0.0001	67.38	57.25	43.77	<0.0001
Cholindex high	29.41	12.17	8.37	<0.0001	37.59	25.65	20.67	<0.0001

Table V: Prevalence of altered values in the different atherogenic index 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	
	Percentage	Percentage	p-value	Percentage	Percentage	p-value
Cholesterol/HDL-c moderate	9.54	6.36	<0.0001	16.57	10.44	<0.0001
Cholesterol/HDL-c high	0.00	0.00		0.00	0.22	
LDL-c/HDL-c high	9.54	6.80	<0.0001	24.44	17.23	<0.0001
Triglycerides/HDL-c high	8.78	5.26	<0.0001	34.55	22.72	<0.0001
Cholesterol no HDL-c/HDL-c high	46.95	41.01	<0.0001	54.21	52.22	<0.0001
Cholindex high	16.41	14.47	<0.0001	28.65	22.98	<0.0001

Table VI: Logistic regression analysis.

	Men	Age ≥50 years	Smokers	MET low-moderate	Predimed low	Social class II-III
	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)	OR (CI 95%)
Cholesterol/HDL-c moderate-high	2.26 (1.56-3.26)	ns	1.73 (1.21-2.48)	2.69 (1.74-4.15	1.53 (1.08-2.17)	ns
LDL-c/HDL-c high	3.81 (2.70-5.38)	ns	ns	2.40 (1.67-3.44)	1.48 (1.08-2.01)	0.60 (0.39-0.92)
Triglycerides/HDL-c high	6.04 (4.26-8.58)	ns	1.65 (1.21-2.25)	1.90 (1.37-2.63)	1.69 (1.26-2.26)	ns
Cholesterol no HDL-c/HDL-c high	1.64 (1.32-2.06)	1.97 (1.56-2.50)	ns	1.85 (1.47-2.34)	1.24 (1.01-1.54)	0.47 (0.34-0.65)
Cholindex high	2.16 (1.63-2.85)	ns	ns	1.65 (1.23-2.22)	1.32 (1.01-1.72)	0.50 (0.35-0.72)

Discussion

In our study, all the atherogenic indices analyzed improved as the level of physical activity determined with the IPAQ questionnaire increased. Something similar was observed when adherence to the Mediterranean diet increased.

In the multivariate analysis, the variable that most increased the risk of presenting high values of all the atherogenic indices was being over 50 years of age, followed by low or moderate physical activity and low adherence to the Mediterranean diet.

Practically, all the studies consulted reveal a beneficial effect of physical activity on the values of the atherogenic indices, as we have found.

A study carried out in the same geographical area as ours and also in the working population, specifically in more than 60.000 workers, assessed the influence of physical activity and a diet rich in vegetables and fruit on the prevalence of elevated values of different atherogenic indices, showing that both high cholesterol/HDL and LDL/HDL or triglycerides/HDL were more frequent in the groups that did not engage in frequent physical activity or in those who did not consume high amounts of fruit and vegetables[18]. These results are similar to ours. Another study in more than 200 Norwegian adults also found a beneficial effect of physical exercise, in this case on the atherogenic LDL/HDL index[19]. Data from two health surveys, one in the United States[20] and the other in Chile,[21] assessed the effect of physical activity on the values of the log triglyceride/HDL atherogenic index, also finding, like us, a beneficial effect. Similar data were found in another study, in this case carried out in a younger population, specifically in almost a hundred Colombian recruits, in whom physical exercise improved the values of several atherogenic indices[22].

The joint effect of physical activity and a low-calorie diet was evaluated in 327 overweight Romanian adults in whom an improvement in lipid profile and atherogenic indices was also observed[23]. Something similar was found in the American National Health and Nutrition Examination Survey[24] conducted in more than 2700 adults in which an improvement in atherogenic indices was observed with physical exercise and healthy eating, although in this case an additive effect of both was not observed.

A sub study of the PREDIMED study carried out in 772 participants who were given a Mediterranean diet supplemented with olive oil and nuts showed that after 3 months there was an improvement in the lipid profile (increase in HDL and decrease in LDL) as well as a decrease in the markers of inflammation related to arteriosclerosis[25].

The effect of the different types of fat in the diet on the values of the log triglyceride/HDL atherogenic index were also studied[26] and the consumption of less healthy fats (saturated) was found to worsen their values.

Among the strengths of this study are the large sample size, the number of atherogenic indices analyzed (specifically eight), and the fact that the assessment of physical activity and adherence to the Mediterranean diet was conducted with validated questionnaires (IPAQ and Predimed).

The main limitation of the study is that it was carried out in a very specific geographical area, which may make it difficult to extrapolate the results to other countries.

Conclusions

High physical activity (high METs) and high adherence to the Mediterranean diet decrease the values of all the atherogenic indices analyzed in this study and thus the risk of suffering arteriosclerosis. People in social class I have a higher risk of presenting elevated values of LDL/HDL, non-HDL/HDL cholesterol, and Cholindex.

Conflict of Interest

The authors declare that they have no conflict of interest.

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ORIGINAL

Allocation and development of hospital formulary for obstetrics and gynecology department in a tertiary care teaching hospital of southwest India

Asignación y desarrollo del formulario hospitalario para el departamento de obstetricia y ginecología en un hospital universitario de atención terciaria del suroeste de la India

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Abstract

Objective: The goal of the research is to Preparation and implement a hospital formulary in the obstetrics and gynecology department. To provide updated information about the use of medicines to physicians, pharmacists, and other health care professionals in the hospital for appropriate use of the drugs in Tertiary Care Teaching Hospital of Southwest India.

Methodology: Prospective study is conducted for 6 months in the department of obstetrics and gynecology of CSI Holds worth Memorial (Mission) Hospital Mysore, Karnataka, India. A survey was conducted using a validated questionnaire for the identification of the need and content of obstetrics and gynecology formulary among physicians in the hospital. The obstetrics and gynecology formulary was developed and the quality was evaluated using a validated questionnaire form. The content of the formulary was framed based on the opinion of physicians. Finalized drug list was obtained from the P & T committee and monographs were prepared as per the recommendations of the P & T committee.

Result: The total number of drugs evaluated was 195. With the help of listed drugs of WHO model formulary and master drug list, some more sources and suggestions from Doctors of OBG department and decision of P and T committee, 61 more drugs were included in the OBG hospital formulary. Out of 61 drugs included in the formulary, 45 (43.26%) were available in the Oral route (Tablets, Capsules, Syrups, Suspensions, and other solutions) followed by Parenteral route (IV, IM, SC) 44(42.30%), Topical preparations 10 (9.61%) followed by rectal, vaginal, nasal and parenteral routes. 11 (18.03%) were Anti-infective medicines (Antibiotics) and 11 (18.03%) were drugs affecting endocrine and hormones followed by Vitamins and Electrolytes 8 (8.19%).22 (36.06%) drugs were under pregnancy and lactation category-C, 14 (22.95%) dugs were under category-B, 10 (16.39%) drugs were under category-A. The feedback questionnaire containing the objective type of questions was distributed to all eight gynecologists and PGs who responded to it thoroughly.

Conclusion: The formulary was handy, user-friendly, and saves the precious time of busy physicians. It may promote the safe and effective use of medicines thereby minimizing drug-related problems in the obstetrics and gynecology department.

Key words: Formulary, obstetrics and gynecology, physicians, drug use pattern.

Resumen

Objetivo: El objetivo de la investigación es preparar e implementar un formulario hospitalario en el departamento de obstetricia y ginecología y proporcionar información actualizada sobre el uso de los medicamentos a los médicos, farmacéuticos y otros profesionales de la salud del hospital para el uso adecuado de ellos en el Hospital Docente de Atención Terciaria del Suroeste de la India.

Metodología: Se realizó un estudio prospectivo durante 6 meses en el departamento de obstetricia y ginecología del CSI Holds worth Memorial (Mission) Hospital Mysore, Karnataka, India. Se realizó una encuesta mediante un cuestionario validado para identificar la necesidad y el contenido del formulario de obstetricia y ginecología entre los médicos del hospital. Se elaboró el formulario de obstetricia y ginecología y se evaluó su calidad mediante un cuestionario validado. El contenido del formulario se elaboró basándose en la opinión de los médicos. La lista de medicamentos finalizada se obtuvo del comité de P y T y las monografías se prepararon según las recomendaciones del comité de P y T.

Resultado: El número total de medicamentos evaluados fue de 195. Con la ayuda de la lista de medicamentos del modelo de la OMS y la lista maestra de medicamentos, algunas fuentes más y sugerencias de los médicos del departamento de obstetrician y la decisión del comité P y T, se incluyeron 61 medicamentos más en el formulario del hospital de obstetricia. De los 61 medicamentos incluidos en el vademécum, 45 (43,26%) estaban disponibles por vía oral (comprimidos, cápsulas, jarabes, suspensiones y otras soluciones), seguidos por la vía parenteral (IV, IM, SC) 44 (42,30%), preparados tópicos 10 (9,61%), seguidos por las vías rectal, vaginal, nasal y parenteral. 11 (18,03%) eran medicamentos antiinfecciosos (antibióticos) y 11 (18,03%) eran medicamentos que afectaban al sistema endocrino y a las hormonas, seguidos de vitaminas y electrolitos, 8 (8,19%). 22 (36,06%) medicamentos pertenecían a la categoría C (embarazo y lactancia), 14 (22,95%) a la categoría B y 10 (16,39%) a la categoría A. El cuestionario con preguntas objetivas se distribuyó a los ocho ginecólogos y médicos de cabecera, que respondieron de forma exhaustiva.

Conclusión: El formulario era práctico, fácil de usar y ahorra el valioso tiempo de los ocupados médicos. Puede promover el uso seguro y eficaz de los medicamentos, minimizando así los problemas relacionados con los mismos en el departamento de obstetricia y ginecología.

Palabras clave: formulario, obstetricia y ginecología, médicos, patrón de uso de medicamentos.

Introduction

The hospital formulary is expected to help the physicians in choosing appropriate medicines, upgrade the chance of rational drug use, and assist the stock control with using the spending plan allocated most appropriately. By designing a formulary, hazardous and inadequate drugs can be eliminated which can subsequently diminish morbidity and mortality. Studies have shown that models help health care practitioners in executing quality care. Hospital models originally began life in hospitals as a collection of commonly prescribed drug arrangements, delivered primarily for reference purposes. As time continued, the hospital formulary was adjusted to the definite data on the expanding number and variety of medicines. It advances the great evidence-based recommending and lessens variety in the degree of treatment given to patients and can be used as an apparatus to rationalize the medicines used in standard practice[1].

The World Health Organization (WHO) release the principal edition of the WHO model rundown of drugs in 2002. The core of the Formulary System is the Pharmacy and Therapeutics Committee (PTO) Membership will be included agents of the expert offices/administrations, pharmacy, house staff, nursing administration, and other invested individuals.PTC reviews the formulary one or more times in a year, for the addition and deletion of drugs. The study was to prepare a hospital drug formulary for the specialty departments in tertiary care hospitals. Consequently, the developed formulary will be useful for reducing the brands accessible in the hospital which helps in rational drug use. Several different issues known to exist in most health care systems are restricted drug financial plans, expanding the number of drug options, irrational prescribing and use of medications, rate of perilous and on-useful medications, being shy of fair-minded drug information, high costs of medications[2].

The rationale for formulary advancement is that prescribers come out as comfortable with the pharmacological activities, signs for treatment, secondary effects, cooperations and contraindications for a defined range of drugs for normal Formulary systems are used in various settings and associations with strategy articulations on the use of models and formulary systems in hospitals and health care systems. Several different issues known to exist in most drug systems are restricted drug financial plans, expanding the number of therapeutic other options, ill-advised prescribing and use of medications, presence of perilous and non-solid drugs, absence of impartial drug information, high costs of dealing with an enormous number of drugs, drugs of questionable quality on the market[3]. The Formulary system is used in many different settings, and including hospitals, acute care facilities, home care, settings, and long-term–care facilities as well as by payers such as Medicaid, insurance companies, and managed care organizations[4].

Consequently, hospital pharmacists evolved to improve physician prescriptions through pharmacy and therapeutics committees, the development of clinical pharmacy services, and formulary systems[5]. Pharmacy and therapeutics committees are using the medicine formulary to facilitate prescribing[6]. The importance of formulary development is that the prescribers have a complete understanding of the pharmacological actions, indication for treatments, adverse effects, possible interactions, and contraindications to be used in the specified group of drugs for common diseases[7]. Many organizations have some policies in case of using the formularies. Hospital formulary systems are being used in different settings, including, but not limited to, payers, such as Medicaid, Medicare, managed care organizations, and insurance companies. Furthermore, they are used at in-home care settings, hospital acute care facilities, and hospital long term care facilities[8-13].

To provide information about the use of medicines. Consequently, the focal goals of the formulary are to help prescribers in the appropriate drug of the decision to the reasonable treatment and to settle on prescribers follow the uniform selection of medicines. The advancement of the formulary will significantly affect prescribers and health care professionals' for clinical practice to support the quality of life in the patients, by promoting rational use of drugs towards patient care to improve therapeutic outcomes ensure efficacy, safety, and quality of the drugs to promote rational use, thereby ensuring the availability of drugs according to the needs of the population. To help the transformation of the handbook into electronic format made the drug information available at the fingertip of the healthcare professionals.

Materials and methods

This Prospective study was conducted in Obstetrics and Gynaecology the departments of CSI Holdsworth Memorial (Mission) Hospital Mysore, Karnataka. Inpatients' profile forms/data were collected from the OBG department. From the WHO model formulary 2010, we prepared a list of drugs that were being used in the OBG department and submitted it to the staff for selecting the drugs to be included in the formulary. Subsequently, a discussion was held in the P & T committee regarding the design of the hospital formulary. By soliciting suggestions from the committee members, contents to be added, monographs, appendices, and the overall design of the formulary were specified. Also, the purpose was to design the formulary in a concise, precise, and handy form. Furthermore, all the members of the P & T committee were asked to select the drugs and brands to be included in the formulary as per the requirements of the health care needs of the local population. Committee members, under the suggestion of OBG doctors, selected the drugs and brands coming under the drug classes relevant to the

OBG department after which a comprehensive finalized hospital drug list was prepared. Two questionnaires with the objective type of questions were prepared with the help of clinical pharmacists and OBG doctors. These questionnaires were designed to gather information like indications, precautions, dose, interactions, and adverse drug reactions for them to be included in each drugs monograph. The drugs in the finalized list were classified based upon Pharmacologic-Therapeutic classification into classes or categories. In addition, the monographs for those drugs were prepared as per the recommendation of the P & T committee members with the help of the Master Drug List (which contains total brands of drugs available in the hospital with their generic name, quantity, and cost per unit) together with some standard drug information from such sources like, British National Formulary (BNF) 2017[14], WHO Model Formulary 2008[15], Martindale The Complete Drug Reference[16], Comprehensive Pharmacy Review[17], Essentials of Medical Pharmacology[18] and CIMS[19]. As suggested by committee members, information regarding indications, mechanisms of action, pharmacological classes, doses, contraindications, precautions, adverse effects, pregnancy risk category, and counseling points in each monograph of the drugs were all included.

Result and discussion

The total number of drugs evaluated was 195. With the help of listed drugs of WHO model formulary and master drug list, some more sources and suggestions from Doctors of OBG department and decision of the P and T committee, 61 more drugs were included in the OBG hospital formulary.

Out of 61 drugs included in the formulary, 45 (43.26%) were available in the Oral route (Tablets, Capsules, Syrups, Suspensions, and other solutions) followed by Parenteral route (IV, IM, SC) 44 (42.30%), Topical preparations 10 (9.61%) followed by rectal, vaginal, nasal, and parenteral routes as shown in **table I**.

Out Of 61 drugs included in the formulary, 11 (18.03%) were Anti-infective medicines (Antibiotics) and 11 (18.03%) were drugs affecting endocrine and hormones followed by Vitamins and Electrolytes 8 (8.19%) as shown in **table II**.

Out of 61 drugs, 19 (29.23%) drugs were available in three brands, 18 (27.69%) drugs were available in four brands, 13 (20%) drugs were available in five brands, 7 (10.76%) drugs were available in single-brand as shown in **table III**.

Out of 61 drugs, 22 (36.06%) drugs were under pregnancy and lactation category- C, 14 (22.95%) dugs were under category- B, 10 (16.39%) drugs were under category- A as shown in **table IV**.

Table I: Route of administration of drugs in the prepared Formulary.

Routes	No. of Drugs (n=61)	Percentage (%)
Oral route- (Tablets, Capsules, Syrups, Suspensions and other solutions)	45	43.26
Parenteral route (IV, IM, SC)	44	42.3
Inhalations	0	0
Topical route	10	9.61
Rectal route	3	2.88
Vaginal route	1	0.96
Nasal route	1	0.96

Table II: Drug use pattern in prepared OBG formulary.

Routes	No. of Drugs (n=61)	Percentage (%)
Anesthetics	1	1.63
Analgesics, antipyretics, NSAIDS	6	9.83
Anticholinergics, (Antihistamines, Antipruritic, Antispasmodics, Antifibrinolytics)	7	11.47
Antidote, Alkalysing agents	3	4.91
Anticonvulsants, Antianxiety agents (Barbiturates, Phenobarbital)	2	3.27
Anti-infective medicines (Antibiotics)	11	18.03
Anticoagulants	1	1.63
Alpha/ Beta adrenergic agonist	1	1.63
Antiarrhythmic	1	1.63
Calcium channel blockers	1	1.63
Diuretics	1	1.63
Vasodilators	1	1.63
Drugs affecting endocrine and hormones	11	18.03
Gastrointestinal medicines	5	8.19
Respiratory system medicines	1	1.63
Vitamins and electrolytes	8	13.11

Table III: Patterns of brands available for generic drugs in the OBG hospital pharmacy.

Brands	Number of generic drugs	Percentage (%)
Single brand	7	10.76
Two brands	2	3.07
Three brands	19	29.23
Four brands	18	27.69
Five brands	13	20
Six brands	3	4.61
Seven brands	1	1.53
Eight brands	1	1.53
Nine brands	0	0
Ten brands	0	0
Eleven brands	1	1.53

Table IV: Pregnancy categories of drugs in the prepared Formulary.

Pregnancy category	No. of drugs(n=61)	Percentage (%)
Category- A	10	16.39
Category- B	14	22.95
Category- C	22	36.06
Category- D	10	16.39
Category- X	5	8.19

The feedback questionnaire containing the objective type of questions was distributed to all eight gynecologists and PGs who responded to it thoroughly.

As shown in **table V**, there were 3 Doctors and 5 PGs in the OBG department. Comments and answers to the feedback questionnaire distributed to the Head, Doctors, and PGs of the OBG the department was as follows. For the first question, 75% of doctors had selected the choice Above average in the form, 12.5% of them had selected Average and 12.5% selected Outstanding, for the second question 6 (75%) of them had picked Great extend and 2 (25%) of them had selected the option Somewhat; for the third question, 5 (62.5%) of them had selected Very useful and 3 (37.5%) of them went for the option Useful; for the fourth question 4 (50%) of them had selected very Helpful and 4 (50%) of them had chosen the option Helpful; for the fifth question 5 (62.5%) of they had selected the option Great to extend and 3 (37.5%) had gone for the option Somewhat option; for sixth question 1 (12.5%) of them had picked the option always, 5 (62.5%) of them had selected the option Very frequently, 2 (25%) of them had picked the Option Occasionally; for the seventh question, 2 (25%) of them had gone for Very Useful and 6 (75%) of them had picked the option Useful; for the eighth question, 2 (25%) of them had selected Strongly active, 5 (62.5%) of them had picked Agree and 1 (12.5%) of them had selected neither of the options available; for the ninth question, 8 (100%) of them had selected the option Yes; for the picked the choice Somewhat satisfied as shown in **table V**.

Table V: Feedback of Doctors on implemented OBG formulary.

Feedback questionnaire/ comment	No of Doctors n= 3 (%)	No of PGs n= 5 (%)	Total n=8 (%)
The content in each drug monograph?			
Outstanding	0	1	12.5
Above average	2	4	75
Average	1	0	12.5
Whether the order of contents in each monograph is convenient to refer to?			
To great extend	3	3	75
Somewhat	0	2	25
Is it useful to become aware of the brands available in the hospital pharmacy?			
Very useful	3	2	62.5
Useful	0	3	37.5
Whether this formulary helps reduce the total cost of treatment of the patients?			
Very helpful	2	2	50
Helpful	1	3	50
Whether this formulary promotes the safe and effective use of medicines?			
To a great extend	2	3	62.5
Somewhat	1	2	37.5
The extent of usage of the formulary			
Always	1	0	12.5
Very frequently	2	3	62.5
Occasionally	0	2	25
Will it be useful in your clinical practice?			
Very useful	1	1	25
Useful	2	4	75
The presence of a clinical pharmacist is essential in daily practice			
Strongly agree	1	1	25
Agree	2	3	62.5
Neither	0	1	12.5
Whether the formulary is handy?			
Yes	3	5	100
No	0	0	0
How satisfied are you with the developed formulary?			
Very satisfied	3	3	75
Somewhat satisfied	0	2	25

A total of 61 drugs were included in the OBG hospital formulary based on the opinion of the medical staff of the OBG department, clinical pharmacy department, and the request from the P& T committee as per the requirements of health care needs of the local population. Our study result is consistent with the findings of the Tahniyath, F et al[20], and Raj, D et al[21]. As with both studies, in line with the different standard references, hospital formulary developed. To substantiate this further, using a formulary system leads to rationalization of drug use, hence reducing the medication errors in giving unbiased useful information to medical representatives. On top of it all, it is a great inventory control measure that helps to improve patient care outcomes.

According to drug use patterns in the OBG department, anti-infective medicines (Antibiotics) were the most commonly used drugs in the OBG department. Using these may be due to the susceptibility of pregnant women to infections. Hence, they are being used to treat common and severe infections before and during delivery, meant to prevent maternal and neonatal complications. Likewise, they were used as prophylaxis before any surgical procedure, such as cesarean section or uterine prolapse operations, aimed at treating infections arising from surgical wounds.[22] What follows is the major group which is drugs affecting endocrine and hormones. In addition, it was discovered in the OBG hospital formulary that the administration of drugs was mainly through oral route owing to the patient compliance, its non-invasiveness, being easy to handle, and the absence of any special sterile settings[23]. Moreover, in the prepared formulary, the distribution of brands available for generic drugs fell mainly under three brands. Also, the availability of more than three brands for a single drug may well be due to marketing strategies, Pharmaceutical companies, physician preference, patient financial condition, Pharmaco-economic factors, and pricing which should not be taken for granted when it comes to such a variation.

According to the FDA, drugs being used during pregnancy are categorized into five groups as A, B, C, D, and X in which category A drugs are the safest and category X drugs are contraindicated for the pregnancy period. Furthermore, it is integral to remember the necessity of the presence of pregnancy categories in the OBG department, as some of the patients who visit this department are pregnant. The majority of drugs included in the formulary were from pregnancy category C followed by category B and category A, of which about 39.34% of drugs were under categories A and B.

Also, a feedback questionnaire, containing 10 questions, was distributed to the medical staff of the obstetrics and gynecology wards. The overall response to the questions showed that the presence of a formulary is incredibly useful.

Selected medicines for the preparation of the Hospital Formulary satisfied the health care needs of the clinicians. The prepared Hospital formulary is unique in its features, as recommended by hospitals' P&T committee to suit its Patient' health care requirements.

Following a prescription investigation at the hospital pharmacy, it was seen that several of the medications in repeated prescriptions were not available, as the result of which patients had no options left but to rely on retail pharmacies outside of the hospital to provide their essentials, while most doctors were unaware of hospital pharmacy being devoid of the most sought after medications. As a result, the hospital formulary ensures that the pharmaceuticals needed by patients arriving at the hospital are available. Furthermore, not all hospitals in India have their formularies. In this world of the advanced health care system, hospitals in India should establish their formulary with an efficient system and P&T committee to achieve rationality in drug use. Numerous medication errors were reported by healthcare providers due to inadequate drug information. Even though our hospital is a teaching center, drug information sources were not sufficiently available for students active in their different wards (nursing, medicine, pharmacies, etc). This is the grounding behind why our department initiated drug information, ADR reporting center, and medication error monitoring as a primary constructive step. Following this further, upon the suggestion of the medical staff of the OBG department, we initiated the establishment of the Hospital Formulary, luckily facilitated with the help of PTC. Equally significant, drug monographs were organized in a way that medical, pharmacy, and nursing students could efficiently promote the concept of rational drug therapy. Not to mention, it also served as an educational tool for them.

Owing to the unsatisfactory information provided by the medical representatives to the physicians, unreasonable prescriptions are written out. To abolish this all, the hospital formulary monographs were created from standard references to provide unbiased information to healthcare professionals. As a result, it provoked the feeling of appreciation of Doctors since it contained a plethora of information about medications, making them aware of all the brands and costs available in the hospital pharmacy, allowing them to prescribe the most cost-effective drug, lowering the total cost of the patients' treatment accordingly.

Conclusion

Hospital formularies are heterogeneous. The prepared Hospital formulary is unique in its features, as recommended by the hospital's P & T committee to suit its patient's health care requirements. Not all hospitals in India have their formularies. In this world of the advanced health care system, hospitals in India should develop their formulary with an effective formulary system and P & T committee to achieve rationality in drug use. P & T committees of the hospitals must implement pharmacoeconomic analysis to select drugs and their products for inclusion into formulary. Pharmaceutical promotion is a delicate area, where it is the responsibility of the hospital's P & T committee to solve if any conflicts in drug products selection and look after that, drug products are selected for the hospital by considering cost, safety, and efficacy. The prepared hospital formulary should be implemented in the hospital with an effective formulary system, which will support and contribute to rationalizing drug use in the hospital., it is informative and will be useful for the health care professionals working in the hospital. By referring to the prepared hospital formulary, prescribers of the hospital can develop of hospital formulary for a rural tertiary care teaching hospital in south India knows about the drugs available in the hospital Pharmacy. Where the prepared pharmaceutical product list can be referred for brand names and other details of the brands approved to use in the hospital. The pharmacy and therapeutics committee of any hospital must be well balanced with active health care professionals like physicians, pharmacists, and nurses. Pharmacists play important role in developing formulary and formulary systems in a hospital. Pharmacist participation in structuring guidelines, policies, and procedures for drug use in the hospital is essential. A well-developed hospital formulary, well-structured policies and procedures for additions and deletions of the drugs from the formulary and to address other drug-related issues in the hospital are essential to run an effective formulary system. Where this in turn gives rise to rational drug use.

Conflict of Interest

The authors declare that they have no conflict of interest.

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ORIGINAL

Evaluation of the menstrual cycle of female infected with SARS-CoV-2 in women aged 36 to 45 years in iranian society

Evaluación del ciclo menstrual de mujeres infectadas con SARS-CoV-2 en mujeres de 36 a 45 años en la sociedad iraní

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Abstract

Introduction: The menstrual cycle's effects on illness susceptibility, development, and severity of acute respiratory syndrome coronavirus 2 (SARSCoV2) infection are poorly understood. It is estimated that more than a third of regularly menstruating women developed irregular cycles during the pandemic, with associated depression, anxiety, and stress. Another study indicates that among patients with confirmed COVID-19, a quarter have altered bleeding.
Methods: The results of real-time reverse transcriptase polymerase chain reaction (RTPCR) tests and symptoms in two women infected with SARSCoV2 are described in this paper.
Results: After being discharged from the hospital, the first patient experienced a fever on the first day of her menstrual period and again on the first day of her following menstrual period. The findings of the RTPCR test were positive during the first menstrual period before to admission, then went negative during hospitalization, and then were positive again during the second menstrual period following release. After being released from the hospital, another woman experienced a fever on the first day of her monthly period. Before admission and during hospitalization, the RTPCR test was negative, but it became positive during the first menstrual period after discharge.
Conclusions: According to the cases, SARSCoV2 infection may be aided by sex hormones. The menstrual status of women who have been exposed to SARSCoV2 should be assessed as part of the care procedure.

Key words: COVID-19, fever, menstrual cycle, SARS-CoV-2.

Resumen

Introducción: Los efectos del ciclo menstrual sobre la susceptibilidad, el desarrollo y la gravedad de la infección por coronavirus 2 del síndrome respiratorio agudo (SARSCoV2) son poco conocidos. Se estima que más de un tercio de las mujeres que menstrúan regularmente desarrollaron ciclos irregulares durante la pandemia, con depresión, ansiedad y estrés asociados. Otro estudio indica que entre los pacientes con COVID-19 confirmado, una cuarta parte tiene sangrado alterado.
Metodología: En este artículo se describen los resultados de las pruebas y los síntomas de la reacción en cadena de la polimerasa con transcriptasa inversa en tiempo real (RTPCR) en dos mujeres infectadas con SARSCoV2.
Resultados: Después de ser dada de alta del hospital, la primera paciente experimentó fiebre el primer día de su período menstrual y nuevamente el primer día de su siguiente período menstrual. Los resultados de la prueba RTPCR fueron positivos durante el primer período menstrual antes de la admisión, luego fueron negativos durante la hospitalización y luego fueron positivos nuevamente durante el segundo período menstrual después del alta. Después de ser dada de alta del hospital, otra mujer experimentó fiebre el primer día de su período menstrual. Antes del ingreso y durante la hospitalización, la prueba RTPCR fue negativa, pero se volvió positiva durante el primer período menstrual después del alta.
Conclusiones: Según los casos, las hormonas sexuales pueden ayudar a la infección por SARSCoV2. El estado menstrual de las mujeres que han estado expuestas al SARSCoV2 debe evaluarse como parte del procedimiento de atención.

Palabras clave: COVID-9, fiebre, ciclo menstrual, SARS-CoV-2.

Introduction

The COVID-19 epidemic is already in its seventh month over the world. Infections with the novel SARS-CoV-2 virus are on the rise globally, with increasing numbers of mortality. International and local public health reactions came almost simultaneously, imposing limits to prevent the virus from spreading, overburdening health systems, and a lack of personal protective equipment.

Since December 2019, the 2019 new coronavirus infection (COVID19), caused by the severe acute respiratory syndrome coronavirus 2 (SARSCoV2), has become a major worldwide health issue. The pandemic had resulted in 9 473 214 illnesses and 484 249 fatalities as of June 27, 2020. 5 A population-level observational investigation by Sun et al 6 found a substantial increase in COVID19 among adults aged 30 to 50 years, with 40% of the patients being female, indicating that women of childbearing age are at high risk of infection. Female immunity appears to alter throughout the menstrual cycle, according to growing research. The menstrual cycle's effects on illness susceptibility, development, and severity of COVID19, on the other hand, remain mainly unclear. We provide the epidemiologic and clinical characteristics of two female SARSCoV2 infected individuals, as well as the infection's relationship to the menstrual cycle.[1]

On January 12, 2020, a 37-year-old lady who had previously been healthy (gravida 2, para 2, regular menstrual cycle, and no history of hormonal therapy) had supper with a relative. Her relative developed a fever five days later and was diagnosed with SARSCoV2. Until the first day of her menstrual period on January 28, 2020, the woman experienced no fever or other gastrointestinal or respiratory symptoms. She had a mild and sporadic fever at initially. She experienced a high fever, fatigue, and a lack of appetite the next day afternoon.

A community physician prescribed ibuprofen, oseltamivir (75 mg every 12 hours orally), arbidol (0.2 g every 8 hours orally), and moxifloxacin (0.4 g every day orally) due to the likelihood of SARSCoV2 infection. Her antiviral regimen was supplemented two days later with lopinavir and ritonavir tablets (200 mg/50 mg every 12 hours orally). Her symptoms persisted, prompting her to visit the emergency department on February 2, 2020. Despite the fact that chest auscultation was normal, chest CT scans revealed bilateral lower lobe infiltrates .

She was recommended ibuprofen, oseltamivir (75 mg every 12 hours orally), arbidol (0.2 g every 8 hours orally), and moxifloxacin (0.4 g every day orally) by a community physician due to the likelihood of infection with SARSCoV2. Her antiviral regimen was supplemented 2 days later with lopinavir and ritonavir tablets (200 mg/50 mg orally every 12 hours). Her symptoms persisted, prompting her to seek medical help on February 2, 2020. Chest computerized tomography (CT) scans revealed bilateral lower lobe infiltrates, despite the fact that chest auscultation was normal .

The patient was admitted to the hospital with COVID19 on February 4, 2020. On admission, the physical examination revealed a body temperature of 97.5 degrees Fahrenheit (36.4 degrees Celsius), blood pressure of 98/61 millimeters of mercury, pulse rate of 78 beats per minute, respiration rate of 20 breaths per minute, and oxygen saturation of 95 percent on room air. Her laboratory tests revealed a Creative protein count of 12.3 mg/L (low risk of cardiovascular disease: 1 mg/L; medium risk of cardiovascular disease: 13 mg/L; high risk of cardiovascular disease: >3 mg/L; and infection or inflammation: >10 mg/L) and an erythrocyte sedimentation rate of 30 mm/H (normal range: 1030 mm/H).

Complete blood count, coagulation tests, liver function tests, kidney function tests, metabolic panel testing, and high-sensitivity cardiac troponin tests did not yield any clinically relevant results. On February 8, 2020, a follow-up chest CT scan revealed that the shadow on both lungs had partially disappeared (Figure 2B). As a result, she was taken off all of her antiviral and antibacterial drugs. Three- and six-days following admission, RTPCR testing for SARSCoV2 nucleic acid on oropharyngeal swabs were done, and the findings were positive.[2]

The oropharyngeal swab RTPCR tests were repeated 10- and 12-days following hospitalization, and both times the results were negative. A subsequent chest CT scan on February 14, 2020, revealed that groundglass opacification had improved even more. During her stay in the hospital, her temperature stayed normal. This patient was discharged on February 18, 2020, based on Iranian hospital discharge criteria, which included (a) a normal temperature for at least three days, (b) resolution of respiratory symptoms, (c) significantly improved radiological signs, and (d) negative results in two consecutive RTPCR tests performed more than or equal to 24 hours apart.[3]

The patient was asked to stay in quarantine at home for another 14 days after being released from the hospital. She felt fine till the first day of her monthly cycle on February 24, 2020. The patient did not report any other interaction, although he did develop a fever, which peaked at 100.2°F (37.9°C). She had no additional symptoms at the time save exhaustion. For three days, she took arbidol (0.2 g orally every 8 hours) and moxifloxacin (0.4 g orally every day). A RTPCR test on February 25, 2020, and a follow-up test on oropharyngeal swabs four days later both came back positive. Chest CT scans, on the other hand, revealed no alterations from the previous results. Until the last day of her menstrual period on February 29, 2020, the patient experienced a minor and intermittent

fever. Her temperature had stayed normal since then. On 10 oropharyngeal swabs, the RTPCR test was done.

A 45-year-old lady working as a nurse in a hospital in Qom, Iran, was previously healthy (gravida 1, para 1, regular menstrual cycle, and no history of hormonal therapy). She developed a mild fever on January 24th, with a high of 100.4°F (38°C) at night . She was prescribed arbidol (0.2 g every 8 hours orally) by a physician due to the likelihood of infection with SARSCoV2 due to occupational contact history. She suffered weariness, muscle discomfort, palpitation, and a lack of appetite on January 26, 2020, the first day of her menstrual period. During her menstrual month, she continued to take arbidol, but her symptoms did not improve. The patient was admitted to a hospital's outpatient department on February 2nd.

Multiple infiltration was seen in the bilateral lung view on chest CT images. A blood test revealed a white blood cell count of 3.88 109/L and a lymphocyte count of 0.94 109/L. Despite the fact that an oropharyngeal swab RTPCR test came back negative, the woman was diagnosed with COVID19 based on her occupational exposure history, symptoms, and chest CT findings. The patient was admitted to the hospital with COVID19 on February 3, 2020. On admission, the physical examination revealed a body temperature of 99.5 degrees Fahrenheit (37.5 degrees Celsius), blood pressure of 105/85 millimeters of mercury, pulse rate of 110 beats per minute, respiration rate of 20 breaths per minute, and oxygen saturation of 94 percent on room air. Her lab tests revealed a Creactive protein concentration of 14.8 mg/L and an erythrocyte sedimentation rate of 40 mm/H. The serum specific IgM antibodies to eight respiratory pathogens, including respiratory syncytial virus, adenovirus, type A and type B influenza virus, parainfluenza virus, Legionella pneumophila, Mycoplasma pneumoniae, and Chlamydia pneumoniae, were found to be negative. After her admission, her temperature returned to normal the next day.

All of her antibacterial meds had been revoked. On February 8, 2020, a follow-up chest CT scan revealed decreasing infiltration in both the left and right lungs . Three, seven, nine-, and eleven-days following admission, RTPCR testing for SARSCoV2 nucleic acid on oropharyngeal swabs were done, and the results were negative. A repeat chest CT scan on February 14, 2020, revealed considerable improvement in infiltration in all lesions . During her stay in the hospital, her temperature stayed normal. The patient was ordered to stay at home for 14 days after being discharged from the hospital on February 18, 2020. She felt fine till the first day of her monthly cycle on February 21, 2020. Her fever returned, this time with weariness and dizziness, reaching 99.3°F (37.4°C). For 5 days, she took arbidol (0.2 g orally every 8 hours) and moxifloxacin (0.4 g orally every day). On February 23, 2020, an RTPCR test for SARSCoV2 nucleic acid on oropharyngeal swabs yielded positive results. Both IgG and IgM antibodies against SARSCoV2 were found in her blood. Chest CT scans, on the other hand, revealed no signs of increasing invasion. The patient had a mild and intermittent fever till February 25, 2020, the day before her menstrual period ended. Her temperature had stayed normal since then. On February 28, 2020, an oropharyngeal swab was tested for RTPCR, and the results were negative.

Discussion and Conclusions

There have been reports of sex variations in infectious illness susceptibility and outcomes. 9 and 10 SARSCoV2 may have a longer incubation period and less apparent symptoms in women than in men, according to a recent epidemiological investigation of the COVID19 outbreak. 11 The mechanism behind these distinctions, however, is unknown. In this paper, we describe two SARSCoV2 infected women whose RTPCR test findings and symptoms altered during their menstrual cycle. After being discharged from the hospital, the first patient experienced a fever on the first day of her menstrual period and again on the first day of her following menstrual period. The RTPCR test was positive during the first menstrual period before admission, turned negative during hospitalization, and then returned to positive during the second menstrual period following release.[4]

After being discharged from the hospital, another woman got a fever on the first day of her menstrual period. Before admission and during hospitalization, the RTPCR test was negative, but it became positive during the first menstrual period after discharge. These findings suggest that sex hormones may play a role in SARSCoV2 infection.

The levels of sex hormones, primarily estrogens and progesterone, fluctuate over the menstrual cycle in female humans and drop rapidly before menstruation. 12 Changes in immunological function and response to respiratory virus infections are linked to substantial fluctuations in sex hormone levels. 13 Estrogen has been shown to be a strong anti-inflammatory hormone that reduces adaptive immune responses and protects hosts from influenza A virus-mediated pathogenesis in an animal model of influenza A virus infection.[5]

Treatment with an oestrogen receptor antagonist or ovariectomy can increase mortality in females in another animal model of SARSCoV infection, demonstrating that oestrogen receptor signaling is important in shielding females against severe SARSCoV infection. 15 in line with earlier research, our findings in this case revealed a strong link between symptoms, positive RTPCR test results, and menstruation. The observations of Chadchan et al. may help to explain this phenomenon. 16 They discovered that in human endometrial stroma,

the expression of angiotensin converting enzyme 2 (ACE2), which allows SARSCoV2 to enter human cells, is high and increases throughout the secretory phase[6&7]. Progesterone also promotes ACE2 expression in the human endometrial stroma. Future research should focus on the role and mechanism of sex hormones in the pathogenesis of SARSCoV2 infection. In the first example, the fever started on the first day of her period and went away on the last day. When menstruation began in the second case, symptoms intensified. These findings show that the menstrual state should be taken into account during the observation period. Rather than symptoms, the findings of RTPCR testing or CT scans should be used to identify potentially infected patients throughout the observation period.[8&9]

During their first menstrual period after being discharged from the hospital, the patients in this study experienced a return of fever and had positive RTPCR test results. Despite the possibility that negative RTPCR test findings during hospitalization are false negatives, 17 there are an increasing number of reports of positive RTPCR test results among COVID convalescent patients 19. 18, 19, 20 These findings show that some of the rehabilitated patients may still be viral carriers. The hospital discharge management strategy may need to be reevaluated, and female patients' menstruation status should be assessed during the 14-day home quarantine period.

Conflict of Interest

The authors declare that they have no conflict of interest.

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ORIGINAL

The effect of intraoperative subcutaneous heparin on prophylaxy of deep vein thrombosis (DVT) in surgical treatment of acetabular fractures

El efecto de la heparina subcutánea intraoperatoria en la profilaxis de la thrombosis venosa profunda (TVP) en el tratamiento quirúrgico de las fracturas acetabulares

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Abstract

Introduction and objective: Thromboembolism after surgery is a significant problem in patients with acetabular fractures. This study aimed to evaluate the effect of intraoperative administration of subcutaneous heparin on prophylaxy of deep vein thrombosis and pulmonary thromboemboli during and after surgery.

Materials and methods: This study is a non-blinded trial in which 42 patients over 18 years old with acetabular fractures who required surgery were divided into two groups matched by age and sex. Patients were randomly assigned to one of two treatment groups: with and without heparin injection during surgery.

Inclusion criteria included patient with unstable posterior coloumn or wall acetabular fractures that open reduction and internal fixatinon was the choice of treatment, patient more than 18 years old underwent this study. Exclusion criteria included a history of heparin-induced allergy and thrombocytopenia, a history of coagulopathy such as hemophilia.

Results: In this study 42 patients with acetabular fractures admitted to the orthopedic ward, 36 patients (85.7%) were male and 6 patients (14.3%) were female with a mean age of 49.2 ± 8.1 years. 20 patients (47.6%) received subcutaneous heparin during surgery and the other 22 patients (52.4%) did not receive heparin. In the group receiving subcutaneous heparin, proximal deep vein thrombosis was observed in one patient, while 5 patients (22.7%) in the group without heparin showed proximal deep vein thrombosis during surgery. There was no significant difference between the mean age of patients and the volume of intraoperative bleeding in the group receiving heparin (700 ± 50 ccs) and the group without heparin (600 ± 50 ccs).

Conclusion: Intraoperative subcutaneous injection of heparin can prevent deep vein thrombosis and pulmonary thromboembolism and reduce patient mortality.Intraoperative injection of subcutaneous heparin was not associated with a significant increase in intraoperative bleeding and had no considerable side effects.

Key words: Acetabular fractures, heparin, thromboembolism, Deep Vein Thrombosis, bleeding heparin.

Resumen

Introducción y objetivo: El tromboembolismo después de la cirugía es un problema importante en los pacientes con fracturas acetabulares. Este estudio tiene como objetivo evaluar el efecto de la administración intraoperatoria de heparina subcutánea en la profilaxis de la trombosis venosa profunda y la tromboembolia pulmonar durante y después de la cirugía.

Material y métodos: Este estudio es un ensayo no ciego en el que 42 pacientes mayores de 18 años con fracturas acetabulares que requerían cirugía fueron divididos en dos grupos emparejados por edad y sexo. Los pacientes fueron asignados aleatoriamente a uno de los dos grupos de tratamiento: con y sin inyección de heparina durante la cirugía. Los criterios de inclusión incluían a los pacientes con fracturas acetabulares inestables de la columna o la pared posterior cuyo tratamiento elegido era la reducción abierta y la fijación interna; los pacientes mayores de 18 años se sometieron a este estudio. Los criterios de exclusión incluían antecedentes de alergia a la heparina y trombocitopenia, y antecedentes de coagulopatía, como la hemofilia.

Resultados: En este estudio 42 pacientes con fracturas acetabulares ingresados en la sala de ortopedia, 36 pacientes (85,7%) eran hombres y 6 pacientes (14,3%) eran mujeres con una edad media de 49,2 ± 8,1 años. 20 pacientes (47,6%) recibieron heparina subcutánea durante la cirugía y los otros 22 pacientes (52,4%) no recibieron heparina. En el grupo que recibió heparina subcutánea, se observó trombosis venosa profunda proximal en un paciente, mientras que 5 pacientes (22,7%) del grupo sin heparina mostraron trombosis venosa profunda proximal durante la cirugía. No hubo diferencias significativas entre la edad media de los pacientes y el volumen de hemorragia intraoperatoria en el grupo que recibió heparina (700 ± 50 cc) y el grupo sin heparina (600 ± 50 cc).

Conclusiones: La inyección subcutánea intraoperatoria de heparina puede prevenir la trombosis venosa profunda y el tromboembolismo pulmonar y reducir la mortalidad de los pacientes.La inyección intraoperatoria de heparina subcutánea no se asoció a un aumento significativo de la hemorragia intraoperatoria y no tuvo efectos secundarios considerables.

Palabras clave: Fracturas acetabulares, heparina, tromboembolismo, trombosis venosa profunda, sangrado Heparina.

Introduction

Treatment of pelvic and acetabular fractures remains a challenge[1-3]. Venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE) is a complication associated with these fractures[4,5]. Studies have shown that in the absence of thromboprophylaxis, the incidence of DVT in patients with pelvic fractures is variable up to 61%[6]. Deep vein thrombosis is the most common cause of death of lower limb fractures (hip and pelvis) after the seventh day of addmition.

In most of these patients, PE was difficult to diagnose before death, suggesting that PE may be the first manifestation of asymptomatic DVT[7]. Each year, about 10 million cases of venous thromboembolism are reported worldwide[8]. According to a Korean study in 1990 on the autopsy of patients undergoing spinal surgery, deep vein thrombosis accounted for 1.3% of deaths[9]. Patients can be classified according to their age, the presence or absence of other risk factors for VTE, and the type of surgery to be performed. Patients at lower risk of VTE require no special treatment but prophylaxy of DVT is needed as soon as possible , while patients at moderate or higher risk of DVT[10].

Patients with pelvic trauma are at risk for thromboembolic complications, but effective guidelines have still to be adopted[11]. A variety of thromboprophylaxis drugs are recommended in high-risk trauma patients. Low-dose heparin or intermittent pneumatic compression devices alone are not always effective in preventing DVT[12,13], whereas low molecular weight heparin (LMWH) has been shown to decrease DVT rates in patients with pelvis or lower limbs fractures[11]. Anticoagulants, such as unfractionated heparin (UFH), low molecular weight heparin (LMWH), and warfarin, or antiplatelet agents, especially acetylsalicylic acid (aspirin), are pharmacological agents used for thromboprophylaxis. Prophylaxis of DVT is usually done with low-dose heparin (LDH). First, a subcutaneous dose of 5,000 units is injected 2 hours before surgery and repeated every 12 hours for up to 6 days. This method produces a good preventive effect in most patients[14].

According to the literature and the predictable risk, anticoagulant therapy should be started as soon as possible. In a study by O'Donnell et al., low molecular weight heparin (LMWH) or warfarin was suggested as the treatment of choice for patients with spinal cord anesthesia and all patients with major trauma[15]. The results of a study by Wang et al showed that the risk of developing DVT is higher in patients older than 60 years, patients with trauma, patients with associated injuries, and surgery after 2 weeks in nonambulate multi trauma patients[16]. Steele et al.[17] reported that LMWH if initiated without delay, is a safe and effective method of thromboprophylaxis in high-risk patients with major pelvic or acetabular fractures. If remains unrecognized, DVT can lead to long-term complications from post-phlebitic (post-thrombotic) syndrome and predispose patients to recurrent VTE[10]. Because VTE in hospitalized patients is often asymptomatic, it is inappropriate to rely on early detection. In addition, non-invasive tests, such as ultrasound, have limited sensitivity for the diagnosis of asymptomatic DVT. Therefore, thromboprophylaxis is the most effective strategy to reduce morbidity and mortality from VTE in surgical patients. Despite this evidence, thromboprophylaxis is not used in clinical practice as surgeons believe that the risk of VTE is much lower to justify the potential hemorrhagic complications from the use of anticoagulants[18]. Despite the use of preoperative prophylaxis, patients are predisposed to DVT due to prolonged prone position, prolonged surgery time, and the use of blood transfusions. this study was the first to evaluate the effect of intraoperative administration of subcutaneous heparin on the surgical complications of acetabular fractures, including venous thrombosis, mortality, intraoperative bleeding, etc.

Materials and methods

This study aimed to evaluate the effect of intraoperative administration of subcutaneous heparin on the surgical complications of acetabular fractures. The study population included patients with acetabular fractures admitted to the orthopedic ward of Imam Khomeini Hospital affiliated with the Urmia University of Medical Sciences. The number of people in each group was determined to be 33 based on the following formula. Convenience sampling was used in this study.

$$n=\frac{(Z_{1-\alpha/2}+Z_{1-\beta})^2\,[P_1(1-P_1)+P_2(1-P_2)}{(P_1-P_2)^2}$$

$Z1-\beta=0.84$, $Z1-\alpha/2=1.64$

Method

This study is a non-blinded trial in which 42 patients over 18 years old with acetabular fractures who required surgery were divided into two groups matched by age and sex. Inclusion criteria included individuals with acetabular fractures with posterior involvement who required surgery, individuals over 18 years of age, and consent to participate in the study. Exclusion criteria included a history of heparin-induced allergy and thrombocytopenia, a history of coagulation disorders, and a history of hemophilia and thalassemia. Based on the codes provided by Random Allocation software, the patients were randomly assigned to one of two treatment groups: the group with heparin injection and the group without heparin injection. For

patients treated with subcutaneous heparin, 5.000 units of heparin were injected subcutaneously before the surgical incision and after placing the patients in the prone position, while no anticoagulants were injected into the other group. Depending on the surgical site and patient's condition, the patients underwent a certain form of general anesthesia. Patients with primary embolism thrombosis and preoperative venous thrombosis were excluded from the study. According to common treatment methods, all patients should receive anticoagulants, including subcutaneous enoxaparin and antithrombotic stockings, from the time of admission and after surgery. Patients undergoing surgery in the prone position (lying on the abdomen) were placed in a group undergoing intraoperative prophylaxis with 5.000 units of subcutaneous heparin. The two groups were compared for complications including venous thrombosis, mortality, morbidity, intraoperative cardiovascular findings, intraoperative hemorrhage -estimated based on the amount of blood collected in the suction tank and the number of blood-soaked gauzes- and postoperative hemorrhage - estimated based on the volume of the Hemovac reservoir. After surgery, patients were visited daily and were evaluated for clinical symptoms including swelling, erythema, and pain in the lower extremities. In the case of clinical evidence, the patients were further evaluated using color Doppler ultrasound. All patients underwent color Doppler ultrasound on day 14 after surgery for deep vein thrombosis of the lower extremities. Data collection tools in the present study included checklists and a review of patient records.

Statistical analysis

Descriptive statistical methods were used in this study. Frequency analysis test (chi-square) was used to compare qualitative data and statistical analytical methods (independent t-test) were used to compare quantitative data between the two groups. Statistical analysis was performed using SPSS17/win software and a P-value less than 0.05 was considered significant.

Results

This study included 42 patients with acetabular fractures admitted to the orthopedic ward of Imam Khomeini Hospital affiliated to the Urmia University of Medical Sciences, of which 20 patients (47.6%) received subcutaneous heparin and other 22 patients (52.4%) did not receive heparin during surgery. The results showed that 85.7% of patients with acetabular fractures were males and 14.3% were females. The mean age of the patients was 49.2 ± 8.1 years. The results of the Fisher test showed that there was no significant difference between the sexes of patients with acetabular fractures admitted to the orthopedic ward in different study groups (the group receiving subcutaneous heparin and the group without heparin during surgery) ($P < 0.05$). Therefore, male and female participants were matched between the two groups. The comparison results for the frequency of mortality, the frequency of proximal deep vein thrombosis (iliac and femoral), and drug side effects in patients with acetabular fractures between the two groups are presented in **table I**.

The results of the t-test showed that there was a significant difference in patients' mean age between the two groups (subcutaneous heparin receiving group and non-receiving group during surgery) ($P < 0.05$). Also, there was a significant difference in the mean intraoperative bleeding volume estimated in the group receiving heparin (700 ± 50 ccs) and the group without heparin (600 ± 50 ccs) during surgery ($P < 0.05$). However, no significant difference in the mean bleeding volume estimated in Hemovac was found between the two groups (300 ccs vs. 250cc, respectively) ($P < 0.05$). Moreover, no significant difference was also observed in the other variables (hospitalization time/ post-operative bleeding in Hemovac, cc/ heartrate / systolic hypertension / diastolic hypertension) between the two groups of subcutaneous heparin receiver and non-receiver during surgery. (**Table II**).

Discussion

The present study evaluated the effect of intraoperative administration of subcutaneous heparin on the surgical complications of acetabular fractures in patients admitted to Imam Khomeini Hospital. In the study of Wang et al[16] to investigate the incidence and risk factors of deep vein thrombosis (DVT) in patients with pelvic and acetabular fractures, thirty-two (29.09%) patients sustained DVT, twenty-one (19.09%) patients showed proximal thrombosis, and three patients developed pulmonary embolism. Steele et al[18] evaluated the outcome of a prophylaxis protocol for deep vein thrombosis (DVT) in 103 patients who underwent open reduction and internal fixation of pelvic and acetabular fractures. Low molecular weight heparin (LMWH) was administered within 24 hours of injury or in hemodynamically stable patients. The incidence of proximal DVT and pulmonary embolism was 10% and 5%, respectively. Proximal DVT occurred in 2 of 64 patients (3%) who received LMWH within 24 hours of injury and also in 8 of 36 patients (22%) who received LMWH more than 24 hours after injury. In the present study, lower extremity color Doppler ultrasound was performed for patients with clinical evidence of deep vein thrombosis and for all patients on a postoperative day 14. According to the results of this study, there was no significant difference between the mean age of patients and the volume of intraoperative bleeding in the group receiving subcutaneous heparin and the group without heparin ($P<0.05$). Although previous studies have reported that patients over 30 are

Table I: Comparison of the frequency of mortality, proximal deep vein thrombosis, and drug side effects between the two groups.

	Group	Yes	No	Total
Mortality	Intraoperative heparin No intraoperative heparin	0 (0%) 2 (9.1%)	20 (100%) 20 (90.9%)	20 (100%) 22 (100%)
P-value		0.489		
Proximal deep vein thrombosis	Intraoperative heparin No intraoperative heparin	1 (5%) 5 (22.7%)	19 (95%) 17 (77.3%)	20 (100%) 22 (100%)
P-value		0.04		
Drug side effects	Intraoperative heparin No intraoperative heparin	0 (0%) -	20 (100%) -	20 (100%) -

Table II: Research variables between the subcutaneous heparin receiving and non-receiving groups during surgery.

Variable	Group	N	Mean	SD	t-value	P-value
Age	intraoperative heparin No intraoperative heparin	20 22	47.4 52.4	7.4 6.5	2.31	0.026
Time of hospitalization	intraoperative heparin No intraoperative heparin	20 22	5.85 6.63	1.49 1.17	1.9	0.064
Intraoperative bleeding, cc	intraoperative heparin No intraoperative heparin	20 22	3.2250E2 2.8091E2	54.95213 61.01593	2.31	0.026
Post-operative bleeding in Hemovac, cc	intraoperative heparin No intraoperative heparin	20 22	91.2500 88.1818	9.01388 7.7988	1.18	0.244
Heart rate	intraoperative heparin No intraoperative heparin	20 22	91.2 92	7.24460 6.02376	0.39	0.698
Systolic hypertension	intraoperative heparin No intraoperative heparin	20 22	122.7 123.6	12.29 12.55	0.231	0.819
Diastolic hypertension	intraoperative heparin No intraoperative heparin	20 22	87.5 86.9	6.78 6.83	0.281	0.78

at higher risk of developing DVT[19], some studies have found no association between DVT and patient age[20]. However, older age is often considered one of the factors associated with the higher risk for DVT[21]. Similarly, Kim et al[22] reported a significant increase in DVT rates in patients with pelvic and acetabular fractures over 50 years of age. Therefore, elderly patients with pelvic acetabular fractures should be evaluated more precisely for DVT.

One of the reasons for the high prevalence of DVT in patients is the failure of effective anticoagulant therapy in the early periods after the injury due to the risk of bleeding[19]. For patients undergoing acetabular fracture surgery, ACCP guidelines recommended the use of LMWH, low-dose UFH, VKA, fondaparinux, aspirin (all grade 1B), or IPCD (grade 1C) for at least 10 to 14 days and up to 35 days[23]. There is a limited number of studies comparing different pharmacologic agents and the results of these studies have not yet clarified which thromboprophylaxis agent is preferred[24,25]. The incidence of DVT was 10% in the LMWH group versus 30% in the dextran 70 groups. The need for postoperative injection was higher in the Dextran 70 group, but there were no other differences in bleeding complications between the two groups. Gerhart et al[26] found lower DVT rates with the same LMWH (Org 10172) versus warfarin (7% and 21%, respectively) but there was no significant difference in PE or major bleeding complications. It is difficult to interpret the results of these comparative studies because of different medication doses, dosing regimens, population data, rehabilitation protocols, and methods for diagnosing thromboembolic phenomena. Previous studies included both symptomatic and asymptomatic DVT since most of or all patients underwent postoperative imaging. These studies also included distal DVT, which has been found to have little clinical significance in the progression of PE compared with proximal DVT[27].

Conclusion

In acetabular fracture surgeries, prone positioning of the patients during surgery and prolonged surgical time make the patient more prone to DVT and eventually pulmonary thromboembolism. Therefore, intraoperative subcutaneous heparin, can prevent deep vein thrombosis and pulmonary thromboembolism and reduce patient mortalityas well as not significantly increasing the patient's intraoperative bleeding and having no specific drug side effects.

Conflict of interest

The authors declare that they have no conflict of interest.

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ORIGINAL

Quantitative digito-palmar dermatoglyphics analysis in essential hypertension in a Nigerian population

Análisis cuantitativo de los dermatoglifos digito-palmares en la hipertensión esencial en una población nigeriana

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Abstract

Background: Hypertension is estimated to affect over a billion people globally, with that number likely to rise to 1.56 billion by 2025. Palmer dermatoglyphic is a non-invasive scientific study of epidermal ridges of the volar surfaces of the hands which is currently finding relevance in the management of gene-linked diseases.
Objectives: The goal of this study was to explore the relevance of quantitative palmar dermatoglyphic parameters in predicting the likelihood of developing essential hypertension in the study population.
Methods: The study was carried out with a total sample of 200 respondents consisting of 100 essential hypertensive and 100 normotensive individuals between the age group of 20-70 years. Interviewer administered structured questionnaire was used to collect relevant information from participants. Finger and palm prints were obtained through the use of CanoScan LiDE 300 scanner. Collected data were statistically analyzed using Statistical Package for the Social Science (SPSS) version 26.0 at a significance level of $p<0.05$. Results: The results obtained in this study showed that a-b ridge count in both hands was significantly lower ($p<0.05$) in the test group (34.61±3.550) compared to the control (41.83±5.019). Likewise the left atd angle of the test group (40.84) was significantly lower ($p<0.05$) compared to the control (42.54).
Conclusion: The findings in this study suggested that a significant association exists between palmer dermatoglyphic features and essential hypertension predicting the possibility of being a veritable tool in identifying those who are at higher risk of developing essential hypertension very early thereby allowing for targeted preventive measures.

Key words: Hypertension, Palmer dermatoglyphic, epidermal ridges.

Resumen

Antecedentes: Se calcula que la hipertensión afecta a más de mil millones de personas en todo el mundo, y es probable que esa cifra aumente a 1.560 millones en 2025. El dermatoglifo de Palmer es un estudio científico no invasivo de las crestas epidérmicas de las superficies volares de las manos que actualmente está encontrando relevancia en el tratamiento de enfermedades vinculadas a los genes.
Objetivos: El objetivo de este estudio fue explorar la relevancia de los parámetros dermatoglíficos palmares cuantitativos en la predicción de la probabilidad de desarrollar hipertensión esencial en la población de estudio. Métodos: El estudio se llevó a cabo con una muestra total de 200 encuestados, compuesta por 100 hipertensos esenciales y 100 normotensos con edades comprendidas entre los 20 y los 70 años. Se utilizó un cuestionario estructurado administrado por un entrevistador para recoger la información pertinente de los participantes. Las huellas dactilares y palmares se obtuvieron mediante el uso del escáner CanoScan LiDE 300. Los datos recogidos se analizaron estadísticamente con el Paquete Estadístico para las Ciencias Sociales (SPSS) versión 26.0 a un nivel de significación de $p<0,05$.
Resultados: Los resultados obtenidos en este estudio mostraron que el recuento de crestas a-b en ambas manos fue significativamente menor ($p<0,05$) en el grupo de prueba (34,61±3,550) en comparación con el control (41,83±5,019). Asimismo, el ángulo atd izquierdo del grupo de prueba (40,84) fue significativamente menor ($p<0,05$) en comparación con el control (42,54).
Conclusión: Los hallazgos de este estudio sugieren que existe una asociación significativa entre las características dermatoglíficas de la palma de la mano y la hipertensión esencial, lo que predice la posibilidad de ser una verdadera herramienta para identificar a aquellos que tienen un mayor riesgo de desarrollar hipertensión esencial de forma muy temprana, permitiendo así medidas preventivas específicas.

Palabras clave: Hipertensión, dermatoglifo de Palmer, crestas epidérmicas.

Introduction

The scientific study of epidermal ridges and their arrangement on the volar surface of the hands, fingers, feet, and toes is known as dermatoglyphics[1]. Dermatoglyphics is derived from the Greek words "Derma" (skin) and "glyphic" (carvings)[2]. The majority of dermatoglyphic features are formed in the womb between weeks 17 and 24 and do not alter throughout a person's life[1]. Any form of growth disruption during the early stages of fetal life development might result in an aberrant dermatoglyphic pattern[3]. Dermatoglyphics has long been a valuable method for identifying gene-related abnormalities and disorders. A dermatoglyphic relationship has been found in a number of studies to be associated with a wide range of genetic diseases[4].

Essential hypertension is described as persistently high blood pressure that is caused by a combination of genetic and environmental variables. For example, siblings of hypertensive parents or parents are more likely to acquire hypertension later in life[4]. Essential hypertension can go unnoticed for a long time, but it can eventually lead to changes in artery elasticity, ocular lesions, and occasionally irreversible damage including myocardial infarction and apoplexy. Essential hypertension is defined by a systolic blood pressure of more than 140 mmHg and a diastolic blood pressure of more than 90 mmHg for a prolonged period of time. Dermatoglyphics is an advanced branch of medical research in which practitioners analyze skin ridge patterns to help detect chromosomal and other medical abnormalities[5]. Several investigations have found a link between dermatoglyphic characteristics and hypertension. Given these findings, it's been hypothesized that the likelihood of developing hypertension later in life is linked to the development of dermatoglyphic features during the first trimester. If this hypothesis is proven, dermatoglyphic indicators could be utilized to screen out people who are at risk of becoming hypertensive[6]. Given the high mortality and morbidity rates associated with essential hypertension worldwide, particularly in Nigeria, the goal of this study is to see if the palmar dermatoglyphics pattern may be utilized to predict individuals at risk of developing essential hypertension in Ondo State, Nigeria.

Table I: Classification of blood pressure according to the ESC (European Society of Cardiology) Guidelines

Category	Systolic (mmHg)	Diastolic (mmHg)
Optimal	<120	<80
Normal	120-129	80-84
High normal	130-139	85-89
Grade 1 hypertension	140 – 159	90 -99
Grade 2 hypertension	160 – 179	100 – 109
Grade 3 hypertension	>= 180	>=110
Isolated systolic hypertension	>=140	<90

(Niebauer, *et al*., 2018)[12].

Materials and Methods

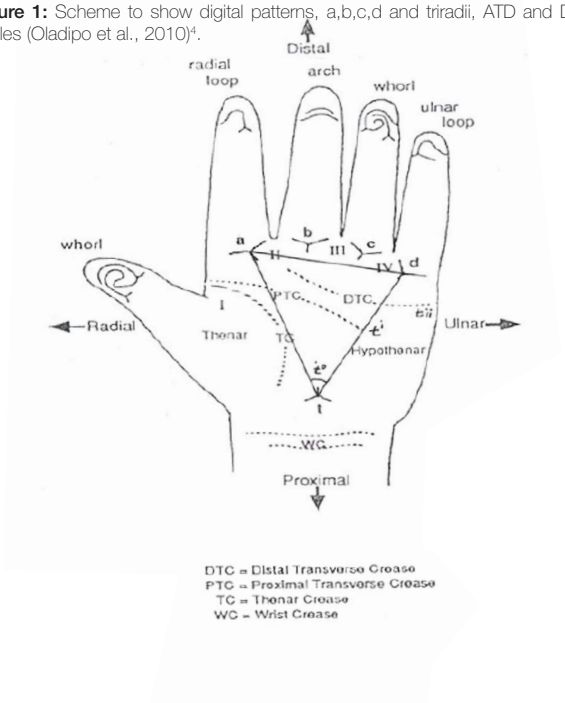
This is a cross-sectional observational study. The study was conducted at Federal Medical Centre, Owo, Ondo State, Nigeria and Oluwarotimi Specialist and Daignostic Centre Akure, Ondo State. This study was carried out with a total sample of 200 adult human subjects. The subjects were divided into two disjoint groups; test group (TG) [100 essential hypertensive patients (50 Males and 50 females) between the age group of 20-70 years] and control group (CG) [100 normotensive individuals (50 Male and 50 Female) between the age group of 20-70years].

Inclusion criteria: 1. Known essential hypertensive or newly diagnosed essential hypertensive by a competent clinician whether on treatment or not whose age is between 20 -70 years. 2. Normotensive individuals who has never been diagnosed of any form of hypertension and whose blood pressure was within normal limit and not below 20years or above 70 years.

Exclusion criteria: People with deformities and deep burns of fingers and palm, people below the age of 20 and above 70 years and people who were critically ill.

The palm prints were taken with a palm print scanner. The participants were asked to clean their hands to remove any dirt that may be associated with the skin ridges and place it on the electronic palm scanner. The palm prints were captured with the scanner and projected to the screen of the laptop connected to it. The palm prints were studied quantitatively for palmar angle parameters [Axial triradius (atd) and Digital triradius (dat) angles) using an AutoCAD software (**Figure 1**).

Figure 1: Scheme to show digital patterns, a,b,c,d and triradii, ATD and DAT angles (Oladipo et al., 2010)[4].



Data collection was done within the period of March 2021 to May 2021. Using a well-structured interviewer administered questionnaire, in which personal information, parameters investigated and blood pressure of participants were recorded. The questionnaire was divided into three sections A, B and C. Section A contained the bio-data of the subject, section B contained health related data and section C contained palmar dermatoglyphics data of the subject which were analysed.

Ethical Consideration

Ethical approval for the study was obtained from Federal Medical Centre, Owo, Ondo State, Nigeria with the reference number: FMC/OW/380/VOL.CX/162. Informed consents was taken from individual persons, explanations about the purpose of the research was given to them.

Blood Pressure Measurement

A digital Sphygmomanometer was used to measure blood pressure. The subject was asked to sit on a chair with feet flat on the floor and arm on the table at heart height. The cuff was wrapped around the upper arm, about 2-3 cm above the elbow, directly against the skin. The start button was pressed and machine was allowed to record measurement. The individual stayed still and did not move his/her arm until the measurement was complete. The arm cuff was completely deflated and removed after measurement. The systolic and diastolic values were recorded in mmHg and the sphygmomanometer was turned off.

Palmar Dermatoglyphics Parameters

CanoScan LiDE 300 scanner version 1.5.0 was used to obtain the fingerprint of individuals. The right and left hands of the respondent were cleaned and placed gently on the screen of the scanner which was connected to a HP Folio 13-laptop computer and a digital image of the hands were obtained. The lid of the scanner was closed when scanning to minimize undesirable stray of light. The scanned images were immediately coded with an ID number. Palm angles were measured using AutoCAD software. The a-b ridge counts were determined by counting the number of ridges that cross a straight line drawn from a' triradius (at the base of index finger) to 'b' triradius (at the base of middle finger) of the palm in each hand.

Data were analyzed using the Statistical package for social sciences (SPSS) software version 26.0. Descriptive variables such as age, gender, anthropometric measurements and dermatoglyphic values were presented as frequencies, percentage and means (±standard deviation). The independent Student's t-test was used to determine significant differences between means of quantitative variables. The P value was regarded as significant at $P<0.05$ at a confidence interval of 95%.

Results

Results of the study were presented in **tables II-XII**. **Table II** shows the biodata of respondents. The means age of the test group was 48.67±14.70 while that of the control was 39.43±13.87. The mean Body Mass Index (BMI) of the test group was 25.18±6.51 and that of the control was 22.69±4.28.

Table III shows the a-b ridge count of respondent among test and control group. The mean of right a-b ridge count in the control group (41.83±5.019) was significantly ($p<0.001$) higher than the test group (34.61 ±3.550). The mean of left a-b ridge count in the control group (40.91±4.907) was significantly ($p<0.001$) higher than the test group (34.39±3.038).

Table IV shows the a-b ridge count of male respondent among the test and control group. The mean of right a-b ridge count and left a-b ridge count were significantly ($p<0.001$) higher in the control group than the test group.

Table V shows the a-b ridge count of female respondent among the test and control group. The right a-b ridge count was statistically ($p<0.001$) higher in the control group (42.56±4.949) than the test group (34.96±3.301). The left a-b ridge count was significantly ($p<0.001$) higher in the control group (41.46±5.504) than test group (34.64±2.884).

Table VI shows the a-b ridge count between male and female test group. There was no significant difference in the a-b ridge count among the genders.

Table VII shows the a-b ridge count between male and female control group. There was no significant difference in the a-b ridge count among the genders.

Table VIII shows the palmar angles of respondent. The left atd angle was significantly higher in the control group than the test group. There was no significant difference in the right atd angle, right dat angle and left dat angle in the test and control group among the genders.

Table IX shows the palmar angles between male and female test group. The right atd angle was significantly ($p=0.032$) higher in females (42.66±6.573) than in males (40.20±4.562). The left atd angle was significantly ($p=0.005$) higher in females (42.34±5.770) than in males (39.34±4.706). However, there was no significant difference in the right dat angle and left dat angle among the genders.

Table X shows the palmar angle between male and female control group. There was no statistical significant

difference in the palmar angle among the male and female control group.

Table XI shows the palmar angle between female respondent among the test and control group. There was no statistical significant difference in the palmar angle (atd and dat angles) of females among the test and control group.

Table XII shows the palmar angle between male respondent among the test and control group. The left atd angle was significantly higher in the control group (41.8±5.460) than the test group (39.34±4.706). However, there was no significant difference in the right atd angle, right dat angle and left dat angle among the test and control group.

Table II: Showing the Age distribution and Body Mass Index of respondents.

Parameters	Test group (n=100)	Control group (n=100)	Total (n=200)
Age (Yrs)	48.67(14.70)*	39.43(13.87)*	44.05(14.99)*
20-30	15	28	43
31-40	13	29	42
41-50	21	21	42
51-60	26	11	37
61-70	25	11	36
BMI (Kg/m^2)	25.18(6.5)*	22.69(4.28)*	23.93(5.66)*

[mean (SD)]*

Table III: a-b ridge count of respondent.

Parameters	Test Group N=100		Control Group N=100		P value
	Mean	SD	Mean	SD	
Right a-b	34.61	3.55	41.83	5.019	<0.001
Left a-b	34.39	3.038	40.91	4.907	<0.001

*

Table IV: a-b ridge count of male respondent.

Parameters	Male N=100				P value
	Test Group N=50		Control Group N=50		
	Mean	SD	Mean	SD	
Right a-b	34.26	3.784	41.10	5.032	<0.001
Left a-b	34.14	3.194	40.36	4.213	<0.001

*

Table V: a-b ridge count of female respondent.

Parameters	Female N=100				P value
	Test Group N=50		Control Group N=50		
	Mean	SD	Mean	SD	
Right a-b	34.96	3.301	42.56	4.949	<0.001
Left a-b	34.64	2.884	41.46	5.504	<0.001

*

Table VI: a-b ridge count of test group.

Parameters	Test Group N=100				P value
	Male N=50		Female N=50		
	Mean	SD	Mean	SD	
Right a-b	34.26	3.784	34.96	3.301	0.327
Left a-b	34.14	3.194	34.64	2.884	0.413

*

Table VII: a-b ridge count between male and female control group.

Parameters	Control Group N=100				P value
	Male N=50		Female N=50		
	Mean	SD	Mean	SD	
Right a-b	41.10	5.032	42.56	4.949	1.470
Left a-b	40.36	4.213	41.46	5.504	0.265

*

Table VIII: Palmar angles of respondent.

Parameters	Test Group N=100		Control Group N=100		P value
	Mean	SD	Mean	SD	
Right atd	41.43	5.763	42.63	6.483	0.168
Left atd	40.84	5.4517	42.54	5.704	0.032
Right dat	59.10	5.526	58.73	5.380	0.632
Left dat	59.35	5.876	58.06	5.169	0.101

*

Table IX: Palmar angles between male and female test group.

Parameters	Test Group N=100				P value
	Male N=50		Female N=50		
	Mean	SD	Mean	SD	
Right atd	40.20	4.562	42.66	6.573	0.032
Left atd	39.34	4.706	42.34	5.770	0.005
Right dat	60.34	4.939	57.86	5.845	0.240
Left dat	60.02	6.146	58.68	5.575	0.256

*

Table X: Palmar angle between male and female control group.

Parameters	Control Group N=100				P value
	Male N=50		Female N=50		
	Mean	SD	Mean	SD	
Right atd	41.62	6.315	43.64	6.555	0.120
Left atd	41.84	5.460	43.24	5.909	0.221
Right dat	58.86	5.139	58.60	5.660	0.810
Left dat	58.50	4.791	57.62	5.536	0.397

*

Table XI: Palmar angle between of female respondent.

Parameters	Female N=100				P value
	Test Group N=50		Control Group N=50		
	Mean	SD	Mean	SD	
Right atd	42.66	6.573	43.64	6.555	0.457
Left atd	42.34	5.770	43.24	5.909	0.443
Right dat	57.86	5.845	58.60	5.660	0.522
Left dat	58.68	5.575	57.62	5.536	0. 342

*

Table XII: Palmar angle between of male respondent.

Parameters	Male N=100				P value
	Test Group N=50		Control Group N=50		
	Mean	SD	Mean	SD	
Right atd	40.20	4.562	41.62	6.315	0.200
Left atd	39.34	4.706	41.84	5.460	0.016
Right dat	60.34	4.939	58.86	5.139	0.145
Left dat	60.02	6.146	58.50	4.791	0.171

*

* *[Data expressed as mean and SD. P-value < 0.05 was considered as statistically significant]*

Discussion

A number of studies have found that dermatoglyphic features are linked to essential hypertension. The importance of dermatoglyphics is not to diagnose an illness that has already occurred, but to avoid sickness by identifying people who have a hereditary susceptibility to specific diseases[7]. The present study consist of 200 (100 males and 100 females) Nigerian adults who were selected randomly irrespective of their ethnic groups.

In this study, the mean a-b ridge count in the control group was significantly ($p<0.001$) higher than the test group. This is similar to a study conducted in India by Devi et al.[8] who reported that a significant difference was observed between hypertensive and control group in their a-b ridge counts where control group found to have significantly higher a-b ridge counts than hypertensive patients.

In males, the mean of right and left a-b ridge count was significantly ($p<0.001$) higher in the control group than the test group. This was similar to the study by Tafazoli et al.9 in Iran where it was observed that in male group, the mean a-b ridge count was less in patients than in healthy people. In females, the mean of right and left a-b ridge count was significantly ($p<0.001$) higher in the control group than the test group. This was contrary to a similar study by Tafazoli et al.[9] in Iran where it was observed that there was no significant difference in the a-b ridge count of both hands of female test and control groups. The difference observed in this study may be due either to the varying sample size or racial and ethnic variation.

In the present study, the left atd angle was significantly higher in the control group than the test group, however, there was no significant difference in the right atd angle. This is contrary to a study by Nancy et al.[10] in India whereby it was reported that the mean atd angle in hypertensive patients for both hands was statistically significantly higher than controls. In males, the left atd angle was significantly higher in the control group (41.8±5.460) than the test group (39.34±4.706). This is similar to the study of Devi et al.8 whereby it was observed that in males, controls have higher 'atd' value than patients (Means = 47.57 and 45.22 respectively).

There was no statistical significant difference in the atd angles of females among the test and control group. This is contrary to the study done in Iran by Tafazoli et al.9 whereby it was stated that in females, atd angle was significantly higher in the test group than the control group.

In the test group, the right atd angle was significantly ($p=0.032$) higher in females (42.66±6.573) than in males (40.20±4.562). The left atd angle was significantly ($p=0.005$) higher in female test group (42.34±5.770) than male test group (39.34±4.706). This is contrary to the study done by Deepa[11] in India who observed decreased atd value for both sexes in hypertensive patients.

In the present study, there was no significant difference in the right and left dat angle in the test and control group among the genders. In males, there was no significant difference in the dat angle among the test and control group. This is similar to the study of Devi et al.[8] whereby it was reported that no significant difference was observed between groups and hands (left and right) for mean of 'dat' angles in males.

There was no statistical significant difference in the palmar angle among the male and female control group. This is similar to the study of Oladipo et al.[4] whereby it was reported that no significant difference was found in the DAT angle between male and female control group.

The results obtained in this study shows a definite association exists between palmar dermatoglyphics and essential hypertension. a-b ridge count and atd angle are lesser in essential hypertensive population compared to normal people. Thus, measurement of a-b ridge count can be used as a reliable predictive tool in early identification of individuals who are at higher risk of developing essential hypertension and preventive measures can be undertaken to prevent the occurrence of essential hypertension in those at risk.

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ORIGINAL

Relationship of muscle stretching exercise with reducing fatigue in renal failure patients chronic

Relación del ejercicio de estiramiento muscular con la reducción de la fatiga en pacientes con insuficiencia renal crónica

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Abstract

Introduction: Chronic kidney failure is a failure of kidney function to maintain metabolism and fluid and electrolyte balance. Fatigue is one of the most frequent complaints of hemodialysis patients.
Objective: The purpose of this study was to determine the relationship between muscle stretching exercises and decreased fatigue in chronic renal failure patients undergoing hemodialysis.
Methods: This type of research is quantitative with cross-sectional. The population in this study was 140 patients who were taken using the purposive sampling technique and 28 patients were obtained as the sample. Analysis of this study using the Pearson test.
Results: Pearson test results with a p-value of 0.000 <0.05 so that the conclusion is that there is a training relationship stretching of this muscle with decreased fatigue in chronic renal failure patients undergoing hemodialysis.
Conclusion: There is a relationship between muscle stretching exercises and decreased fatigue in chronic renal failure patients undergoing hemodialysis.

Key words: Fatigue, stretching, chronic kidney failure.

Resumen

Introducción: La insuficiencia renal crónica es un fallo de la función renal para mantener el metabolismo y el equilibrio de líquidos y electrolitos. La fatiga es una de las quejas más frecuentes de los pacientes en hemodiálisis.
Objetivo: El propósito de este estudio fue determinar la relación entre los ejercicios de estiramiento muscular y la disminución de la fatiga en pacientes con insuficiencia renal crónica sometidos a hemodiálisis.
Metodología. Este tipo de investigación es cuantitativa con corte transversal. La población de este estudio fue de 140 pacientes que se tomaron mediante la técnica de muestreo intencional y se obtuvieron 28 pacientes como muestra. El análisis de este estudio se realizó mediante el test de Pearson.
Resultados: Los resultados de la prueba de Pearson con un valor p de 0,000 <0,05 por lo que la conclusión es que existe una relación entre el entrenamiento de estiramiento de este músculo con la disminución de la fatiga en los pacientes con insuficiencia renal crónica en hemodiálisis.
Conclusión: Existe una relación entre los ejercicios de estiramiento de este músculo con la disminución de la fatiga en los pacientes con insuficiencia renal crónica sometidos a hemodiálisis.

Palabras clave: Fatiga, estiramiento, insuficiencia renal crónica.

Introduction

Kidney disease is a disorder that affects the kidney organs that arises due to various factors, such as infections, tumors, congenital abnormalities, metabolic or degenerative diseases. These abnormalities can affect the structure and function of the kidneys with varying degrees of severity. Patients may feel pain, have urinary problems, etc[1].

According to Pernefri[2] stated that there were 17,193 new patients undergoing hemodialysis, an increase in 2015 of 21,050 new patients undergoing hemodialysis. The action of acute hemodialysis is not too much, only about 0.9%. In North Sumatera Province, of the 14 registered hemodialysis units, there were 1,075 new patients undergoing hemodialysis, and 1,236 patients actively undergoing hemodialysis.

Fatigue is one of the most frequent complaints of hemodialysis patients and is associated with health problems related to the quality of life. Fatigue is the most common symptom of hemodialysis and is associated with poor quality of life[3]. Study El and Bayumi[4] stated a high frequency of fatigue in hemodialysis patients. Overall, men had more fatigue than women when treated with hemodialysis.

Hemodialysis nurses are expected to monitor fatigue, provide health education about physical exercise and provide holistic nursing care[5]. According to Seshadri et al[6], interventions to increase physical activity should be considered as a possible approach to managing fatigue and insomnia.

This research has novelty from other research. This study suggests a cause-and-effect relationship between muscle stretching exercises with decreased fatigue in chronic renal failure patients. Stretches should be adapted to muscle structure, flexibility, and varying degrees of tension. The key is to be organized and relaxed. The goal is to reduce muscle tension, allowing movement to be freer than focusing on gaining extreme flexibility, which often results in overstrain and injury[7].

Methods

This type of research is pre-experimental with a one-group pre-post test design, which is to reveal a causal relationship by involving one group of subjects. This research was conducted at the Royal Prima General Hospital, Medan.

The population in this study were all patients with kidney failure who underwent hemodialysis at the Royal Prima General Hospital Medan as many as 140 patients with kidney failure who underwent hemodialysis. The sampling technique in this research is purposive sampling. Thus the number of samples in this study was 28 people.

The data collection technique used a questionnaire prepared by researchers according to the needs of patients in the field. Guide to doing muscle stretching exercises based on Anderson and Anderson[7]. Ethical clearance from the Ethics Committee of Universitas Prima Indonesia.

The data analysis technique used univariate and bivariate analysis. Univariate analysis with a description of the frequency distribution of muscle stretching exercise activity and fatigue in patients. Bivariate analysis to determine the relationship between the independent variable and the dependent variable using the Pearson test. The measurement results are obtained with a significance degree (α) of 0.05, if x^2 count > x^2 table then Ho is rejected and Ha is accepted indicating that there is a relationship between the independent variable and the dependent variable.

Results

Univariate Analysis

1. Characteristics of Respondents

Table I: Distribution of frequency and percentage of respondents.

Characteristics			
No.	**Characteristics of Respondents**	**Total (n)**	**Percentage (%)**
1.	**Gender**		
	Man	15	54
	Woman	13	46
	Total	**28**	**100**
2.	**Age**		
	17-25 Years	5	18
	26-35 Years	3	11
	36-45 Years	12	43
	46-55 Years	8	28
	Total	**28**	**100**
3.	**Start HD**		
	4 years	3	11
	3 years	4	14
	2 years	10	36
	1 year	11	39
	Total	**28**	**100**

Based on **table I** above, it is known that from the 28 respondents the majority were male as many as 15 people (54%), and the female minority as many as 13 people (46%). The majority were aged 36-45 years as many as 12 people (43%) and 26-35 years as many as 3 people (11%). The majority started hemodialysis for 1 year amounted to 11 people (39%) with the minority for 4 years amounted to 3 people (11%).

Exercise Muscle Stretch

Table II: Distribution of fatigue frequency in chronic kidney failure patients undergoing hemodialysis.

No.	Muscle Stretching Exercises	Amount	Percentage(%)
1.	Active	26	93
2.	Not active	2	7
	Total	**28**	**100**

Based on **table II**, it is known that after muscle stretching exercises, the majority of active exercises were 26 people (93%) while the minority of inactive exercises were 2 people (7%).

Patient Fatigue

Table III: Distribution of Fatigue Frequency in Chronic Kidney Failure Patients Undergoing Hemodialysis.

No.	Fatigue	Amount	Percentage(%)
1.	Acute	26	93
2.	Chronic	2	7
	Total	**28**	**100**

Based on **table III** above, it can be seen that after doing stretching exercises the majority of acute fatigue was 26 people (93%) while the minority of chronic fatigue was 2 people (7%).

Bivariate Analysis

Based on the results of research on the relationship between muscle stretching exercises and decreased fatigue in renal failure patients undergoing hemodialysis.

The relationship of muscle stretching with patient fatigue

Table IV: Frequency Distribution of Muscle Stretching Exercises with Reduction of Fatigue in Chronic Kidney Failure Patients Undergoing Hemodialysis.

Muscle Stretching Exercises	Fatigue						
	Chronic		Acute		Total		*P-value*
	f	%	*f*	%	N	%	
Not active	2	7.1	0	0.0	2	7.1	0.00
Active	0	0.0	26	92.9	26	92.9	
Total							

Based on **table IV** above, it can be seen that the results of the Pearson test when the p-value was obtained was 0.000 < 0.05 so that the conclusion was Ho was rejected and Ha was accepted, it was concluded that there was a relationship between muscle stretching exercises and decreased fatigue in chronic kidney failure patients undergoing hemodialysis at home Royal Prima Medan General Hospital.

Discussion

Based on the data after muscle stretching exercise, the majority of active exercises were 26 people (93%) while the minority of inactive exercises were 2 people (7%). This is indicated by the response of respondents who are willing to be given muscle stretching exercises after undergoing hemodialysis. Respondents wanted to do the muscle stretching exercises independently at home according to what had been taught by previous researchers.

Based on data previously obtained from respondents who felt their head felt heavy, yawned frequently, felt tired and drowsy. Respondents also often complain that the length of time undergoing hemodialysis makes them feel tired. According to research Jhamb et al[8], patients with advanced chronic kidney disease experience profound fatigue. Symptoms of depression, restless leg syndrome, excessive daytime sleepiness, and low albumin levels may provide targeted interventions to increase fatigue in patients.

The results of this study it can be seen that the results of the Pearson test when the p-value was obtained was 0.000 <0.05 so that the conclusion was Ho was rejected and Ha was accepted, it was concluded that there was a relationship between muscle stretching exercises and decreased fatigue in patients with chronic kidney failure undergoing hemodialysis.

Exercise can help HD patients to reduce the severity of Restless legs syndrome (RLS) or restless legs syndrome, depression, and fatigue[9]. Stretching exercises are not only done to reduce fatigue but can also be useful for reducing the intensity of pain felt by the elderly[10]. Study Agisha Mol et al[11] showed that leg ergometric exercises were effective in reducing fatigue levels in Chronic Kidney Disease patients undergoing Hemodialysis. There is a significant relationship between age and duration of illness with the level of fatigue.

Muscle stretching exercises can help patients reduce fatigue. Fatigue is a common phenomenon among patients with kidney disease, but often goes unrecognized[12]. Fatigue, anxiety, depression, and sleep quality are significant problems for patients undergoing hemodialysis[13]. Fatigue is an important symptom for patients with advanced chronic kidney disease[8].

Muscle range of motion exercises can be an excellent alternative to reduce the patient's level of fatigue. If the movement is not done at all and the patient's fatigue is not identified and cannot be described, the patient can worsen the treatment process that is being undertaken. Nurses need to assess fatigue through nursing care, to assess and identify the possible impact on patients while being diagnosed with chronic kidney failure. Decreased quality of life and cardiovascular disorders are further impacts that must be prevented so that fatigue does not get worse and can be anticipated.

Conclusion

The results showed that the majority of muscle stretching exercises had active exercises, experienced acute fatigue. The results of the Pearson test showed that the p-value was 0.000 so that Ho failed to be rejected. The conclusion is that there is a relationship between muscle stretching exercises and decreased fatigue in patients with chronic kidney failure undergoing hemodialysis.

Interests conflict

The authors declare that they have no conflict of interest.

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ORIGINAL

Helicobacter Pylori infection among asymptomatic schoolchildren: Link with parental educational level

Infección por Helicobacter Pylori en escolares asintomáticos: Relación con el nivel educativo de los padres

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Abstract

Objectives: Helicobacter pylori is a bacterium that infects the gastric mucosa and causes both local and systemic diseases in children and adults. We aimed to establish Helicobacter pylori prevalence in the population studied and relate its presence with known risk factors for its infection, including parental educational level and nutritional variables.
Methods: This was an analytical cross-sectional study conducted in a public school in Tegucigalpa, Honduras, in August 2019, where 101 students between 6 and 12 years old were randomly selected after the signing of an informed consent form by their legal guardians and the child's own acceptance. Subsequently, a demographic survey was completed, and a stool sample was obtained from the participants to detect Helicobacter pylori antigen.
Results: Of the 101 schoolchildren studied, 18 (17.82%) tested positive. The mean age of participation was 8.9 ± 1.88 years, 58.4% female, 42.6% male. Educational level of the mother and father in relation to the prevalence of Helicobacter pylori had an odds ratio: 6.8 (CI 95: 2.17 - 21.63) and odds ratio: 5.7 (1.45 - 23.8), respectively.
Conclusions: The prevalence of Helicobacter pylori was lower than in similar studies carried out in developing countries, and higher than in research on populations in developed countries. A relationship was identified with the educational level of both parents. No association was found with age, gender, body mass index, overcrowding, housing characteristics, access to basic services, pet ownership, family history of Helicobacter pylori infection or gastric cancer.

Key words: Helicobacter pylori, prevalence, education, body mass index.

Resumen

Objetivos: Helicobacter pylori es una bacteria que infecta la mucosa gástrica y que causa enfermedades tanto locales como sistémicas en niños y adultos. El objetivo fue establecer la prevalencia de su infección en la población estudiada y relacionar su presencia con factores de riesgo conocidos, incluyendo el nivel educativo de los progenitores.
Métodos: Estudio analítico, transversal, en una escuela pública de Tegucigalpa, Honduras, en agosto de 2019, donde se seleccionaron aleatoriamente 101 escolares entre 6 y 12 años, previa firma de un consentimiento informado por parte de sus tutores legales, y la aceptación del propio infante. Se completó una encuesta sociodemográfica y se obtuvo una muestra de heces de los participantes para detectar el antígeno de Helicobacter pylori.
Resultados: De 101 escolares estudiados, 18 (17.82%) dieron positivo. La edad media de participación fue de 8.9 ± 1.88 años, 58,4% mujeres y 42.6% hombres. El nivel educativo de la madre y del padre con respecto a la positividad de Helicobacter pylori tuvo un odds ratio: 6.8 (IC 95: 2.17 - 21.63) y odds ratio: 5.7 (1.45 - 23.8), respectivamente.
Conclusiones: La prevalencia de Helicobacter pylori fue inferior a la de estudios similares realizados en países en vías de desarrollo, y superior a la de investigaciones realizadas en poblaciones de países desarrollados. Se identificó una relación con el nivel educativo de ambos padres. No se encontró ninguna asociación con la edad, sexo, índice de masa corporal, hacinamiento, características de la vivienda, acceso a los servicios básicos, posesión de animales domésticos, antecedentes familiares de infección por Helicobacter pylori o de cáncer gástrico.

Palabras clave: Helicobacter pylori, prevalencia, educación, índice de masa corporal.

Introduction

Initially classified and described by a team of Australian physicians through gastroscopic biopsies of the antral muscosa[1], Helicobacter pylori (H.pylori) is a microaerophilic, 4- to 6-flagellated, urease-, catalase- and oxidase-producing, spiral-shaped, gram-negative bacillus-like bacterium[2], that has the capacity to invade the gastric mucosa and reduce the natural acidity of this tissue, thus enabling it to survive in this environment and contribute to the deterioration of human health[3,4].

Even though its infection can occur asymptomatically[5], within the spectrum of diseases to which H. pylori has been related to, in the adult population, we encounter a span extending from chronic gastritis, gastroduodenal ulcer, and vitamin B12 deficiency[6-8], all the way to esophageal and gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue lymphoma (MALT), being neoplasms its most feared consequence[9-11]. In fact, the International Agency for Research on Cancer categorized it as a type I carcinogenic agent due to evidence that demonstrates both a correlative and etiological relationship with gastric cancer in human beings[12,13].

Then again, in children, idiopathic thrombocytopenic purpura has been described as a disease related to H. pylori infection[14], as well as a decreased growth rate and the development of iron deficiency anemia due to the presence of the sabA gene, an encoder of one of the adhesin type proteins in H. pylori[15,16]. In a literary review of international studies published between 1991 and 2014, researches from the University of Urmia, Iran, not only demonstrated the presence of iron deficiency anemia in infected individuals but also the resolution of refractory cases, of the aforementioned type of anemia, once H. pylori was eradicated[17].

Its role as a carcinogenic agent and its connection with a multiplicity of diseases has motivated a variety of studies, including research on the extent of its worldwide presence. Regarding this, prevalence rates corresponding to 79.1% in the African region, 63.4% in Central America and the Caribbean, 54.7% in Asia, 47% in Europe, 37.7% in North America and 24.4% in Oceania have been exposed; figures derived from the analysis of data of studies in the general population from 1970 to 2016[18]. Then again, pediatric population data suggest prevalences higher than 80% in Oceania, higher than 50% in Africa, about 45% in Central America and the Caribbean, about 30% in Asia, less than 20% in Europe and close to 15% in North America[19].

For both adults and infants the prevalence of H. pylori fluctuates widely depending on the characteristics of the population studied. Therefore, although the regions of Europe, North America, and Oceania present a low prevalence for the general population compared to Latin America, Africa and Asia, even within these territories there are significant variations according to the subpopulation studied[19]. Thus, we find in children figures as low as 3.4% in Iceland, close to 24% in Poland and over 40% in indigenous communities in Canada[20-22]. In Latin American, Asian, and African countries, specific analyses of pediatric subpopulations have also shown results ranging from 14.2% in Ghana, 44.3% in Uganda, 41.2% in Ecuador, 77.3% in Colombia, and 31.7% in the United Arab Emirates[23-27].

Regardless of the differences between subpopulations in countries with similar statistical background for Helicobacter pylori, it has been shown that the prevalence in the general population has decreased significantly since 2000 for the territories of Oceania, North America, and Europe; in contrast to Asia and Latin America, where it has remained constant as a plateau, and Africa, where the scarce amount of data prior to the year 2000 does not allow for comparison[18].

Generally, the acquisition of the bacterium, whose onset is suggested to occur during infancy[28-30], is explained by its apparent routes of transmission, being oral-fecal, oral-oral and gastro-oral, the ones proposed[31-33]. Although not necessarily mutually exclusive, the three of them are more likely to occur in conditions of overcrowding, poor hygiene, contact with domestic animals, parental low educational level in pediatric cases, open defecation, and ingestion of uncontrolled or poorly treated water, among other risk factors[34-36], reaching prevalence figures close to 99% in these circumstances[37,38].

In Honduras, the data obtained estimates prevalences ranging from 84.7% in adults in the western part of the country[39], and between 61% and 64% in hospital-based studies in adults with gastric symptomatology[40,41].

In accordance with the information stated above, the present investigation aims to report the prevalence of Helicobacter pylori in schoolchildren ages 6 to 12 years from an urban school in the city of Tegucigalpa, capital of Honduras, and its association with known risk factors.

Methods

This is an analytical cross-sectional study carried out in August 2019 in asymptomatic children enrolled in the Escuela Mixta Los Robles, located in neighborhood Los Robles, in the urban area of Tegucigalpa. The inclusion criteria included age between 6 and 12 years old, active enrollment in Escuela Mixta Los Robles, Honduran nationality, and signature of informed consent by the legal guardians

and assent of the ward. The exclusion criteria included having gastrointestinal symptoms in the last 15 days and ingestion of antibiotics, proton pump inhibitors, histamine 2 receptor antagonists or bismuth in the last 30 days, due to a decrease in the performance of the stool antigen detection test in these situations[42,43].

The project was approved by both the Institutional Review Board of the Catholic University of Honduras, complying with the Helsinki Declaration, and the local board of education. Meetings were held with the teachers and an informed consent form was sent to each parent explaining the details of the study so that they could evaluate the possibility of participating in the research. A total of 129 signed informed consents were received, after which 101 participants were randomly selected after sample size and sample method were determined using EpiInfo 7.2.4.0 and STATS 2.0, with 5% margin of error and 95% confidence interval.

Measurements of weight and height were taken with a calibrated analog body weight scale and a metal strip tape measure. Each child was given a survey to be answered at home by their legal guardians to be returned on the days of the stool sample collection. A total of 101 stool samples were obtained over 5 collection days. Two new children were included after two of the originally selected failed to provide the stool sample.

To obtain the stool sample parents were provided with a collection jar to deposit it in, instructing them that the sample should be obtained in the morning before the infant attended school or, failing that, to collect an overnight stool sample to be kept in an icebox or refrigerator for no more than 24 hours before its delivery to the research team.

Upon delivery, each sample was placed in an icebox at a temperature of 5 degrees and then transferred to the laboratory 4 hours later where tests were run by means of a qualitative enzyme adsorption immunoassay. The sensitivity and specificity reported for the Quantitative Fecal H. pylori Antigen ELISA Kit according to the manufacturer is, under the indicated conditions, 100% of both specificity and sensitivity[44].

101 stool samples were processed. A sample was considered positive when it was above the cut-off index suggested by the manufacturer, which was greater than 1.1 for the qualitative cut-off index.

The results were computed in Excel 365 and analyzed with EpiInfo 7.2.4.0 statistical software. For the association of H. pylori with categorical variables, the chi-square or Fisher test was used as appropriate, and for numerical variables, the T-student test was used. Statistical significance was considered $p < 0.05$.

Results

According to the sociodemographic variables of the schoolchildren participating in this study, it was evident that the prevailing sex was female, with 57.42% girls and 42.58% boys. The average age was 8.97 years old with a standard deviation of 1.88. The prevalence of Helicobacter Pylori infection in school children aged 6 to 12 years in an urban educational unit in Tegucigalpa, Honduras, was of 17.82 % (IC:95 10.92 % - 26.7%) due to 18 positive tests out of 101 samples analyzed, as shown in **table I**.

Open defecation was nonexistent among the infants studied, with 98.02% having access to a flush toilet and 1.98% having access to a latrine. All the children ingested drinking water in their homes and 96.04% of their homes also used it for cooking. The type of construction floor of each house was reported as 82.28% ceramic and 17.82% cement; no parent reported that the house they currently lived in had dirt floors. Exactly 47.52 % stated that their dwelling houses had brick walls, while 44.55 % reported they had block walls, 5.94 % wooden walls, and 1.98% adobe walls.

Regarding the relationship of risk factors with Helicobacter pylori infection, statistical significance was found, with $p < 0.05$, for the educational level of the parents as shown in **table II**; 36.1 % of the children of mothers with completed or incomplete primary school were positive compared to 8.33 % of the children of mothers with more than 9 years of schooling. On the other hand, 28.1 % of the children of fathers with complete or incomplete primary schooling were positive compared to 6.25 % positivity for those whose fathers have more than 9 years of schooling.

Table I: Frequency distribution of Helicobacter pylori presence among schoolchildren 6-12 years old.

Variable	Frequency	Percentage
Helicobacter pylori (+)	18	17.82 %
Helicobacter pylori (-)	83	82.18 %
Total	101	100 %

Table II: Parent´s educational level and its relationship to Helicobacter pylori prevalence among schoolchildren 6-12 years old.

Evaluated factors		Presence of H. pylori		OR (IC:95)	p - value
		Yes	No		
Mother´s educational level	More than 9 years of schooling	5	60	6.8 (2.17-21.63)	0.000351
	9 years of schooling or less	13	23		
Father´s educational level	More than 9 years of schooling	3	45	5.7 (1.45-23.8)	0.0105
	9 years of schooling or less	9	23		

Table III: Relationship between other risk factors and Helicobacter pylori prevalence among schoolchildren 6-12 years old.

Other risk factors studied		Presence of H. pylori		OR (IC:95)	p - value
		Si	No		
Age	6 to 8 years 9 to 12 years	5 13	30 53	0.68 (0.22-2.09)	0. 498
Sex	Male Female	8 10	35 48	1.1 (0.39-3.06)	0.859
School grade	1 - 3 4 - 6	6 12	31 52	0.84 (0.29-2.46)	0.748
Abnormal BMI	Yes No	10 8	35 48	1.71 (0.61-4.69)	0.3
Shares sleeping room	Yes No	16 2	66 17	2.06 (0.43-9.84)	0.513
Shares bed	Yes No	11 7	42 41	1.53 (0.54-4.34)	0.418
Has pets at home	Yes No	10 8	41 42	1.28 (0.46-3.57)	0.636
Number of adults at home	More than 3 3 or less	7 11	40 43	0.68 (0.24-1.94)	0.473
Number of children at home	More than 3 3 or less	6 12	27 56	1.04 (0.35-3.06)	0.947
Overcrowding	Yes No	4 14	23 60	0.75 (0.22-2.5)	0.774
Monthly economic income	More than 10,000 L.* Less than 10,000 L.	9 9	60 23	2.61 (0.92-7.39)	0.065
Family history of Helicobacter pylori	Yes No	6 12	23 60	1.3 (0.44-3.89)	0.633
Family history of gastric cancer	Yes No	1 17	11 72	0.39 (0.05-3.19)	0.688

* L. Stands for Honduran currency: Lempira. As of August 2019: L. 24.4 = 1 USD https://www.bch.hn/estadisticos/GIE/_layouts/15/WopiFrame.aspx?sourcedoc=%7B90EEBD7C-D458-446A-AB96-FF39D6D7CB00%7D&file=Precio%20Promedio%20del%20D%C3%B3lar%20-%20Serie%20Mensual.xlsx&action=default

Table IV: Frequency distribution of nutritional variables regarding Helicobacter pylori presence among schoolchildren 6-12 years old.

Studied variables		Helicobacter pylori (+)	Total (%)
BMI for age	Normal Risk of overweight Overweight Obesity	8 / 56 (14.28) 5 / 24 (20.8) 4 / 18 (22.2) 1 / 3 (33.3)	56 /101 (55.4) 24/101 (23.8) 18/101 (17.8) 3/101 (3)
Height for age	Normal	18 /101 (17.8)	101 /101 (100)

For the other risk factors evaluated in **table III**, such as age, sex, school grade, BMI, room sharing, bed sharing, pets at home, adults at home, children at home, overcrowding, economic income, family history of H. pylori, and family history of gastric cancer, no statistically significant association was found.

As height for age and BMI for age are nutritional variables, they were evaluated according to the WHO growth charts for children and adolescents between 5 and 19 years of age, the results are shown in **table IV**. No statistically significant difference was shown for BMI and Helicobacter Pylori.

Discussion

The prevalence of H. pylori obtained in this study was obtained by stool antigen detection due to its wide application in microbiology, cost, high sensitivity and specificity, and because it is a non-invasive method[45]. El-Shabrawi et al. demonstrated in Cairo, Egypt the applicability of the stool antigen test in children, detecting a sensitivity between 89% and 98% and a specificity between 94 and 100%; only slightly lower than the C-13 urea breath test whose operation implies higher economic costs for laboratories and less tolerance by infants[46]. Other non-invasive methods include serological tests and molecular tests on saliva and stool samples[47].

Regarding the results obtained according to the objectives of the study, the prevalence of H. pylori in the population studied, 17.8%, contrasts considerably with other national results in which a higher prevalence of H. pylori than that reported in our study has been stated. In 2006, Morgan et al. identified that 85% of the asymptomatic adult population participating in their study in the western part of the country had a positive seroprevalence[40] Subsequently, in 2013, through positive cultures of gastric biopsies, Morgan et al. also reported 61.4% of 189 adult patients with gastric symptomatology in Hospital de Occidente, as carriers of Helicobacter pylori[39].

In both cases, the conditions of space, time, and population in which the study was carried out should be considered, since although the decline in the prevalence of H. pylori has been demonstrated mainly

in the inhabitants of socioeconomically developed territories [48-50], similar behavior has also been observed in increasingly industrialized countries such as China and Brazil, where its decrease has been attributed to better living conditions[51,52]. Therefore, the high percentage coverage of flush toilets, the absence of open defecation, the construction materials used in dwellings, the high consumption of drinking water, and the pediatric study population probably explain the low prevalence found.

Similarly, in Jordan, a developing country, Eyad Altamimi et al. found in 2019 that the prevalence of H. pylori for asymptomatic pediatric patients, probed by carbon 13 breath test, stood at 14.6 % for infants aged 4 to 17 years, and 25% for those aged 6 to 11 years[53]. In sub-Saharan Africa, in 2017, a study conducted in Ghana by Awuku et al. demonstrated a prevalence, by stool antigen, of 14.2 percent in pediatric villagers aged 5 to 16 years and 14.5 percent in patients aged 5 to 10 years. In those positive patients, open defecation, female gender, and source of drinking water represented risk factors[23].

Regarding the educational level of the mother, at least since 2001 information has been obtained identifying it as a risk factor for H. pylori infection, as demonstrated by Malaty et al. when they studied 356 children between 2 and 16 years of age from the Houston area in the United States between 1996 and 1998, obtaining statistically significant results regarding maternal education as a risk factor with p<0.001 for mothers who had not completed at least 12 years of education[54]. Later Galal et al. examined 630 Egyptian children with gastric symptomatology and found a prevalence of 64.9 % by stool antigen detection and an association between illiterate mothers and stool antigen positivity for H. pylori[55].

In our study, statistically significant differences were found for H. pylori positivity according to the educational level of both parents, not only the mother, taking 9 school years as the cut-off educational level, since in Honduras, according to article 22 of the Fundamental Law of Education published in 2012, basic education consists of 9 years of compulsory schooling[56]. Similarly, in Portugal, Bastos et al. found a lower prevalence in adolescents whose parents had a higher level of education[57]. Wangda et al. also found a similar association in children from 8 public schools in Bhutan where H. pylori positivity reflected a statistically significant difference when comparing children of college-educated mothers with those of non-college educated mothers[58]. Muhsen et al. obtained, in 2012, an association between the fathers' educational level and H. pylori positivity by dividing male parents into 2 groups: those with more than nine grades of schooling and those with less than nine grades of schooling. With respect to the mothers' education, no significant differences were found in that study[59].

The statistical results between the association of Helicobacter pylori and body mass index has sometimes proven to show contradictory data. Previously, Arslan et al. had shown some association in their analysis of 103 obese adult patients and 111 controls, regarding Helicobacter pylori infection and BMI, obtaining results with statistical significance $p < 0.01$ and odds ratio greater than two[60]. Chen et al. also obtained results showing an association between body mass index and H. pylori infection, specifically in adult patients under 50 years of age[61]. However, in pediatric patients, associations inversely proportional to BMI have been found, where after H. pylori eradication this parameter increases[62], even reaching morbid obesity levels[63]. Moran - Lev et al. showed the same phenomenon in symptomatic Israeli children diagnosed by means of gastric biopsies; 31% of the non-infected children presented obesity or overweight, in contrast to the infected children, of only whom 11% presented obesity, generating a statistically significant difference, suggesting an inverse relationship between the ordinal value of BMI and H. pylori positivity[64]. The results of our project have yielded data with no significant statistical difference between BMI, both in its ordinal and numerical values, and H. pylori infection, as can be seen in the publications of Pundak et al. and Choi et al. where, in the former, they report the lack of relationship between obesity or overweight and infection by H. pylori infection[65] whereas in the latter they report that after eradication of the bacteria, the treated infants presented a significantly greater weight gain than those who were not treated, without specifying whether or not the magnitude of the weight gain caused them to move from one BMI category to another[66]. The present investigation did not have the scope to treat infants with positive results.

Conclusions

More studies covering larger populations will be needed to confirm H. pylorí's prevalence in children. Nonetheless, within the scope of the present report, a lower prevalence was found when compared to similar studies. Moreover, a particular association was observed between the lower educational level of both parents and Helicobacter pylori stool antigen positivity.

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Conflict of Interests

The authors have no conflict of interest.

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ORIGINAL

A review on endometrial cancer; artificial intelligence, imaging modalities

Una revisión sobre el cáncer de endometrio; inteligencia artificial, modalidades de imagen

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Abstract

Endometrial cancer is one of the most common cancers among women especially in urban areas. The appearance of symptoms such as abnormal uterine bleeding or infertility on clinical examination increases the risk of endometrial lesion. Vaginal ultrasound and diagnostic hysteroscopy are common gynecological examinations for endometrial lesions. Endometrial cancer is often diagnosed in the early stages, in which case surgical removal of the uterus often cures endometrial cancer. However, screening and treatment programs are important in the timely diagnosis and treatment of this disease. Due to the importance of the topic, the present study was conducted to investigate the prevalence of this disease, the relationship between artificial intelligence as well as various imaging methods and the diagnosis of endometrial cancer.

Key words: Artificial intelligence, endometrial cancer, imaging modalities.

Resumen

El cáncer de endometrio es uno de los cánceres más comunes entre las mujeres, especialmente en las zonas urbanas. La aparición de síntomas como sangrado uterino anormal o infertilidad en el examen clínico aumenta el riesgo de lesión endometrial. La ecografía vaginal y la histeroscopia diagnóstica son exámenes ginecológicos comunes para detectar lesiones endometriales. El cáncer de endometrio a menudo se diagnostica en las primeras etapas, en cuyo caso la extirpación quirúrgica del útero a menudo cura el cáncer de endometrio. Sin embargo, los programas de detección y tratamiento son importantes en el diagnóstico y tratamiento oportuno de esta enfermedad. Debido a la importancia del tema, el presente estudio se realizó para investigar la prevalencia de esta enfermedad, la relación entre la inteligencia artificial, así como diversos métodos de imagen y el diagnóstico de cáncer de endometrio.

Palabras clave: Inteligencia artificial, cáncer de endometrio, modalidades de imagen.

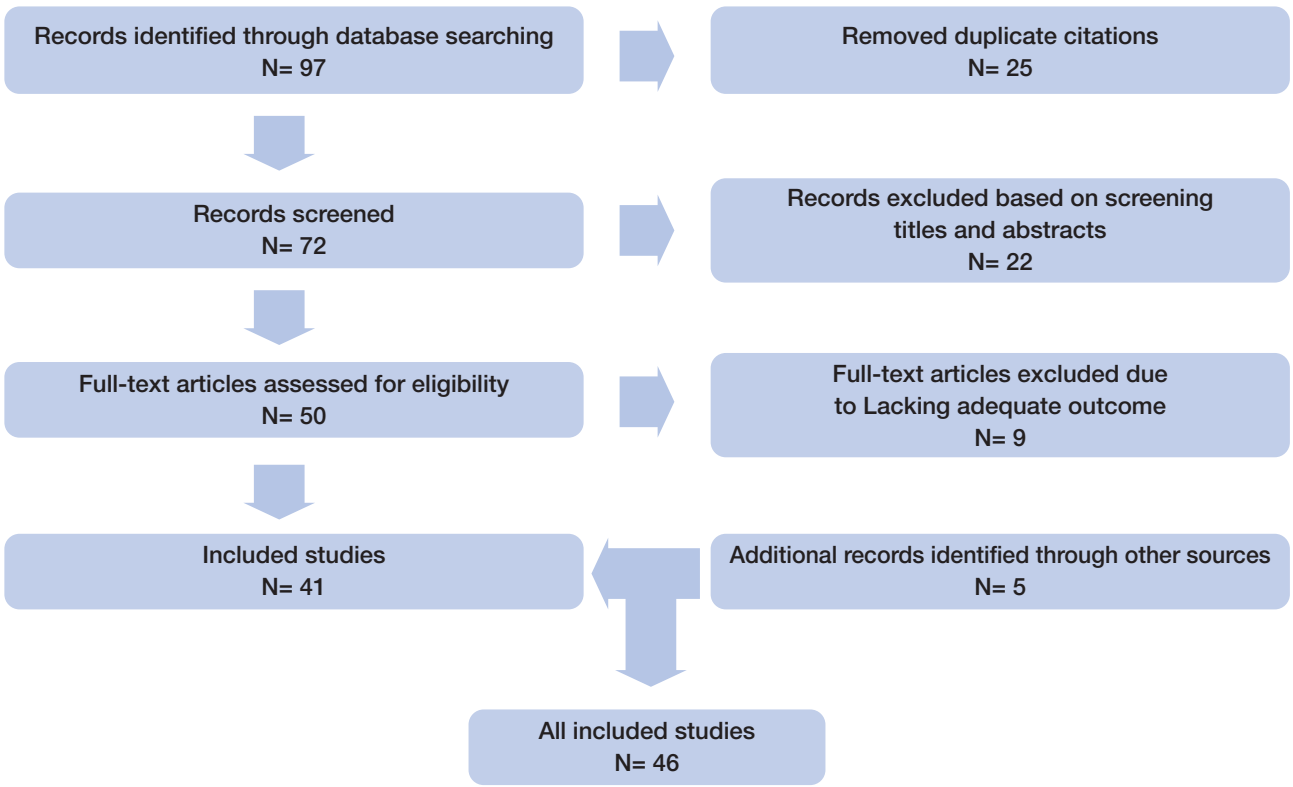
Introduction

Endometrial cancer (EC) is the fourth most common cancer among women, and its prevalence has increased steadily, especially in urban areas, due to the increase in obesity (BMI > 30) and longevity[1,2]. EC is the most common genital cancer, with about 320,000 newly diagnosed cases reported worldwide each year[3]. A total of 61,880 new cases and 12,160 EC-related deaths were estimated in the United States in 2019[4]. In general, the appearance of symptoms such as abnormal uterine bleeding or infertility on clinical examination increases the risk of endometrial lesion[5]. Vaginal ultrasound and diagnostic hysteroscopy are common gynecological examinations for endometrial lesions[6]. Due to abnormal vaginal bleeding, endometrial cancer is often diagnosed in the early stages, in which case surgical removal of the uterus often cures endometrial cancer[7]. Although uterine cancer is highly preventable, it is still one of the most common causes of cancer death in women of developing countries, therefore screening and treatment programs are important in the early diagnosis and treatment of this disease. Nowadays, the use of artificial intelligence technology will be beneficial about endometrial cancer. However there have not been many publications about artificial intelligence applications in endometrial cancers. In the present paper we summarized the characteristics of studies on the use of artificial intelligence, imaging methods and clinical factors for the diagnosis of endometrial cancer.

Literature search

We conducted a comprehensive review of the English-language literature involved endometrial cancer. The electronic databases MEDLINE, PUBMED, and EMBASE were searched on July 2021 for reporting the outcomes of endometrial cancer. Reference lists of published papers were then also hand-searched in an attempt to identify further reports. The following key words were used: endometrial cancer; artificial intelligence; deep learning; imaging modalities. The search terms were then entered onto Google Scholar, to ensure that articles were not missed. Papers were excluded if they were case reports or had a patient cohort, were not written in English, lacked documentation, non-human studies, narrative reviews, studies without clinical outcomes data, systematic reviews that did not pool data or perform a meta-analysis, and technique articles without outcomes. We then obtained full manuscripts for those studies that met the inclusion criteria. Search algorithm of articles included in the literature review is presented in **figure 1**.

Figure 1: PRISMA flow diagram.



Artificial intelligence (AI) features

Radiologists use artificial intelligence (AI) to read medical images for different diseases[8]. Artificial intelligence includes a set of algorithms, mathematical functions, interconnected practical approaches, and areas of mathematical and statistical overlap that are very suitable for radiology because the pixel values of the MRI image are measurable[9]. Although literature on artificial intelligence assistance in the diagnosis of endometrial cancer focuses on the function of "postoperative" diagnosis made by convolutional neural network-based classification[10], however research that examines the "preoperative" MRI stage, the function of interpreting AI in endometrial cancer are limited. Although current AI technology may not be able to replace the expertise and experience of physicians, it can be used as an auxiliary tool[11]. Due to the probability of human active errors and passive errors, the use of AI technology will be beneficial about endometrial cancer. There have not been many publications about AI applications in endometrial cancers. The research of Dong et al.[11] was the first attempt to use AI technology in order to evaluate the invasion depth of myometrium in early stage of endometrial cancers. However, creating a deep learning model is necessary to increase the precision. Generally, artificial intelligence as an appropriate option for preoperative assessment has the ability to help radiologists.

Deep learning is a discipline that has recently played an important role in areas such as computer vision and speech recognition. Deep learning as an important branch of artificial intelligence made outstanding contributions in the clinical prediction models and radiomics[12]. Based on the review of literature, artificial intelligence technologies have significant clinical applications. Each technology has a different role in predicting and detecting clinical outcomes. Zhang et al.[13] conducted a study, in order to create a convolutional neural network model that can automatically classify endometrial lesions using hysteroscopic images as input. After the images were preprocessed, a training set of 6478 images was input into a tuned VGGNet-16 model; and 250 images were used as the test set to evaluate the model's performance. They compared the model's results with the diagnosis of gynecologists and concluded that the VGGNet-16 model performs well in classifying endometrial lesions from hysteroscopic images and can provide objective diagnostic evidence for hysteroscopists. Chen et al.[14] used the deep learning model for detecting myometrial invasion depth in endometrial cancer and compare with radiologists for evaluating clinical application. In their study two stages CNN based deep learning method - trained with YOLOv3 for detection then used Resnet for classification. They concluded that diagnosis and classification of myometrial invasion depth by radiologists improved with deep learning method for lesions >2cm, radiologists better accuracy for lesions <2cm and false positive error most common for both radiologists and computer.

Imaging modalities

Magnetic resonance imaging (MRI) is widely used to determine and classify female malignancies[15]. Sensitivity and specificity related to the evaluation of the myometrial invasion depth in MRI reported varied (sensitivity of 42 -100 and specificity of 85-93) in various studies[14]. The accurate pre-operative assessment of the depth of myometrial invasion depends on MRI, especially T2-weighted imaging (T2WI) and contrast-enhanced T1-weighted imaging[16]. Some findings suggested that diffusion-weighted imaging (DWI) may have good diagnostic accuracy for assessing myometrial invasion[17]. However, in pre-operative MR examination the uterine cavity is often filled with polypoid tumors and tumors located in uterine cornu may lead to incorrect evaluations on myometrial invasion[18]. Han et al.[19] by evaluate whether whole-uterine MRI radiomic features can predict myometrial invasion depth in endometrial cancer (EC), reported that whole-uterine MRI radiomic features based on sagittal T2WI and axial DWI show potential in predicting myometrial invasion in endometrial cancer.

Ueno et al.[20] in a study aimed at building diagnostic radiomic model and evaluate its accuaracy for assessment of deep myometrial invasion, lymphovascular space invasion, histologic high-grade endometrial cancer, concluded that diagnostic accuracy of the random forest model was 81%, 76.6% and 78.1% to predict deep myometrial invasion, lymphovascular space involvement, and high-grade tumors, respectively, as well as random forest model performance analogous to diagnosis by three radiologists. Luo et al.[21] also reported that the radiomic-based machine-learning model using a nomogram algorithm achieved high diagnostic performance for predicting lymphovascular space invasion of endometrial carcinoma preoperatively, which could enhance risk stratification and provide support for therapeutic decision-making. Performance evaluation of MRI based radiomics model for detection of deep myometrial invasion in endometrial cancer by Stanzione et al.[22] showed that radiologist diagnostic accuracy improved with the aid of machine learning compared to without, however not statistically significant and model aided radiologists in diagnosing deep myometrial invasion on MR T2w images. Yan et al.[23] reported that the MRI-based radiomics model could be used to assess the status of pelvic lymph node and help radiologists improve their performance in predicting pelvic lymph node metastasis in endometrial carcinoma. Yan et al.[24] also showed that the radiomics nomogram achieved the highest diagnostic performance compared with the radiomics signature and the clinical parameters models. Bereby-Kahane et al.[25] reported that there was no association between apparent diffusion coefficient and high grade or lymphovascular space invasion.

Clinical features and sample sizes

This section of the present paper summarizes information on clinical factors and sample sizes used in studies. The study of Yan et al.[23] was a multi-center study on 622 endometrial cancer patients (age 56.6±8.8 years; range 27-85 years), which 358 features extracted and 37 features used to build the model. Stanzione et al.[22] conducted a single center study by analyzing 54 patients that preprocessed images randomly split to training and test sets. Bereby-Kahane et al.[25] also performed a single center study on 73 patients to evaluate the capabilities of two-dimensional MRI-based texture analysis features, tumor volume, tumor short axis and apparent diffusion coefficient in predicting histopathological high-grade and lymphovascular space invasion in endometrial adenocarcinoma. The sample size of a study by Xu et al.[26] as the first subgroup analysis on different sized lymph nodes with preoperative nomogram study in EC (benign vs. malignant) was 200 patients. Fasmer et al.[27] and Chen et al.[28] enrolled 138 and 102 patients, respectively, in their studies. A total of 163, 78 and 115 patients were analyzed in the studies by Han et al.[29], Gillen et al.[30] and De Bernardi et al.[31], respectively. Summary of studies and reviews conducted on endometrial cancer is presented in **table I.**

Conflict of Interests

The authors have no conflict of interest.

Table I: Characteristics of studies conducted on endometrial cancer.

Author (s)- Ref.	Characteristics: AI method Imaging modality Cohort size Center Classification task	Objective	Year	Conclusions
Yan, et al. (23)	Deep learning Preop MRI 622 patients Multi center Positive vs negative lymph nodes	Build MRI radiomic model and assess performance compared to radiologist to diagnose PLNM also, evaluate correlation with immunohistochemical indices	2021	glcm_Correlation feature from T2WI best for differentiating positive vs negative PLNM AUC, CDC, MRI, IDI measures showed higher diagnostic performance and net clinical benefits with radiomics aid than radiologists alone
Jacob et al. (32)	Machine learning MRI 338 patients Single center N/A	Build RPI model for survival prediction and assess association with gene expression profiles.	2021	High RPI associated with advanced FIGO, deep myometrial invasion, LN metastasis and poorer 5 year survival RPI not associated with age, histological subtype, grade. High RPI associated with 46 genes – mainly COMP and DMBT1, with poorer disease survival Linking radiomic and transcriptomic tumor profiles potential for more tailored and targeted treatment strategies in EC pts
Yan et al. (24)	Classical machine learning MRI 717 patients Multicenter study High risk vs low risk EC	Radiomics nomogram developed with MRI-based radiomic feature selection and clinical parameters	2020	11-15 per 100 patients were found to have better surgical planning with radiomics nomogram model compared to actual surgical procedure the radiomics nomogram achieved the highest diagnostic performance compared with the radiomics signature and the clinical parameters models
Stanzione et al. (22)	Classical machine learning MRI 54 patients Single center DMI + vs -	Performance evaluation of MRI based radiomics model for detection of Deep Myometrial Invasion in EC	2021	Radiologist diagnostic accuracy improved with the aid of ML compared to without, however not statistically significant Model aided radiologists in diagnosing DMI on MR T2w images
Bereby-Kahane et al. (25)	Classical ML 2D MRI 73 patients Single Center High grade vs low grade and LVSI +/-	Evaluate MRI based texture features, tumor volume and short axis and ADC for prediction of high tumor grade and LVSI in endo adenocarcinoma	2020	Tumor vol >14.3 cm^3 and SA >20 mm : High vs low grade Tumor vol > 26.3 cm^3 and SA > 26 mm : LVSI +/- association between ADC and high grade or LVSI SA >20 mm: best predictor
Xu et al. (26)	Classical machine learning? MRI 137 patients single center study NA	Build diagnostic radiomic model and evaluate its accuaracy for assessment of deep myometrial invasion, lymphovascular space invasion, histologic high-grade endometrial cancer	2017	Diagnostic accuracy of the RF model to predict DMI was 81%, LVSI 76.6% and high-grade tumors 78.1% model performance analogous to diagnosis by three radiologists
Fasmer et al. (27)	Classical machine learning MRI 138 patients Pathology confirmed Single center study Outcome of interest acc to set cut-off.	To develop MRI-based whole-volume tumor radiomic signatures for prediction of aggressive EC disease	2021	MRI-based whole-tumor radiomic signatures yield medium-to-high diagnostic performance for predicting aggressive EC. The signatures may aid in preoperative risk assessment and guide personalized treatment strategies in EC.

Author (s)- Ref.	Characteristics: AI method Imaging modality Cohort size Center Classification task	Objective	Year	Conclusions
Chen et al. (28)	Classical machine learning MRI 102 patients Pathology confirmed Single center study Low risk vs intermediate to high risk	to establish a model based on magnetic resonance imaging (MRI) and clinical factors for risk classification of Preoperative EC	2021	MRI-based radiomic model has great potential in prediction of low-risk ECs. the combined model had a robust predictive value for patients of low risk or intermediate-high risk EC The nomogram based on this model a noninvasive and applicable tool for the clinical diagnosis and optimal decision-making of EC
Luo et al. (21)	Classical machine learning Pre-operative MRI 144 PATIENTS Pathology confirmed Single center study Prediction of Lymphovascular space invasion	To develop a multiparametric MRI-based radiomics nomogram for predicting LVSI in EMC and provide decision-making support to clinicians.	2020	The radiomic-based machine-learning model using a nomogram algorithm achieved high diagnostic performance for predicting LVSI of EMC preoperatively, which could enhance risk stratification and provide support for therapeutic decision-making.
Gillen et al. (30)	Deep learning CT 78 patients multicenter study Treatment survival with Bevacizumab	To examine associations of body mass index subcutaneous fat area and density visceral fat area and density and total psoas area to outcomes among patients receiving chemotherapy with or without bevacizumab for advanced or recurrent endometrial cancer (EC).	2019	Obesity has been associated with increased levels of vascular endothelial growth factor (VEGF), the main target for bevacizumab therapy. Imaging measurements of VFA may provide prognostic information for patients with EC but no adiposity marker was predictive of improved response to bevacizumab
Han et al. (29)	Classical ML Preop T2WI/DWI MRI 163 pts Center Classification task	Assess whole uterine MRI based radiomic model in EC pts for detection predicting depth of myometrial invasion	2020	Models performances – no significant diff Combined model vs subjective diagnosis – no significant diff Single-sequence models vs subjective: lower specificity and accuracy but higher sensitivity
Chen et al. (14)	Deep Learning MRI 530 patients Single Center Deep vs shallow MI	DL model for detecting MI depth in EC and compare with radiologists for evaluating clinical application	2020	Diagnosis and classification of MI depth by radiologists improved with DL method for lesions >2cm. Radiologists better accuracy for lesions <2cm False positive error most common for both radiologists and computer

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ORIGINAL

Orbital rhabdomyosarcoma in the pediatric population: A prospective, observational study from Mid-West Nepal

Rabdomiosarcoma orbital en la población pediátrica: Un estudio prospectivo y observacional del Medio Oeste de Nepal

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Abstract

Background: This study was aimed to find out the demographic characteristics, clinical characteristics and prevalence of rhabdomyosarcoma in children presenting to a tertiary level hospital of terrain Nepal, over a period of nine years. The study also aimed to explore the current understanding of rhabdomyosarcoma management.

Methods: This prospective, observational study was carried out in a tertiary hospital of Mid-Western part of Nepal from November 2011 to April 2019. Histopathologically confirmed cases of rhabdomyosarcomas were included in the study. Demographics, clinical characteristics and other relevant findings were entered in a specified proforma for the study and analyzed by Statistical Package for Social Services 24. Point estimate at 95% Confidence Interval was calculated along with frequency and percentage for binary data.

Results: Among 1180 suspected children, eight (0.68%) (0.29-1.3 at 95% CI) study subjects were diagnosed to have unilateral orbital rhabdomyosarcoma. Males six (75%) outnumbered the females. The mean age of presentation was seven, 7+-1.8 (Range: 6-8) years. Embryonal variant of rhabdomyosarcoma (6, 75%) was the commonest type followed by the alveolar type (2, 25%). Proptosis was the commonest presenting feature and was present in all (8, 100%) study subjects.

Conclusions: The prevalence of rhabdomyosarcoma was higher in the current study when compared with similar international studies. The embryonal variant of rhabdomyosarcoma was the commonest type encountered. Male predilection for rhabdomyosarcoma was high when compared to the females.

Key words: orbital rhabdomyosarcoma, children, chemotherapy, metastasis, oncologist.

Resumen

Antecedentes: El objetivo de este estudio era averiguar las características demográficas, las características clínicas y la prevalencia del rabdomiosarcoma en los niños que se presentan en un hospital de nivel terciario de Nepal, durante un período de nueve años. El estudio también pretendía explorar el conocimiento actual del tratamiento del rabdomiosarcoma.

Métodos: Este estudio prospectivo y observacional se llevó a cabo en un hospital de nivel terciario del Medio Oeste de Nepal desde noviembre de 2011 hasta abril de 2019. Se incluyeron en el estudio los casos de rabdomiosarcomas confirmados histopatológicamente. Los datos demográficos, las características clínicas y otros hallazgos relevantes se introdujeron en una proforma especificada para el estudio y se analizaron mediante Statistical Package for Social Services 24. Se calculó una estimación puntual con un intervalo de confianza del 95% junto con la frecuencia y el porcentaje para los datos binarios.

Resultados: Entre los 1180 niños sospechosos, ocho (0,68%) (0,29-1,3 con un IC del 95%) sujetos de estudio fueron diagnosticados de rabdomiosarcoma orbitario unilateral. Los varones superaron en seis (75%) a las mujeres. La edad media de presentación fue de siete, 7+-1,8 (rango: 6-8) años. La variante embrionaria del rabdomiosarcoma (6, 75%) fue el tipo más común, seguido del tipo alveolar (2, 25%). La proptosis fue la característica de presentación más común y estuvo presente en todos (8, 100%) los sujetos del estudio.

Conclusiones: La prevalencia del rabdomiosarcoma fue mayor en el presente estudio en comparación con estudios internacionales similares. La variante embrionaria del rabdomiosarcoma fue el tipo más común encontrado. La predilección masculina por el rabdomiosarcoma fue elevada en comparación con la femenina.

Palabras clave: Rabdomiosarcoma orbital, niños, quimioterapia, metástasis, oncólogo.

Introduction

Rhabdomyosarcoma (RMS) is rare yet the most common soft tissue sarcoma in children[1]. The clear histologic definition of RMS was recognized by Stout in the year 1946 however, Weber first described rhabdomyosarcoma in 1854. The name is derived from Greek literature, which suggests rod shape for rhabdo and muscle for myo[2]. With an annual incidence of 4.3 cases per million children, RMS is one of the rarer malignancies[3]. First reported by Bayer orbital Rhabdomyosarcoma (RMS) is the most common primary malignant orbital tumor of childhood. RMS is a rare tumor, with an annual incidence of 4.3 cases per million children[3]. The primary site of involvement is the orbit in 9-10% of all childhood RMS[3]. Metastasis from orbital RMS is often to the lungs, liver and bone. Lymph node metastasis is seen only in 10% of cases[3].

Like other childhood malignancies, orbital RMS can often present as a masquerading disease. There are reported incidences of RMS masquerading acute lymphocytic leukemia (ALL)[4]. The first contact clinicians like the Ophthalmologist or a pediatrician plays an important role in the management of rhabdomyosarcoma due to the aggressive nature of the disease which can threaten both life and sight in children[4].

The sudden onset of the disease, aggressive in nature with a possibility of sight loss as well as loss of life warrants an excellent core of team dealing with this disease with the Ophthalmologists and Pediatricians playing a vital role. Rhabdomyosarcoma being the commonest primary malignancy in the orbit in children needs more attention especially in developing countries and countries like Nepal due to the varied and aggressive presentation of the disease. The paucity of knowledge in the developing countries about RMS regarding early diagnosis and management protocols further elaborates the importance of the disease. When timely diagnosed and treated orbital RMS does have high five-year survival rates. This study thus was aimed at finding out the demographics, clinical characteristics, and prevalence of rhabdomyosarcoma in a tertiary care hospital of Mid-West Nepal, besides exploring the current management protocols.

Materials and methods

This was a prospective, observational hospital-based study carried out in a tertiary level hospital of Mid-Western Nepal from November 2011 –April 2019. The hospital serves as a center for patients coming across the Indo-Nepal border and also millions of people from Western–Far western Nepal. Ethical clearance was obtained from the Institutional Review Board (IRB) before the study was commenced. The study strictly adhered to the tenets of declaration of Helsinki. A convenience sampling technique was used to reach a sample size. After explaining the purpose of the study and confidentiality of data collection, informed consent was obtained from the parent /guardian.

All patients visiting the department of Ophthalmology willing to get enrolled in the study were included in the study. The patients who were not willing, who did not provide informed consent were automatically excluded.

Demographic characteristics of the study participants were entered using a specified proforma for the study. The study participants were evaluated clinically in detail in the following sequence: visual acuity measurement of each eye separately (unaided and with a pinhole), extra-ocular movement assessment, cover test, cover-uncover test, refraction using a Heine Beta 200 retinoscope, anterior segment examination with a slit lamp, and dilated fundus examination using an indirect Ophthalmoscope using +90 D Volk lens, Tropicamide eye drops were used for fundus dilatation. Evaluation of proptosis was carried out separately. Local lymph nodes were palpated to rule out local spread. Clinical photography was done in a few cases for record purposes. Radiologically, clinically and histopathologically confirmed cases needing referral were referred accordingly to higher oncology centres of Nepal and abroad.

In subjects where the initial diagnosis was not confirmed, communication with the referral hospital and the patient informant was maintained to reach the final diagnosis and also the management process. In cases where the informants expressed their willingness to go abroad, the subjects were referred abroad with proper documentation.

Protocols used in the study:

An international guideline was followed for the management of study subjects[4].

Histologically RMS was classified into the following histological subsets in the study subjects;

1. Embryonal RMS (ERMS): Most common accounts for 60-70% of all childhood RMS. Histologically ERMS is characterized by spindle-shaped cells which have a stromal-rich appearance morphologically and are similar to developing muscle cells. ERMS also has two variants and they are Botryoid ERMS and Spindle-shaped ERMS[5-7].
2. Alveolar RMS (ARMS): Aggressive variant of RMS with potential to metastasize quickly[6,7].
3. Anaplastic RMS: This subtype has the worst prognosis of all RMS5,[8-11].

Due to unclear origin and potential association with ERMS, an extremely rare variant of RMS known as sclerosing RMS was not included as a histological subtype in the current study[11].

Different parameters were taken into account for the prognosis of orbital RMS as per the literature[12]. The current Children's Oncology Group protocols for the treatment of RMS were used in staging and predicting the outcome of the treatment of orbital RMS. Risk classification was done using the tumor site[13,14].

Statistical analysis

An interobserver value of Kappa was used for the validity of diagnosis and any value more than 0.8 was considered strong agreement. Data entry and analysis were done using Statistical Package for the Social Sciences (IBM SPSS Inc, Chicago, Delaware, United States) version 24. Descriptive statistics were applied, and results were expressed as frequencies whereas continuous variables were expressed as mean±SD or median. Prevalence and Point estimate at 95% Confidence Interval (CI) was calculated.

Results

Among 1180 suspected children during the study period, eight (8, 0.68%) (0.29-1.3 at 95% CI) study subjects were diagnosed to have unilateral orbital rhabdomyosarcoma. Male study subject (6, 75%) dominated the females (2, 25%). Two (2, 25%) of the study subjects were across the border while the remaining six (6, 75%) were from Nepal. The mean age of presentation of the study subjects was 7+-1.8 years (Range 6-8). All study subjects (8, 100%) of RMS were sudden in onset. There was no difference in the laterality of the orbit involved (4) 50% right and 4 (50%) left orbit. The demographic characteristics, clinical characteristics, management protocols and outcomes of the participants are summarized in the table (**Table I**).

Discussion

In the current study, eight participants were diagnosed to have rhabdomyosarcoma, all were unilateral, with male predilection, this finding in the study was comparable with studies done elsewhere for RMS[12,15,16]. However, for orbital RMS female predilection is more which differed from the findings of this study. The current study had two non-Nepali citizens as study subjects and six participants from Nepal, a total of just eight cases over nine years all from the Asian continent. This finding of the study again was comparable with the current literature about the disease which says there's slightly a lower prevalence of orbital RMS in Asian children in comparison to others (**Table I**)[15,16].

Table I: Showing epidemiological, and clinical characteristics of the study participants.

Detail Findings of Rhabdomyosarcoma Study Subjects † (N = 8)			
Total Number of Rhabdomyosarcoma Diagnosed ‡ (n = 8)			
Symptoms/Signs/Cases features	**Present/Yes**	**Absent/No**	**Percentage (%)**
Gender: Male (M), Female (F)	6 (75.0% M), 2 (25.0%, F)		100
Any known predisposing risk factors		8(100%)	100
Sudden onset	8 (100%	0	100
Mean age of presentation (Years)		**7 (6-8+-1.8)**	
Pain	6 (75.0%)	2 (25.0%)	100
Swelling	6 (75.0%)	2 (25.0%)	100
Weight loss	2 (25.0%)	6 (75.0%)	100
Fever	4 (50.0%)	4(50.0%)	100
Severe conjunctival chemosis	8 (100%)	0	100
Local spread	2 (25.0%)	6 (75.0%)	100
Bilateral involvement		6 (100%)	100
Laterality of rhabdomyosarcoma: right (R), Left (L) ‡	4 (50.0%, R) 4 (50.0%, L)		100
Non axial proptosis	8 (100%)	0	100
Metastasis	2 (25.0%)	6 (75.0%)	100
Rapid progression	6 (75.0%)	2 (25.0%)	100
Cervical lymph node involvement	2 (25.0%%)	6 (75.0%%)	100
Diminished vision	8 (100%)	0	100
Incisional biopsy done	8 (100%)	0	100
Homogenous soft tissue mass eroding nearby bony structure in CT scan	8 (100%)	0	100
Histological type of rhabdomyosarcoma: Embryonal (E), Alveolar (A) ‡	**6 (75.0%, E) 2 (25.0%, A)**		100
IRS treatment protocol followed	8 (100%)	0	100
Excision of the tumor (Complete: C, Incomplete: IC)	6 (75.0% IC), 2 (25.0% C)		100
Chemotherapy (VAC*, IVA)**	6 (75.0%, VAC), 2 (25.0% IVA)		100
Radiotherapy	6 (75.0%)	2 (25.0%)	100
Sight saved in last follow up	0	8(100%)	100
Lives saved in last follow up	6 (75.0%)	2 (25.0%)	100

*Vincristine, actinomycin D, Cyclophosphamide.
**Ifosfamide, vincristine, actinomycin D
† Total number of study subjects diagnosed with rhabdomyosarcoma.
‡ Total number of rhabdomyosarcomas, not applicable for ticking the box for positive or negative findings.

There have been no established predisposing risk factors in the current study (**Table I**), this correlated fine with the updated literature of rhabdomyosarcoma with regards to pathophysiology and risk factors as it is believed that the reason behind rhabdomyosarcoma is unknown[16].

Genetic level studies weren't carried out in the current study with any subjects thanks to the study limitations. The alveolar variant of RMS is believed to be related to chromosomal translocations and fewer common translocations involving the PAX genes[17,18]. Loss of heterozygosity is seen within the embryonal subtype[19]. There was no history of parental use of cocaine and marijuana among the parents of the study subjects in the current study. The finding of our study did not compare well with a study done elsewhere20, which reported a correlation of parental use of cocaine and marijuana in RMS children.

The mean age of presentation in the current study was 7 years (6-8+-1.8) in the study subjects in our study, this finding from the present study was comparable to the prevailing knowledge that in orbital RMS the mean age of presentation of the children is 5-9 years[21]. In the current study, the demographic characteristics and clinical characteristics of the study findings as summarized in table one was highly comparable to studies done elsewhere (**Table I**)[3,4]. Intergroup Rhabdomyosarcoma Study (IRS) management protocol was followed in the current study,[4] also keeping in mind the present Children's Oncology Group (COG) treatment and management protocols for RMS[13,14]. Chemotherapeutic agents utilized in the study were Vincristine, Actinomycin D, and Cyclophosphamide (VAC) in most subjects whereas, in two study subjects Ifosfamide, Vincristine and Cyclophosphamide were given as that they had local lymph node metastasis and extensive tumor mass, but none of the study subjects received doxorubicin and cisplatin which are believed to extend the survival rate when given along with VAC regimen[22]. On a median within the study subjects, 10 cycles of chemotherapy were given. Local resection of the tumor with a 2 cm tumor-free margin could not be done in two cases owing to the extensive involvement of the orbit and therefore the ocular tissue. Whereas in six cases (75%) resection of the tumor was done with a good excision up to 2 cm from the tumor margin. Radiotherapy was given to all the cases who survived initial chemotherapy and resection of the first tumor. Sight loss was irreversible because the study subjects needed exenteration surgery. During the study, one study subject of the alveolar variety of RMS with metastasis passed away, the other study subject with alveolar type recurred after treatment and subsequently passed away (**Table I**). The management protocol of the current study was comparable to studies done elsewhere[10,16]. Overall, 5-year survival rates have improved to over 80% in RMS subjects with localized disease, consistent with the recent literature on RMS[22]. However, in metastatic disease, the five-year survival rate is reported to be extremely low at just about 30%, the explanation why two of the study subjects with metastatic disease (**Table I**) in the current study passed away during the treatment phase[23]. Even though combined use of high-dose myeloablative therapy and autologous stem-cell rescue has not improved outcomes for these patients with metastatic disease[24]. In an analysis of knowledge collected by the Surveillance, Epidemiology, and End Results (SEER) program, mortality was highly associated with age, size, and histology[25]. The findings from SEER stated that the 5-year survival rate was highest in children aged 1-4 years (77%) and was worst in infants and adolescents (47% and 48%, respectively). Orbital and GU sites were the foremost favorable (86% and 80%, respectively). Unfavorable sites included tumors of the extremities (50%), retroperitoneum (52%), and trunk (52%). The prognosis for the Embryonal variant of RMS was best (67%) when compared with alveolar histology (49%)[25] . Even if the recurrence occurs after initial therapy has been completed most patients with local recurrence are curable with salvage therapy[25]. In the current study explanation for mortality is probably attributed to incomplete resection of the tumor especially within the alveolar RMS subtype, age of the study subjects (adolescents), and presence of metastasis which is comparable with the existing knowledge regarding RMS and its prognosis as per SEER[25].

Recent update on chemotherapy of rhabdomyosarcoma

In a phase II trial of 87 patients with rhabdomyosarcoma who had experienced a primary relapse or disease progression and whose prognosis was unfavorable, temsirolimus (Torisel) proved superior to bevacizumab (Avastin) as add-on therapy. At 6 months, event-free survival in these patients, whose prognosis was unfavorable, was 65% with temsirolimus versus 50% with bevacizumab, when these agents were added to a chemotherapy regimen of vinorelbine and cyclophosphamide[26,27]. At 6 months, the response rate also favored temsirolimus (47.4% vs 27.5%) as did the number of complete responses (5 vs 4) and also the number of partial responses (13 vs 7), the speed of progressive disease was also better with temsirolimus (28% vs 10%)[26,27]. In a second study of 461 children with intermediate-risk rhabdomyosarcoma, adding irinotecan to combination treatment with vincristine, dactinomycin, and cyclophosphamide (VAC) didn't improve overall or event-free survival. However, the regimen containing irinotecan resulted in an exceedingly lower rate of hematologic toxicity and cumulative dose of cyclophosphamide[26,28].

Rhabdomyosarcoma is a very rare malignancy and is difficult to diagnose, a similar study from Nepal or similar settings with a large sample size focusing on orbital rhabdomyosarcoma would be useful. This article provides a baseline for treatment/management of rhabdomyosarcoma along with establishing the diagnosis.

Conclusions

The prevalence of orbital rhabdomyosarcoma in the current study was higher when compared with other studies. Male predilection is more than the female in rhabdomyosarcoma. Embryonal variant of rhabdomyosarcoma is the commonest subtype. Metastatic disease, alveolar variant both are life and sight threatening.

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ORIGINAL

Medical and psychiatric comorbidity in the patients with intellectual disability in a rehabilitation setting, Kingdom of Saudi Arabia

Comorbilidad médica y psiquiátrica en los pacientes con discapacidad intelectual en un entorno de rehabilitación, Reino de Arabia Saudí

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Abstract

Introduction: Intellectual disability (ID) is a prevalent neurodevelopmental issue globally. People having ID suffer invariably from psychiatric, behavioral, and emotional disturbances. It is reported that a high rate of comorbidity predisposes the patients to a poorer prognosis and quality of life especially if undiagnosed and untreated. We specifically aimed to study the comorbid physical and psychiatric disorders in this vulnerable population group and to find any association with various related variables.
Material: The observational cross-sectional study was conducted on male and female patients admitted with disabilities in Rehabilitation Centre Majmaah. The data was entered and analyzed using IBM SPSS 26.0.
Results: The number of participants (n) was 147. The mean age of the patients was 24.32+2.19 years. Out of all patients, 17 (11.6%) had mild, 33 (22.4%) had moderate, 56 (38.1 %) had severe and 41 (27.9%) had profound ID. About 72% of the sample (n=42) had comorbidity with either a medical or a psychiatric illness whereas 12 participants (8.17%) suffered from both physical and psychiatric disorders. In this study, n= 30/147 (20.40%) had psychiatric comorbidity. There was a preponderance of ADHD (attention deficit hyperactivity disorder) and Behavioural Disorders. Around 87 patients out of 147 (59.2%) had one or more physical comorbidities. The most common medical comorbidity was Epilepsy (26.53%). Overall, significant association was found between severity of physical and psychiatric diseases (p=0.023).
Conclusion: Physical and psychiatric comorbidities are common in ID patients. ADHD, Behavioural Disorders and Epilepsy were predominant in the research.

Key words: Physical comorbidity, psychiatric comorbidity, intellectually disabled, rehabilitation.

Resumen

Introducción: La discapacidad intelectual (DI) es un problema de neurodesarrollo prevalente en todo el mundo. Las personas con DI sufren invariablemente trastornos psiquiátricos, conductuales y emocionales. Se ha informado de que una alta tasa de comorbilidad predispone a los pacientes a un peor pronóstico y calidad de vida, especialmente si no se diagnostican y no se tratan. Nuestro objetivo específico es estudiar los trastornos físicos y psiquiátricos comórbidos en este grupo de población vulnerable y encontrar cualquier asociación con diversas variables relacionadas.
Material y métodos: El estudio observacional transversal se realizó en pacientes masculinos y femeninos ingresados con discapacidad en el Centro de Rehabilitación Majmaah. Los datos se introdujeron y analizaron con el programa IBM SPSS 26.0.
Resultados: El número de participantes (n) fue de 147. La edad media de los pacientes fue de 24,32+2,19 años. De todos los pacientes, 17 (11,6%) tenían una ID leve, 33 (22,4%) moderada, 56 (38,1%) grave y 41 (27,9%) profunda. Alrededor del 72% de la muestra (n=42) tenía comorbilidad con una enfermedad médica o psiquiátrica, mientras que 12 participantes (8,17%) padecían tanto trastornos físicos como psiquiátricos. En este estudio, n= 30/147 (20,40%) tenían comorbilidad psiquiátrica. Había una preponderancia del TDAH (trastorno por déficit de atención e hiperactividad) y de los trastornos del comportamiento. Alrededor de 87 pacientes de 147 (59,2%) tenían una o más comorbilidades físicas. La comorbilidad médica más común era la epilepsia (26,53%). En general, se encontró una asociación significativa entre la gravedad y las enfermedades psiquiátricas (p=0,023).
Conclusiones: Las comorbilidades físicas y psiquiátricas son frecuentes en los pacientes con DI. El TDAH, los trastornos de conducta y la epilepsia fueron predominantes en la investigación.

Palabras clave: Comorbilidad física, comorbilidad psiquiátrica, discapacitados intelectuales, rehabilitación.

Introduction

Intellectual disability (ID) is a prevalent neurodevelopmental issue globally. People having ID suffer invariably from psychiatric, behavioral, and emotional disturbances.[1] People with an ID appear to be admitted with more severe problems and receive more interventions than those without ID.[2] It is reported that a high rate of comorbidity is suggestive of significant problems in the diagnosis of multiple psychiatric illnesses in these patients.[3] In Saudi Arabia between 1990 and 2017, the age-standardized percentage of years lived with disability (YLDs) due to mental disorders (i.e., depression and anxiety), substance use disorders (i.e. drug and alcohol use disorders), and neurological disorders, continued to increase. The percentage of YLDs due to mental disorders was found to be 15·6%, 6.34% for substance use disorders and 10.4% for neurological disorders.[4]

A systematic review reported that the prevalence rates of conditions like Epilepsy (22%), Cerebral Palsy (CP) (19.8%), and Anxiety Disorders (10.1%) in children with ID were higher than the prevalence rates in children without ID.[5] Early detection and adequate treatment of comorbid health conditions are important because these conditions may have a negative impact on the well-being and social participation of children with ID and their families.[6]

The life expectancy of people with mental sub normality and co-morbid psychiatric illness is short as compared to the general population.[7] The excess mortality which is about 60% can be attributed to physical illnesses like Nutritional and Metabolic Diseases, Cardiovascular Diseases, Viral Diseases, Respiratory Tract Diseases, Musculoskeletal Diseases, pregnancy complications, and possibly Cancers. The evidence mentioned in studies may identify etiological causes, necessary for the early identification of these conditions and the development of effective programs[8]. The reason could be that mentally subnormal individuals cannot voice their needs as others, as well as mobility limitations specifically in older adults with ID, they are less likely to receive standard levels of care, as mobility is rarely studied in the ID literature.[9]

Considering the complexity of the bio-psychosocial cause and effect relationship in Intellectually disabled patients with mental and physical illnesses, it is important to know the comorbidity pattern of diseases by targeted research. Keeping in mind the scarcity of published data in this domain in Saudi Arabia, this study was conducted to bridge the knowledge gap about the trends, needs, and presentations of people with disabilities living in a rehabilitation center in Majmaah City. We specifically aimed to study the comorbid physical and psychiatric disorders in this vulnerable population group and tried to find any association with various related variables. Therefore the objectives of the study were to find out the prevalence of comorbid psychiatric disorders among ID patients, to find out the prevalence of comorbid medical disorders among ID patients and to explore any association between psychiatric disorders or medical disorders with the severity of the ID.

Materials and methods

The observational cross-sectional study was conducted on patients admitted with disabilities in Rehabilitation Centre Majmaah. The study participants were both males and females with intellectual disabilities. The data was collected using a systematic random sampling technique to select the patients from an approximate sampling frame. The interval size of 03 was calculated by using the following formula. Based on random value every 2nd patient was selected to reach the sample size of l04. K=N/n, Where n=sample size; N=population size; k=size of interval of selection. The age of participants was between 10-60 years.

Data Collection Procedure:

The Rehabilitation Centre was visited by a team of researchers and medical students who were trained in advance to understand disability and GAF (global assessment of functioning) scoring to fill the observer-rated questionnaire. The questionnaire consisted of demographic details, the patient's diagnosis, and the level of severity of intellectual function as well as physical and mental diseases. The information was extracted from the documented records. Collateral information was taken from attending staff that were allocated to each patient. Participation consent from the family (signed informed consent) in advance through administration was taken. All information was kept purely confidential and was only used for research purposes. The research was approved by the Ethical Review Board of Majmaah University vide reference no MUREC-Jan.28 / COM-2020 / l9-3.

Data analysis:

The data was entered and analyzed using IBM SPSS 26.0. Quantitative variables were expressed as Mean SD, whereas qualitative variables were reported as frequencies and percentages. Pearson Chi-square and Fisher Exact test were applied to observe associations between qualitative variables. A p-value of<0.05 was considered statistically significant.

Results

The number of participants (n) was 147. The mean age of the patients was 24.32+2.19 years. Most of the patients (96.6%-n 142) were in the age range of 11-40 years. Females comprised 53.1 % (78) of the sample, the majority (144) were uneducated and single (98.6). Out of all patients, 17 (11.6%) had mild, 33 (22.4%)

had moderate, 56 (38.1 %) had severe and 41 (27.9%) had profound ID. About 72% of the sample (n=42) had comorbidity with either a medical or a psychiatric illness whereas 12 participants (8.17%) suffered from both physical and psychiatric disorders. Most of them (75%) had a speech disorder of varying severity.

1. Psychiatric Disorders and Intellectual Disability

In this study, n= 30/147 (20.40%) had psychiatric comorbidity. There was a preponderance of ADHD and Behavioural Disorders. The most common comorbidity found was ADHD (11.56%-n=17) followed by Behavioural Disorders (11.56 %- n=17) and (10.2%- n=11) Psychotic Disorders/ Schizophrenia. Few cases of Psychosis (n=9) and a Mood Disorder (n=1) were found in records.

Association of Psychiatric Disorders with the severity of Intellectual disability:

A significant association was found between the severity of ID and psychiatric disorders (P=0.023) as seen in table 1 above. This implied that having a severe ID was associated with increased chances of having a psychiatric illness generally.

2. Medical Disorders and Intellectual Disability

About 87 patients (59.2%) had one or more physical comorbidities. In our study, the most common medical comorbidities were Epilepsy n= 39 (26.53%). Quadriplegia was found in n=13 (8.84%) and Paraplegia in n= 15 (10.20%). Diabetes Mellitus (DM) was found in n=8 (5.44%), 8 patients had CP whereas only one patient each had (0.68%) illnesses, such as Hypertension, Cardiac Anomaly, Impaired Vision , Anemia, Urinary Tract Infection (UTI), Aphasia and CP.

Association of Medical Disorders with the Severity of Intellectual Disability:

Two physical disorders were found to have a statistically significant association with the severity of ID, including Epilepsy (p<0.0001) and Paraplegia (p<0.012).

3. Medications Used by Patients

Among 47 out of 147 patients were on medication (50.34%). Forty-six (31.29%) were on antiepileptics and mood stabilizers, and 24 (16.32%) were on antipsychotics. One patient each was taking medicines like cortisol, calcium, and vitamin supplements.

Discussion

In this study, a total of 147 patients with ID have been analyzed, out of which nearly two-thirds suffered from either one or more comorbidities. This finding is in line with a recent study by Platt et al which cited a prevalence of 65.1% comorbid mental disorders in people with ID. The reason for an even higher prevalence in our sample could be that we included both the physical and the mental comorbidities in our study population.[10]

Intellectual Disability and Psychiatric Comorbidity

We found that a significant proportion of our patients with ID, living in the rehabilitation center had psychiatric comorbidity. There was a preponderance of ADHD and Behavioural Disorders in our sample. Whereas only a few cases of Psychosis and Mood Disorder were reported.

If we compare our findings with other studies done on patients with ID, 14.4%[7] of individuals had psychiatric diagnoses which are somewhat near our study where we found the percentage to be 20 %. That study reported a significant proportion of the patients to be having psychosis (4.4%) like our study (7.48%), whereas the prevalence of Mood Disorders (8.8 %) was much more than what we found in our study (1.36%).[7] Another study by Deb et al in 2001 also reported about 5.6% of Mood Disorders which is also in contrast with our study had low number.[11] Also no cases of ADHD and Behavioural Disorders were found in both the studies.[11,12] The possible explanation for the relatively smaller percentage of Psychotic and Mood Disorders and a higher percentage of ADHD and behavioral disturbances could be the differences in setting and patient population.

Our study population primarily comprised of children and adolescents whereas the other studies were carried out in adult outpatient departments. Another reason for low rates of psychosis and mood symptoms could be better control of symptoms due to the inpatient setting and supervised dispensing of the drugs which ensured better compliance.

Table I: Percentage and association of psychiatric disorders and intellectual disability.

Psychiatric Diagnosis	Mental Retardation				
	Mild n (%)	Moderate n (%)	Severe n (%)	Profound n (%)	p-value
ADHD	3 (17.6)	6 (18.2)	8 (14.3)	0 (0.0)	
Autism	0 (0.0)	0 (0.0)	3 (5.4)	3 (7.3)	
Behavioral Disorders	0 (0.0)	3 (9.09)	10 (17.8)	4 (9.8)	
Mood Disorder	1 (5.9)	1 (3.03)	0 (0.0)	0 (0.0)	
Sleep disorder	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	**p=0.023***
Psychotic Disorders	2 (11.8)	3 (9.09)	6 (0.0)	0 (0.0)	
Anxiety Disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Substance Abuse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Organic Disorder	0 (0.0)	0 (0.0)	5 (8.9)	5 (12.2)	

Table II: Percentages and Association between Intellectual Disability and Medical Diagnosis.

Medical Diagnosis	Intellectual Disability				
	Mild n (%)	Moderate n (%)	Severe n (%)	Profound n (%)	p-value
Hypertension					
No	16 (94.1)	33 (100)	56 (100)	41 (100)	p=0.053
Yes	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	
Diabetes Mellitus					
No	16 (94.1)	33 (100)	52 (92.9)	37 (92.5)	p=0.469
Yes	1 (5.9)	0 (0.0)	4 (7.1)	3 (7.5)	
Urinary Tract Infection					
No	17 (94.1)	33 (100)	55 (98.2)	41 (100)	p=0.651
Yes	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	
Spastic Paraplegia					
No	17 (100)	33 (100)	54 (96.4)	41 (100)	p=0.348
Yes	0 (0.0)	0 (0.0)	0 (3.6)	0 (0.0)	
Quadriplegia					
No	17 (100)	33 (100)	53 (94.6)	31 (75.6)	p<0.001*
Yes	0 (0.0)	0 (0.0)	3 (5.4)	10 (24.4)	
Epilepsy					
No	16 (94.1)	25 (75.8)	44 (78.6)	23 (56.1)	p=0.012*
Yes	1 (5.9)	8 (24.2)	12 (21.4)	18 (43.9)	
Paraplegia					
No	17 (100)	31 (93.9)	48 (85.7)	36 (87.8)	p=0.290
Yes	0 (0.0)	2 (6.1)	8 (14.3)	5 (12.2)	
MSKD					
No	17 (100)	33 (100)	56 (100)	41 (100)	---
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Hypothyroidism					
No	16 (94.1)	33 (100)	56 (100)	41 (100)	p=0.053
Yes	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	
Hemiplegia					
No	17 (100)	32 (97.0)	55 (98.2)	40 (97.6)	p=0.904
Yes	0 (0.0)	1 (3.0)	1 (1.8)	1 (2.4)	
Hemiparesis					
No	17 (100)	33 (100)	55 (98.2)	41 (100)	p=0.651
Yes	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	
Down Syndrome					
No	17 (100)	31 (93.9)	55 (98.2)	38 (92.7)	p=0.407
Yes	0 (0.0)	2 (6.1)	1 (1.8)	3 (4.1)	
Cardiac Anomaly					
No	17 (100)	32 (97.0)	56 (100)	41 (100)	p=0.324
Yes	0 (0.0)	1 (3.0)	0 (0.0)	0 (0.0)	
Total	**17**	**33**	**56**	**41**	

Table III: Percentages and association between Intellectual Disability and Medical Diagnosis continued.

Medical Diagnosis	Intellectual Disability				
	Mild n (%)	Moderate n (%)	Severe n (%)	Profound n (%)	p-value
Diabetes Millets					
No	17 (100)	33 (100)	56 (100)	41 (100)	---
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Poor Vision					
No	7 (100)	33 (100)	55 (98.2)	41 (100)	p=0.585
Yes	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	
Anemia					
No	17 (94.1)	33 (100)	55 (98.2)	41 (100)	p=0.651
Yes	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	
Aphasia					
No	17 (100)	33 (100)	55 (98.2)	41 (100)	p=0.651
Yes	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	
Cerebral Palsy					
No	17 (100)	31 (93.9)	54 (96.4)	37 (90.2)	p=0.413
Yes	0 (0.0)	2 (6.1)	2 (3.6)	4 (9.8)	

Attention Deficit Hyperactivity Disorder:

ADHD was found comorbid in about 18 (12.24%) of the patients. Three patients with mild ID (17.64%), six with moderate ID and eight with severe ID (14.28%) had a diagnosis of ADHD. None of those with profound disabilities suffered from ADHD. This finding is supported by various other studies as well.[8,10,14] ADHD includes the symptoms of over activity, inattention, and impulsivity, which occur significantly higher in children with Learning Disabilities. Dekker and Koot (2003) found a 14.8% prevalence of ADHD in children attending special schools.[13] Emerson (2003) reported an 8.7% prevalence of Hyperkinetic Disorder in children with global Learning Disabilities and 0.9% prevalence in the general population.[13]

Another retrospective study was done on patients under 19 years of age. ADHD was diagnosed in 25.5% of the patients. Of these, 28.3% had coexistent Expressive Language Disorder and 38.7% had to coexist mild Mental Retardation.[14] This ascertains the fact that in children and adolescents with ID, symptoms and diagnosis of ADHD is rather a common finding. Another reason for increased percentage of ADHD might seen in light of responsiveness to treatment shown in the study that ADHD symptoms in patients with Mental Retardation may be less responsive to medical treatment and more susceptible to side effects than in patients without Mental Retardation[13].

Behavioural Disorder:

In our study 11.56% of patients had Behavioural Disorders. The results are consistent with a study conducted by Dekker et al in 2001 in Holland among 968 children of age 6 to 18 years with ID that revealed attention problems in 24.0%, delinquent behavior in 13.7%, and aggressive behavior in 19.2%.[12] In another study like ours, 15% of the adults with severe Learning Disabilities were found to have severe Behavioural Disorders, like Self-Injury, Restlessness, Aggressiveness, Destructiveness, and Impulsivity.[16]

Intellectual Disability and Physical Comorbidity

About 87 patients out of 147 had one or more physical comorbidities (59.2%) in our study sample. This finding is supported by literature that the prevalence rates of chronic health conditions in children with ID are higher than the prevalence rates in studies of children without ID.[2]

People with ID experience more chronic illness than the general.[8] In our study, the most common medical comorbidities were Epilepsy (26.53%), Quadriplegia n=13 (8.84%) and Paraplegia n=15 (10.20%) and few had DM, n=8 (5.44%), and only one patient each had (0.68%) illnesses, including Hypertension, Cardiac Anomaly, Hypothyroidism, Impaired Vision and UTI whereas in another study different results were found including; most common physical comorbidities along with mental sub normality are DM, Cardiovascular Disease, Asthma, and conditions affecting the bones and joints-Osteoporosis, Arthritis which were least present in our study.[22]

Epilepsy:

In our study, 26.53% of the participants had comorbid Epilepsy. Out of half of the total patients, 67 (46.2%) 46 were on antiepileptic or mood-stabilizing medications.

Prevalence rates of Epilepsy were reported in 14 studies and ranged from 5.5% to 35.0%[7]. Though a few studies showed a prevalence rate of Epilepsy to be as low as about 5.44% in the people with disabilities16, a systematic review showed not only higher rates (22%,) but also that the most prevalent chronic health condition in children with ID was Epilepsy.[5]

There have been different postulations for this increased prevalence and frequent comorbidity. Corbet, 1981 found that Epilepsy and Mental Retardation have the same root cause, i.e. Cerebral Imperfection. Corbett (1974) found that Epilepsy in mentally subnormal with an intelligent quotient less than 50 is a particular problem of early childhood and the occurrences of seizures increases with the severity of retardation[12].

Diabetes Mellitus:

Various studies have postulated that people with ID are at greater risk of developing both Type 1 and Type 2 diabetes.[20] In our study 8 patients (5.44%) had DM. Unlike our study, McVilly found that the prevalence of diabetes in people with ID was 8.7% whereas it was 5.4% for the general population[21]. Peterson found that the prevalence of diabetes among people with ID was 19.4%.[22]

One reason for not having so high a prevalence of DM in our sample could be that only a few patients were on antipsychotics which are known to increase the propensity of DM and Metabolic Syndrome if used in high doses and for the long term. Also, a major proportion of our population was in the younger age group so their exposure to antipsychotic medication was relatively not a very long term yet. Lack of continuous screening for DM could have been another reason for missing a few potential cases in this population as well.

Cerebral Palsy:

In our study, we found that only 8 patients (5.44%) had a documented diagnosis of CP. A study from Saudi Arabia revealed that CP was the most common neurologic disorder among Saudi children with a prevalence rate of 23.4%.[23] Another study reported overall, CP was the largest proportion of children (N = 163 (45.2%) with disability[7]. A systematic review has shown that the most prevalent chronic health condition in children with an ID is Epilepsy (22%) followed by CP (19.8%).[5]

This was the most unexpected finding of our study because most of our patients had issues of mobility and various motor disorders which are the main hallmarks of CP. One reason could be that the diagnoses were mainly taken from the medical records and the treating doctors synonymized the diagnosis of ID with CP or categorized them under diagnoses, such as Hemiparesis, Hemiplegia etc. Instead of CP.

Hypothyroidism

A systematic review suggested that the most prevalent chronic health conditions in children with ID were Endocrine and Thyroid Gland Disorders (e.g., Phenylketonuria, Hypothyroidism) which ranged from approximately 0.8% to 13.1%.[7] Another study from Finland reported a prevalence of 0.6% of Congenital Hypothyroidism in children with ID.[19]

People with ID were also almost twice as likely as the general population to have Hearing Loss, Eczema, Dyspepsia, Thyroid Disorders, and Parkinson's Disease according to various studies.[19,22]

These findings are in line with our study as we found n=1 (0.68%) prevalence of Hypothyroidism in our patients.

Down Syndrome:

When we look at various relevant studies, we find that the prevalence of Down's Syndrome was variable in different populations and settings. For example, one inpatient study found the prevalence to be between 2.1-20.3%[7] in people with ID whereas another in Finland reported 14.3% individuals with down syndrome in a rehabilitation center for mentally subnormal individuals[23]. In our population, the prevalence of Down's Syndrome was 4.76% (n=6). This is broadly in line with other available literature.

Other Disorders:

In our study, only one patient each had (0.68%) illnesses like Hypertension, Cardiac Anomaly, Impaired Vision and UTI which is somewhat the same as found in some other studies that reported the rates of disorders of Musculoskeletal, genital/urinary, digestive, or Circulatory Systems to be from 0.8% to 13.1%[7].

Limitations

The main limitation of the study was that the design was observational and cross sectional, and the data was collected mainly using the records.

Conclusion

Physical and psychiatric comorbidities are common in ID patients. ADHD, Behavioural Disorders, and Epilepsy were predominant in the research. One third of the patients had both medical and psychiatric comorbidity. In such cases screening can play a major role in proper management of ID patients. Secondly, comorbidity and complexity of diseases makes it difficult to differentiate between both ADHD and Behavioural Disorders which might result in improper medication management.

Recommendations

Considering these findings and a high prevalence of medical and psychiatric disorders in this patient population, we highly recommend a regular physical and medical screening schedule by the experts in relative domains.

Also, improving the methods of record-keeping and reviewing the diagnosis by psychiatrists and medical specialists instead of general physicians will improve the accuracy of information and data. This can help in policymaking and service delivery by analyzing the needs and demands of these patients.

Also, the drug and medication practices would improve, for example, using stimulants in cases of ADHD, which was the most prevalent comorbidity, can bring about a significant improvement in the overall well-being of the individuals.

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Conflict of interests

The authors have no conflict of interest.

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ORIGINAL

Toxicity profiles of the hydroalocholic seed extract of *Psoralea Corylifolia* L Fabaceae in Wistar rats

Perfiles de toxicidad del extracto hidroalcohólico de semillas de Psoralea corylifolia L Fabaceae en ratas Wistar

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Abstract

Introduction: Ayurveda is well known system of medicine and practiced in Indian subcontinent since about 5000 years. Ayurveda offers holistic life style caring for the individual's mind and spirit as well as their body. *Psoralea corylifolia* Linn. (Fabaceae) is well known traditional plant used in Ayurveda and Chinese system of medicines and known for its beneficial actions in skin diseases such as psoriasis, alopecia, leprosy, leucoderma, and vitiligo etc.
Objective: The aim of present study to determine toxicity of hydroalcoholic extract of *P. corylifolia* in acute and sub-chronic toxicity assay models.
Methods: The albino mice were used in cute toxicity study for dose ranging from 10 to 1000 mg/kg, b.w.; and in sub-chronic toxicity assay, albino wistar rat used for dose ranging from 100 to 500 mg/kg, b.w. Daily body weight, food intake and different biochemical and haematological parameters were measured. Macroscopic observation of the vital organ of the test groups when compared to the control group.
Results: The results of toxicity study showed that there are no toxic symptoms produced in acute as well as in sub-chronic toxicity studies upto 1000 mg/kg, b.w. when tested in albino mice and rats orally. The overall behaviour of the animals was more active and healthy during the treatment period. It was found that there was no remarkable difference indicating the non-toxic property of the seed extract on acute toxicity and sub-acute repeated administration causes mild adverse effects.
Conclusion: The current study provides scientific data on safety of *P. corylifolia*.

Key words: Psoralea corylifolia, babchi, fabaceae, acute toxicity assay, sub-chronic toxicity assay.

Resumen

Introducción: El Ayurveda es un sistema de medicina muy conocido y practicado en el subcontinente indio desde hace unos 5000 años. El Ayurveda ofrece un estilo de vida holístico que cuida la mente y el espíritu del individuo, así como su cuerpo. La *Psoralea corylifolia* Linn. (Fabaceae) es una planta tradicional muy conocida que se utiliza en el sistema de medicina ayurvédica y china y es conocida por sus acciones beneficiosas en enfermedades de la piel como la psoriasis, la alopecia, la lepra, la leucodermia y el vitíligo, etc.
Objetivo: El objetivo del presente estudio es determinar la toxicidad del extracto hidroalcohólico de *P. corylifolia* en modelos de ensayo de toxicidad aguda y subcrónica.
Metodología: En el estudio de toxicidad aguda se utilizaron ratones albinos con dosis de 10 a 1000 mg/kg, p.c.; y en el ensayo de toxicidad subcrónica, ratas albinas wistar con dosis de 100 a 500 mg/kg, p.c. Se midieron el peso corporal diario, la ingesta de alimentos y diferentes parámetros bioquímicos y hematológicos. La observación macroscópica de los órganos vitales de los grupos de prueba se comparó con el grupo de control.
Resultados: Los resultados del estudio de toxicidad mostraron que no se produjeron síntomas tóxicos en los estudios de toxicidad aguda y subcrónica hasta 1000 mg/kg, b.w. cuando se probó en ratones y ratas albinos por vía oral. El comportamiento general de los animales fue más activo y saludable durante el período de tratamiento. Se comprobó que no había diferencias notables que indicaran la propiedad no tóxica del extracto de semillas en la toxicidad aguda y que la administración repetida subaguda causa efectos adversos leves.
Conclusión: El presente estudio aporta datos científicos sobre la seguridad de *P. corylifolia*.

Palabras clave: Psoralea corylifolia, babchi, fabaceae, ensayo de toxicidad aguda, ensayo de toxicidad subcrónica.

Introduction

Traditional medicine has a high impact on the prevention, control and treatment of diseases. In this regard, several medicinal plants and essential oils have been developed for treatment and control of diseases[1]. *Psoralea corylifolia* Linn. (Babchi) is an erect annual herb belonging to Fabaceae family. Medicinal values of *P. corylifolia* have been described in Ayurveda and Chinese Traditional system of medicine[2]. *P. corylifolia* has been reported to possess several bioactivities like laxative, stimulant, aphrodisiac, leprosy, leucoderma, vitiligo, and psoriasis etc[2,3]. *P. corylifo* seeds mainly rich in furocoumarins (e.g. psoralens and 8-methoxypsoralen)[4]. *P. corylifolia* has been reported by several authors as potent antibacterial[5], anti-inflammatory[6,7], anticancer[8-10], antipsoriatic[11], hepatoprotective agent, antifungal, antioxidant, estrogenic, immunomodulatory activity[12,13], and also causes vasodilation. This seed mainly used in the treatment of leucoderma (vitiligo), menopausal symptoms, depression, impotence and leprosy[14].

Due to wide application and utilization of *P. corylifolia* plant as medicinal agent, it becomes necessity of the day to examine its toxicity in in-vivo model. Toxicity assays are performed in short term and long term basis; short term assays are known as acute toxicity assay while long term study refers as sub-chronic toxicity assay[15]. Acute toxicity refers to those adverse effects occurring within a short time but in the case of sub-acute toxicity tests are intended to evaluate the toxicity of the plant samples after repeated administration[16,17]. These methods should be based on the OECD guidelines and examination should include the behavioural responses, mortality, food intake and determination of ALP, ACP, SGPT, SGOT and creatinine level along with histopathological parameters[18,19]. Hence the objective of present study to perform acute, sub-chronic toxicity assays including haematological examination to determine its safety and efficacy as medicinal agent[20]. The seed extract is safe on short term acute study and long term chronic toxicity by repeated oral administration causes mild adverse effects.

Materials and methods

Seed collection and Identification

Dried seeds of *Psoralea corylifolia* (500 g) were collected from Tampcol herbal at Chennai, and it was authenticated by the Pharmacognosist at Captain Srinivasamurthy Drug Research Institute (CSMDRI), Anna Hospital Arumbakkam, Chennai, Tamil Nadu India and confirmed by RAPINAT herbarium, St. Joseph College Trichy.

Chemicals and Equipment

Weighing balance, desiccators, empty bottles, EDTA bottles, capillary tubes, water bath, evaporating dish, haematocrit centrifuge, and Haematology meter. Other materials include methanol, chloroform, distilled water and 10 % formalin.

Preparation of the Hydroalcoholic seed extract

Dried seeds of *P. corylifolia* were shade dried for a week. After drying the seeds (100 g) were coarsely powdered using a pulverizer. Size reduced seeds were extracted by cold percolation method using water and ethanol (1:4) as solvent (200 ml). The extract was concentrated by separating the solvent from the extract and drying it in a water bath. The extracts were weighed and kept in the refrigerator at 4°C until needed.

Experimental Animals

The toxicity study utilized healthy Wistar albino rats of either sex and of about the same age, weighing about 170-250 g, and healthy albino mice of either six and of about the same age, weighing around 20 to 35 g. The Institutional Animal Ethical Committee reviewed the experimental protocol and gave it their approval before it could begin. 817 / 04 / ac / CPCSEA is the CPCSEA registration number. The animals were kept in polypropylene cages with standard pellet feed (Tamil Nadu Veterinary University Animal House, Chennai) and water ad libitum, and were kept in regular conditions (12 hr light / 12 hr dark cycles, 20 ºC to 27º C, 36-60 % humidity).

Acute Toxicity studies

The extract's oral median lethal dose (LD50) was measured in rats using the (20) Dixon and Mood method (1948). Healthy adult albino mice of either sex were separated into six groups (n= 6) and orally fed escalating doses of hydroalcoholic extract (10, 50, 100, 250, 500, and 1000 mg/kg b.w.). When given orally in doses up to 1000 mg/kg body weight, the whole hydroalcoholic extract did not cause any toxicity or mortality in mice when observed up to 24 hours after delivery. Clinical Observations (from the time of injection to 14 days later, clinical signs and symptoms). There were no unusual symptoms in any of the three groups. Below is a summary of the general clinical examination report.

Sub-chronic toxicity studies

Healthy adult albino rats of either sex were separated into five groups (n=5) and orally fed escalating dosages (100, 250, 3500, and 500 mg/kg b. w.) of hydroalcoholic extract, while the control group received 1 percent DMSO vehicle for 90 days, according to OECD-425 (21) recommendations. The treatment was done once daily by orally for 90 days. The rats were fasted for 18 hrs at the end of the 90th day, they were sacrificed after giving due anaesthesia. The blood was collected from the jugular vein and used for the determination of body weight changes, (at 9 am once weekly using a sensitive balance before the commencement of dosing), haematological parameters, biochemical parameters like ALP, ACP, SGPT and SGOT, serum urea and serum creatinine. The haematological parameters

were measured by retro-orbital method. Finally, the histopathological studies also carried out.

At the end of the 90-day observation period, all of the animals were necropsied for pathological abnormalities. The brain, heart, liver, kidney, lungs, spleen, GIT tract, and uterus were removed, weighed, and kept in 10% formalin until utilized for histological research. Each group had a portion of organ tissue preserved in 10% formalin and processed for histopathology. Serial slices of 5 µ thicknesses were made after paraffin embedding and block construction. They were inspected under a microscope after being stained with Haematoxylin and Eosin. Photomicrographs of a few sample specimens were also obtained.

Statistical Analysis

The 't' test was used to examine the results reported as mean ±SD, P<0.05 values were deemed statistically significant[21,22].

Results

Acute toxicity test

Toxicity experiments are carried out to find out the pharmacological level (Lethal dose) but they do not produce any toxic symptoms in the animals. Till the dose of 2000 mg/kg, it is found that all the groups have no mortality at all (**Table I**). However, all the animals are unusually behaved immediately after drug administration, but recovered after 24 hrs. Unusual symptoms of mild writhing and stretching of hind limbs are observed half an hour after drug administration but all the animals are recovered completely after 3 hrs.

Table I: Symptoms observed on treatment.

Dose (mg/kg)	Recovery/ Death After 24 hrs	No. of animals died/ animals treated	Toxicity Observed
10	Recovery	0/6	Nil
50	,,	0/6	F
100	,,	0/6	F
250	,,	0/6	F
500	,,	0/6	F
1000	,,	0/6	F

F = abnormal gait

At higher doses i.e., at the dose of 3000 mg/kg and 4000 mg/kg, it is seen that 80 % of the animals are dead. The survived ones have exhibited severe toxic symptoms, but recovered after 24 hrs (**Table II** and **Figure 1**).

From the above data, it may be concluded that the doses of 500 mg/kg and 1000 mg/kg (LD50) might be the appropriate safe doses to be administered to the mice in order to assess the pharmacological effects.

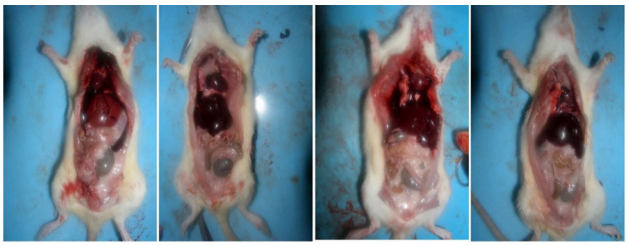
The body weight recorded has given a gradual increase even at higher dosages. The haematological observations for the parameters such as haemoglobin content and RBCs, have recorded decrease in their values in both of the sexes after the treatment with seed extract. But there is no significant reduction in the values. The values of MCV, MCH and MCHC are as comparable to the normal limits. The level of WBC has given increased value for male and PCV has put up similar values in both the sexes before and after the treatment.

Table II: Assessment of LD^{50} dose of *P. corylifolia*.

Dose (mg/kg)	Log Dose	Dead/ Total	% Dead	% Corrected	Probit
10	1.0000	0/6	0	4.17	3.26
50	1.6989	0/6	0	4.17	3.26
100	2.0000	0/6	0	4.17	3.26
250	2.3979	0/6	0	4.17	3.26
500	2.6989	0/6	0	4.17	3.26
1000	3.0000	0/6	0	4.17	3.26
1500	3.1761	0/6	0	4.17	3.26
2000	3.3010	0/6	0	4.17	3.26
3000	3.4771	2/6	33.3	33.3	4.58
4000	3.6021	4/6	66.6	66.6	5.42

Correction for 0% dead = 100(0.25/6); 100 % dead =100X (n-0.25/6)

Figure 1: Rats given with 2000 mg /kg of the extract showing no significant pathological changes at necropsy.



Sub-chronic toxicity

The results of *P. corylifolia* sub-chronic toxicity show that there were significant increases in body weight of female rats given extract at doses of 400mg/kg when compared to the control group. There was no statistically significant difference in the relative organ weights of any of the seed extracts tested. Every animal was monitored on a daily basis for signs of toxicity, body weight, neurological examination, and mortality (**Table III** and **Figure 2**).

On examination, the seed extract did not produce any significant differences in haematological markers (**Figure 3**). At the doses studied, the photomicrograph demonstrated normal architecture in the kidney and liver. On examination, the heart, lungs, spleen, uterus, and ovaries showed no morphological abnormalities in architecture. At the end of the 90-day observation period, all of the animals were necropsied for pathological abnormalities. A thorough post-mortem assessment of all of the animals indicated no major pathological alterations linked to the extract. **Table IV** shows the relative organ weights in detail as well as a summary of necropsy lesions. **Table V** shows the tabulation of lesions at necropsy.

Table III: Sub-chronic toxicity examination through neurological parameters.

S.No	Identification	Locomotor activity	Tail elevation	Ataxic gait	Head position
1	Head	Casual	Normal	None	Without tilt
2	Neck	Casual	Normal	None	Without tilt
3	Body	Casual	Normal	None	Without tilt
4	Tail	Casual	Normal	None	Without tilt
5	Colourless	Casual	Normal	None	Without tilt

Table IV: Relative organ weights.

S.No	Identification	Brain	Lungs	Liver	Kidney	Spleen	Ovary	Heart
1	Head	0.72	0.96	4.8	0.72	0.72	1.2	0.48
2	Neck	1.08	0.81	5.15	1.8	0.54	0.8	0.54
3	Body	91	0.91	4.56	0.68	0.45	1.36	0.45
4	Tail	0.5	0.74	4.7	1	0.5	0.75	0.5
5	Colourless	1.12	0.84	5.36	0.84	0.56	0.84	0.56
Mean ± S.D		0.866 ±0.26	0.854 ±0.08	4.914 ±0.33	0.864 ±0.17	0.554 ±0.10	0.99 ±0.26	0.506 ±0.04

Figure 2: Body weight of sub-chronic oral Toxicity of P. corylifolia by using albino wistar rat.

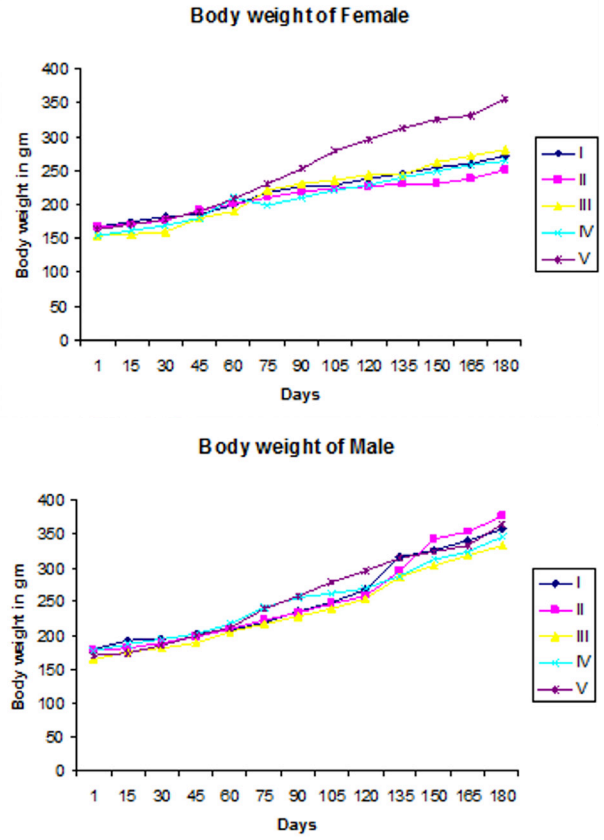


Table V: Tabulation of lesions at necropsy.

Organ	H	N	B	T	C
Liver	NAD	NAD	NAD	NAD	NAD
Lungs	NAD	NAD	NAD	NAD	NAD
Heart6	NAD	NAD	NAD	NAD	NAD
Brain	NAD	NAD	NAD	NAD	NAD
Kidney	NAD	NAD	NAD	NAD	NAD
Stomach	NAD	NAD	NAD	NAD	NAD
Adrenal	NAD	NAD	NAD	NAD	NAD
GIT tract	NAD	NAD	NAD	NAD	NAD
Lymph nodes	NAD	NAD	NAD	NAD	NAD
Testis/ovary	NAD	NAD	NAD	NAD	NAD
Uterus	NAD	NAD	NAD	NAD	NAD

Where, NAD: No abnormal changes detected; H: head; N: neck; B: back; T: tail; and C: colourless.

Histopathology

Histopathological examination of the Heart, Lungs, Liver, Spleen, Pancreas, Kidney, Genital organ, GIT and Leg part of treated and control groups were done. Histopathological observations were carried out for both control and treated group of animals. At the highest dose of 500 mg/kg the results are given for those groups of animals of 90 days' observation after administration of *P. corylifolia* extract can be seen in **figures 3-5**. At 500 mg/kg, the liver architecture showed very minor quiescent inflammatory alterations (Plate 1-E1). At 500 mg/kg, the photomicrograph demonstrated mild acute tubular necrosis with hyperplasia in kidney (Plate 2-E2). However, histology of the GIT tract, heart, spleen, lungs, uterus, and ovaries in the treated groups revealed no aberrant architecture (Plate 1 (A, B, C, D) and 2 (E, G, F, H).

Discussion

According to a recent estimate, nearly 75% of people around the world, mainly in poor nations, rely on traditional medicine and its practice for their health care needs[23]. In rats, the extract's oral median lethal dose (LD_{50}) was determined to be greater than 5000 mg/kg body weight. This indicates that the extract is basically non-toxic when administered acute (orally)[24]. Increased body weight and relative organ weight are usually considered non-toxic effects of extract on animals, resulting in increased food and water consumption[25]. When compared to the control group, the extract generated a rise in body weight, indicating that the extract was rather safe for the rats.

Toxicity experiments were carried out to find out the pharmacological level (lethal dose) but they did not produce any toxic symptoms in the animals till the dose 2000 mg/kg but at higher doses i.e. 3000 mg/kg and 4000 mg/kg exhibit that 80% of the animals died. So that from the result it may be concluded that the doses of 500 mg/kg and 1000 mg/kg (LD_{50}) might be the appropriate safe doses to be administered to the mice in order to assess the pharmacological effects[26]. Whereas the sub-acute toxicity studies exhibit mild abnormal changes were observed in treated animal's liver and kidney organ in comparison with control. Biochemical and haematological parameters were not significantly different between the control and experimental groups of rats[27]. In histopathological studies the pictures do not show any significant shift in the architecture of the heart, lungs, spleen, uterus and ovary of respective organ.

The kidney is a vital organ in the body that helps to maintain homeostasis by performing osmoregulatory functions (electrolyte and blood pressure management, acid-base balance maintenance)[28]. Urea is a by-product of protein metabolism that is eliminated entirely through the kidneys[29], whereas creatinine is a by-product of muscle metabolism that is similarly expelled solely through glomerular filtration[29]. As a result, creatinine, urea,

Figure 3: Pre and Post Haematological reports of sub-chronic oral toxicity of *P. corylifolia* by using albino wistar rats.

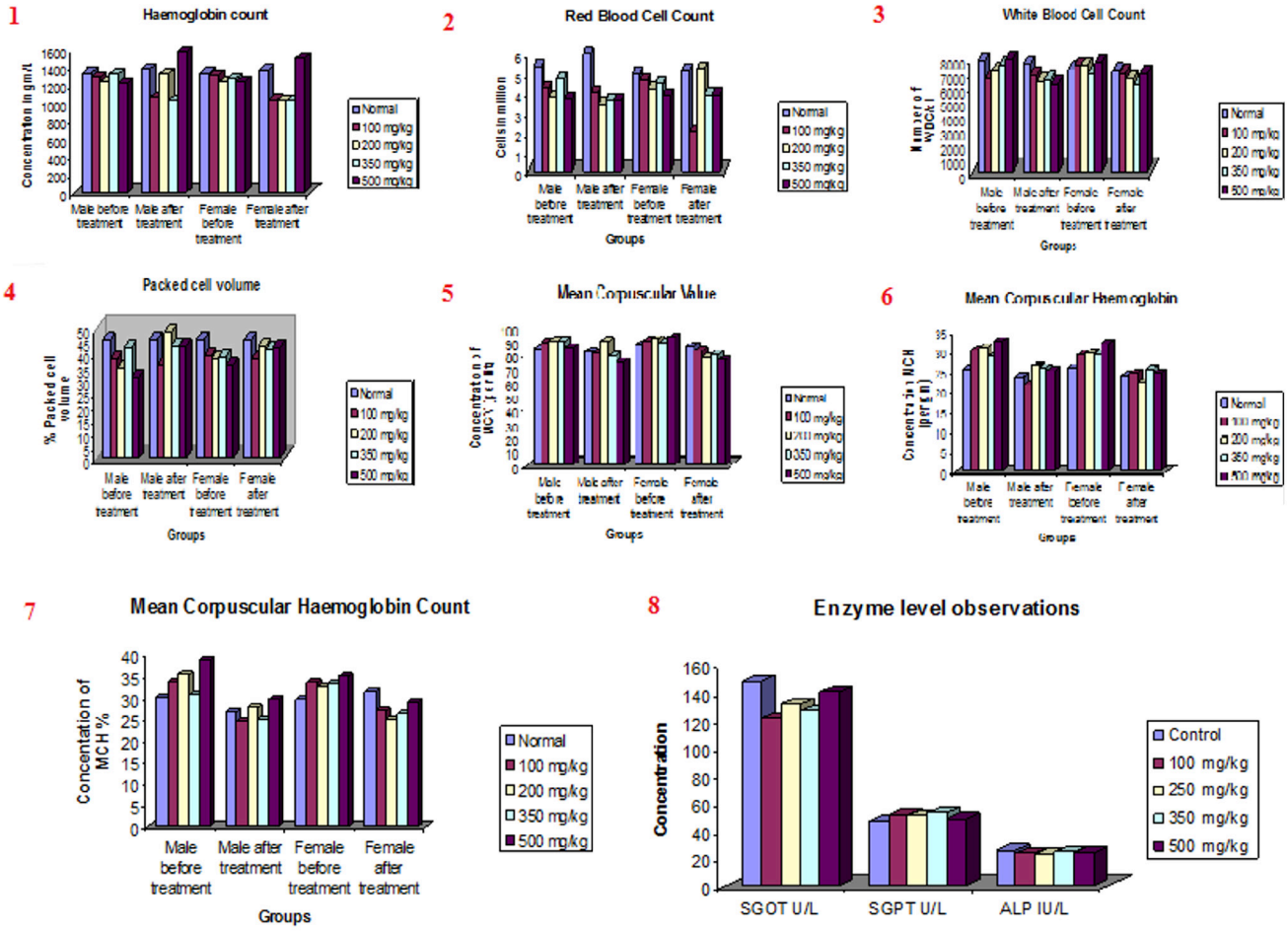


Figure 4: Photomicrographs of a section of tissues (H & Ex250) of Wistar rat's oral administration of hydroalcoholic extract *P. corylifolia*: Heart (A), Lungs (B), Spleen (C), and Liver (D) and Liver (D1).

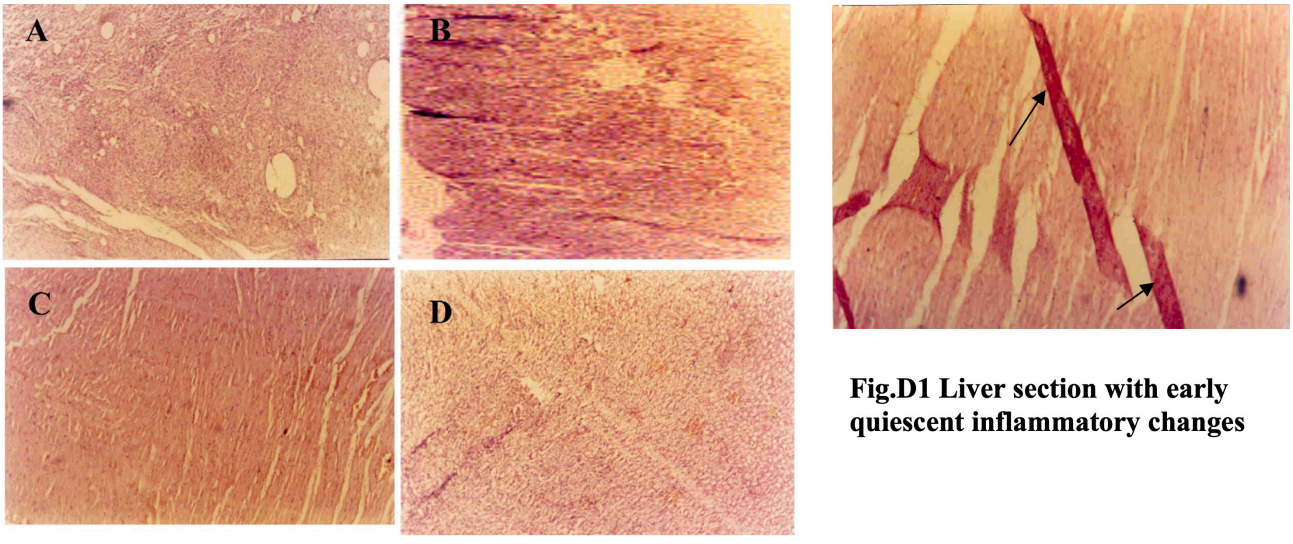
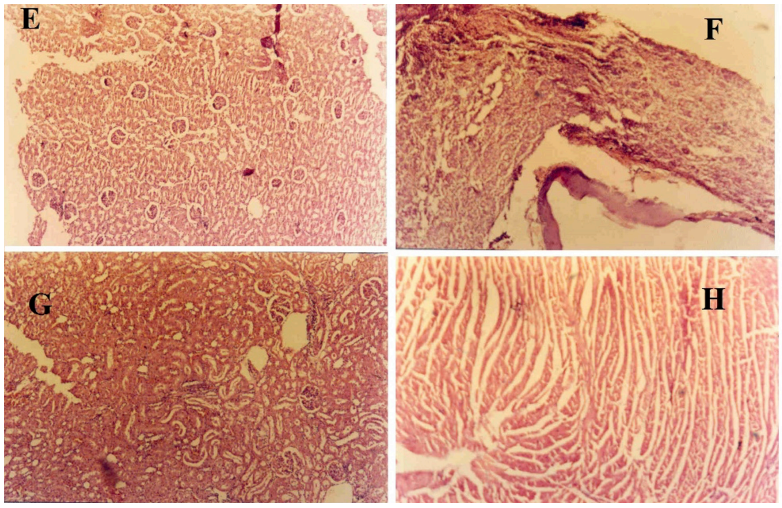


Fig.D1 Liver section with early quiescent inflammatory changes

Figure 5: Photomicrographs of a section of tissues (H & E×250) of Wistar rat's oral administration of hydroalcoholic extract *P. Corylifolia*. Kidney (E), Kidney (E1), Uterus and Ovaries (F), GIT tract (G), and Uterus with histology of ovaries and fallopian tubes (H).



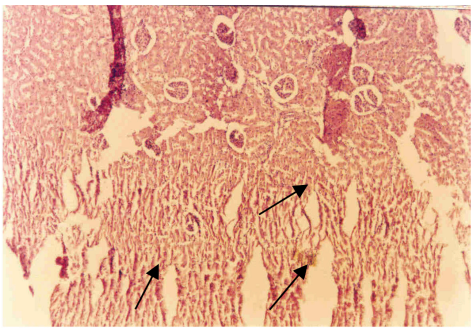


Fig.E1 Kidney with acute tubular necrosis

sodium, potassium, and chloride levels are utilized to assess kidney function[29]. There is no significant increase in the serum levels of renal biochemical parameters tested indicates that the medications tested have no effect on kidney function.

The liver is the most important organ in the living system for drug and xenobiotic metabolism. Biomarkers for assessing liver function include alanine transaminase, aspartate transaminase, and alkaline phosphatase[27,29]. The substantial increases in the level of AST might be an indicator of liver damage, which is suggestive of hepatotoxic impact. Although ALT and AST are commonly employed in the assessment of liver damage caused by extract or any hepatotoxic chemical (since they produce hepatocyte inflammation, cellular leakage, and cell membrane destruction)[30,31], an elevated level of ALT is more specific for liver-related injuries or disorders[32]. A high AST level, on the other hand, can indicate liver damage, myocardial infarction, and muscular injury[33]. ALT is only found in minute amounts in the liver, but it is secreted in the bile, and modest intra-hepatic biliary obstruction causes a significant increase in serum ALP[34]. When testing involves rats, the study of haematological parameters is significant in determining the harmful effect of a chemical since it has a better predictive value of toxicity in humans. When the extract-treated groups were compared to the control group, there was no significant difference in hematological parameters. After 90 days of oral treatment of the seed extract to rats, histopathological analysis revealed that the normal morphology of the heart, lungs, spleen, uterus and ovaries, and the GIT tract were not changed by the examined seed extracts, but liver and kidney had a mild unfavorable effect, suggesting that the extract could be harmful to the liver and kidney.

Conclusion

The hydroalcoholic seed extract of *P. Corylifolia* is a safe drug when taken in small doses; however, repeated use of extracts, may cause toxic effects on certain organs such as the liver and kidney.

Conflict of interests

The authors have no conflict of interest.

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ORIGINAL

Evaluation of sexual dimorphism by radiographic analysis of mental orifice and mandibular height in a sample of Kurdish population of Iraq

Evaluación del dimorfismo sexual mediante el análisis radiográfico del orificio mental y la altura mandibular en una muestra de población kurda de Iraq

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Abstract

Background: A vital part of forensic anthropology is to differentiate between sexes by morphologic analysis of osseous tissue. One of these osseous structures that displays a significant degree of sexual dimorphism is mandibular bone. Gender variances in the mandibular anatomy, from its height, position of mental orifice, gonial angle, bigonial width and bicondylar breadth have been observed in various studies.This study was aimed at evaluating the sexual dimorphism based on the average length between the upper and the lower edge of the mental orifice to the mandibular lower border and the mandibular height on right and left side of the jaw on digital panoramic radiographs in a sample of Kurdish population of Iraq.

Methods: Panoramic radiographs of 460 patients (230 males and 230 females) were included in the study. The length from both inferior and superior margins of mental orifice to the mandibular lower border and the mandibular height in the mental orifice region was measured on both left and right sides. The data was statistically analysed to estimate the differences among the sexes using Independent sample t-test.

Results: The mandibular height in the mental orifice region from alveolar crest to mandibular lower border was more in males as compared to the females, this being statistically significant. The length from superior margin and inferior margin of mental orifice to the mandibular lower border and the mandibular height was more in males as compared to females but was not statistically significant.

Conclusion: The height of the mandible in the mental orifice region showed significant sexual dimorphism in the sample of Erbil population.

Key words: Mandibular height, mental orifice, panoramic radiograph, sexual dimorphism.

Resumen

Antecedentes: Una parte vital de la antropología forense consiste en diferenciar los sexos mediante el análisis morfológico del tejido óseo. Una de estas estructuras óseas que muestra un grado significativo de dimorfismo sexual es el hueso mandibular. Este estudio tenía como objetivo evaluar el dimorfismo sexual basado en la longitud media entre el borde superior e inferior del orificio mental y el borde inferior de la mandíbula, así como la altura de la mandíbula en el lado derecho e izquierdo en radiografías panorámicas digitales en una muestra de población kurda de Iraq.

Métodos: Se incluyeron en el estudio las radiografías panorámicas de 460 pacientes (230 hombres y 230 mujeres). Se midió la longitud desde los márgenes inferior y superior del orificio mentoniano hasta el borde inferior de la mandíbula y la altura de la mandíbula en la región del orificio mentoniano, tanto en el lado izquierdo como en el derecho. Los datos se analizaron estadísticamente para estimar las diferencias entre los sexos mediante la prueba t de muestras independientes.

Resultados: La altura mandibular en la región del orificio mental, desde la cresta alveolar hasta el borde inferior de la mandíbula, fue mayor en los hombres que en las mujeres, siendo esto estadísticamente significativo. La longitud desde el margen superior y el margen inferior del orificio mental hasta el borde inferior de la mandíbula y la altura mandibular fue mayor en los hombres en comparación con las mujeres, pero no fue estadísticamente significativa.

Conclusión: La altura de la mandíbula en la región del orificio mental mostró un dimorfismo sexual significativo en la muestra de la población de Erbil.

Palabras clave: Altura de la mandíbula, orificio mental, radiografía panorámica, dimorfismo sexual.

Introduction

A significant part of forensic sciences has been distinguishing morphometric differences between sexes and among different racial groups. Forensic scientists and anthropologists have been commonly using morphologic features of the lower jaw for sex determination in human skeleton. Significant differences between sexes in the height of mandible (MH), mental orifice location (MF), gonial angle, bigonial width and bicondylar breadth have been shown in numerous studies[1-5].

In forensic field, the radiographs can be an indispensable tool for identification, provided sufficient antemortem records are available. Panoramic radiographs (OPG) show bilateral position of the body, ramus, angle of the mandible, mandibular orifice, and MF. OPG allows MF to be localized more accurately in horizontal and vertical dimensions. On an OPG, MF appears as either rounded, oblong, slit-like or irregular radiolucency, which may be partially or completely corticated, located in between the alveolar margins and inferior border in the mandible[6].

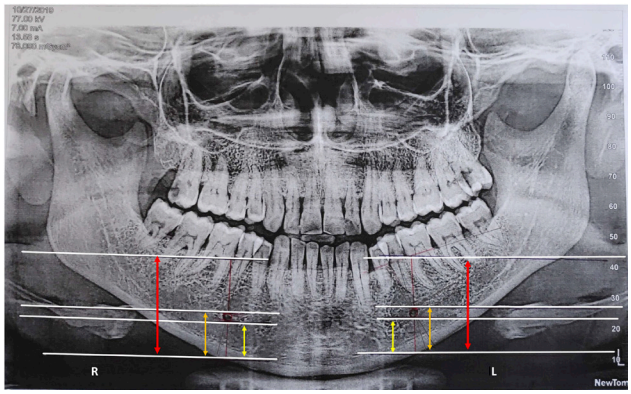
Data regarding gender differentiation in Kurdish population using panoramic radiography based on location of MF and mandibular height (MH) are sparse. With this background, current study was intended to evaluate the gender differences in measurements between the superior border of MF (SMF) and inferior border of MF (IMF) to the MLB and the height of mandible (MH) in the mental orifice region using OPG in a sample of Kurdish population.

Materials and methods

A retrospective study comprising of 460 patients (230 males and 230 females) aged between 20 and 78 years, who underwent conventional OPG for diagnostic, surgical, or periodontal reasons in the radiology department between March 2019 to March 2020. The OPG images were acquired using a Orthopantomograph machine (NewTom Giano, CEFLA s.c., Imola, Italy) with the following technical parameters: Exposure Parameters • Kvp - 72; mA - 8; Exposure time 18 sec Dose to the patient. The inclusion criteria were all patients aged 20 years and over and high quality OPG's with minimum radiographic errors. Exclusion criteria were all patient who had undergone any surgical intervention on mandible and any radiolucent or radiopaque lesions in the mental orifice region. After identifying and marking of the MF on OPG, tangents were marked from IMF, SMF, alveolar crest (AC), and MLB. Perpendicular lines were also marked from these tangents IMF, SMF and AC to the LBM bilaterally. The distance was recorded bilaterally from MLB-SMF, MLB-IMF and MLB-AC (MH) (**Figure 1**).

Standard deviations as well as mean were obtained for MLB-SMF, MLB-IMF and MLB-AC in both genders. Statistical Package for the Social Sciences (SPSS) software version 25 (Armonk, New York: IBM. Corporation) was used to perform the statistical calculations. Mean values calculated and independent sample t-test applied to see the significant differences; P value less than 0.05 was taken to be statistically significant[7,8].

Figure 1: Orthopantomogram showing the measurements – IMF-LMB (yellow line), SMF-LMB (orange line) and MH (red line).



Results

Overall mean measurements between sexes for both sides are shown (**Table I**).

Table I: Total mean measurements between genders on both sides combined.

Total mean measurements				
Gender		**SMF-LBM**	**IMF-LBM**	**MH**
Male	Mean	15.4	12.6	32.7
	N	460	460	460
	Std. Deviation	1.98	1.89	2.67
Female	Mean	13.5	11.1	29.1
	N	460	460	460
	Std. Deviation	1.24	1.19	2.27
Total	Mean	14.4	11.8	30.9
	N	920	920	920
	Std. Deviation	1.88	1.76	3.07

The mean MLB-SMF, MLB-IMF and MH measurements of the whole study sample was 13.9mm,11.4mm and 28.1mm respectively. The average MLB-SMF in males was 14.1mm and in females was 13.6mm. The average MLB-IMF in males was 11.5mm and in females was 11.4mm. The mean MH in males and females were 29.8mm and 26.4 mm respectively. Overall MLB-SMF, MLB-IMF and MH measurement showed significant difference among the genders($p<0.05$). (**Table II**).

Table II: Comparison of mean measurements between genders on both sides combined.

Group Statistics - Combined side						
	Gender	**N**	**Mean**	**Std. Deviation**	**Std. Error Mean**	**Sig. (2-tailed)**
SMF-LBM	Male	460	15.4087	1.98022	.29197	0.000
	Female	460	13.5791	1.24180	.18309	
IMF-LBM	Male	460	12.6770	1.89415	.27928	0.000
	Female	460	11.1183	1.19806	.17664	
MH	Male	460	32.7887	2.67564	.39450	0.000
	Female	460	29.1378	2.27624	.33561	

On the left side (**Table III**), the average MLB-SMF in males was 14.3mm and in females was 13.7mm. The average MLB-IMF in males was 11.5mm and in females was 11.4mm. The mean MH in males and females were 29.9mm and 26.2mm respectively. Again, there was statistically significant difference in MLB-SMF, MLB-IMF and MH on the left side between the genders (p<0.05).

Table III: Comparison of mean measurements between genders on left side.

Group Statistics - Left side						
	Gender	**N**	**Mean**	**Std. Deviation**	**Std. Error Mean**	**Sig. (2-tailed)**
SMF-LBM	Male	230	15.2861	2.06031	.42961	0.001
	Female	230	13.4809	1.23559	.25764	
IMF-LBM	Male	230	12.5543	1.95255	.40713	0.002
	Female	230	10.9774	1.31345	.27387	
MH	Male	230	32.6178	2.64212	.55092	0.000
	Female	230	29.0691	2.48332	.51781	

Comparing the right side (**Table IV**), the average MLB-SMF in males was 13.9mm and in females was 13.5mm. The average MLB-IMF in males was 11.4mm and in females was 11.4mm. The mean MH in males and females were 29.7mm and 26.6mm respectively. Mean MLB-SMF, MLB-IMF and MH measurements did show a statistically significant difference between the genders. (p<0.05).

Table IV: Comparison of mean measurements between genders on right side.

Group Statistics - Right side						
	Gender	**N**	**Mean**	**Std. Deviation**	**Std. Error Mean**	**Sig. (2-tailed)**
SMF-LBM	Male	230	15.5313	1.93505	.40349	0.000
	Female	230	13.6774	1.26781	.26436	
IMF-LBM	Male	230	12.7996	1.86943	.38980	0.001
	Female	230	11.2591	1.08135	.22548	
MH	Male	230	32.9596	2.75711	.57490	0.000
	Female	230	29.2065	2.10267	.43844	

Discussion

Dental studies have been considered a big portion in medical sciences[9-11]. In forensic sciences, sex identification is an imperative aspect involved and many techniques have been utilized including study of skeletal remains, figure prints, polymerase chain reaction and DNA analysis[12-14]. A part from these, gender dimorphism has also been studied using orofacial structures including use of dental records, lip prints, palatoscopy, canine teeth dimorphism, and measurements of orofacial skeleton from radiological studies[15,16]. Radiographs are crucial tools as well as the simplest and cheapest method for age estimation and gender determination when related to the histological and biochemical methods[17].

Extensive studies have been done on gender dimorphism using radiological assessment of skull, maxilla and mandible. Mandible has been sought as a reliable source to study sexual dimorphism as it is a hard and durable bone18. If adequate ante mortem records are lacking, radiographs can perform a valued role in the identification of human remains. Numerous studies have investigated mental orifice in terms of its position concerning sexual dimorphism[19]. Wical et al determined that the distance of mental orifice from the inferior border of the mandible remains relatively constant throughout life despite the age-related resorption of alveolar bone above mental orifice[6]. Apart from this, mandibular height in this region has also been studied extensively for sexual dimorphism[19-21]. For this reason, mental orifice (SMF and IMF), alveolar crest (AC) and lower mandibular border (LMB) in this region was chosen for measurement.

In the present study, the mean of MLB to SMF values and MLB to IMF value were higher in males when comparing to females which was statistically significant(p<0.05). This is in agreement with studies done in other population of the world such as Catovie et al, Mahima et al, and Thomas et al.[2,22,23] This was similar comparing both right and left side between the sexes, which showed higher measurement in males than females. In contrast, Vodanovic et al detected that the mean value of MLB to IMF does not exhibit sexual dimorphism.[24] The differences observed in our study may be due to racial variance and small sample size of our study sample. Overall mean mandibular height in males (32.7± 2.6) was definitely more than the females (29.1 ± 2.2). This difference in the mandibular height was statistically significant (p<0.05). When comparing either sides (right side or left side) mean mandibular height in the premolar region was more in males as related to females and the difference was statistically significant (p<0.05). This result of current study is consistent with studies conducted in other populace of the world[24].

Based on the outcomes in this study, we can deduce that the mandibular height and the position of the mental orifice in relation to mandibular lower border does show sexual dimorphism in this small sample of Kurdish population in Erbil. The drawback of the current study was the small sample number because of which this study results may not be applicable to the whole Kurdish population of Iraq. Additional studies are required on a larger sample size to confirm the gender dimorphism in the mandible among this population group. The present survey showed that despite all advances in dental studies[25-30], several issues need to be assess in more accurate manner

Conclusion

Differentiating between sexes on an OPG based on the height of the mandible and position of mental orifice in relation to the mandibular lower border may be possible. Sexual dimorphism does exist in the mandible among the Kurdish populace. Further studies on a larger sample size can enhance the understanding of this sexual dimorphism in mandible.

Conflict of interests

The authors have no conflict of interest.

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ORIGINAL

The management of human papilloma virus infection: results of the paloma clinical trial and derived research projects

El manejo de la infección por el virus del papiloma humano: resultados del ensayo clínico paloma y proyectos de investigación derivados

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Abstract

We present the results of an investigative trial that very significantly validate the use of Papilocare®, a vaginal application gel, for the clearance of the presence in the lower female genital tract of the human papilloma virus and the regression of low-grade intraepithelial lesions that its infection initially causes in the cervix. Based on these results, two new lines of research are proposed and detailed.

Key words: Papilloma virus, clearance, low grade intraepithelial lesion, conization.

Resumen

Se presentan los resultados de un ensayo de investigación que validan de forma muy significativa el uso de Papilocare®, un gel de aplicación vaginal, para la eliminación de la presencia en el tracto genital inferior femenino del virus del papiloma humano y la regresión de las lesiones intraepiteliales de bajo grado que su infección provoca inicialmente en el cuello uterino. A partir de estos resultados, se proponen y detallan dos nuevas líneas de investigación.

Palabras clave: virus del papiloma, aclaramiento, lesión intraepitelial de bajo grado, conización.

Introduction

In 1974 Harald zur Hausen identified and described the structure of the human papillomavirus (HPV)[1], a sexually transmitted virus[2] that has subsequently been identified as a necessary causative agent of cervical cancer (CC)[3] and of a proportion discharge from other cancers, as shown in **tables I** and **II**.

Table I: Annual number of causal HPV cancers in Europe.

Cancer of	Men	Women
Penis	1.090	
Anus	1.700	2.930
Head and neck	12.700	2.530
Vulva and vagina		3.850
Cervix		23.250

Source: Ref. 4.

The latest data available for Spain are expressed in **table II**:

Table II: Date of Spain.

Cancer of	Number of cases	% HPV +
Anus	360	324
Cervix	1.948	1.948
Penis	330	132
Vulva	570	228
Vagina	105	74
Oro-pharynx	800	216
Pre-neoplastic cervix	54.600	54.600

These data confirm the great relevance of the causal HPV oncological pathologyand, consequently, of the enormous importance of its prevention.

The CLEOPATRE[6] study revealed the prevalence of HPV infection in women in Spain, data that have not been subsequently corrected. The study evaluated 1,918,805 women between 18-65 years of age, distributed proportionally by population rate in all the Spanish Autonomous Communities. **Figure 1** reflects what was

detected in the study: around 30% of women under 30 years of age are HPV + and around 10% from this age, for a global of 14%.

The natural history of CC, perhaps the best known cancer in its development of all of us who suffer, has been precisely identified, encompassing the entire oncogenic process, from the initial viral presence to invasive cancer, passing through intraepithelial lesions, low and high grade[7].

We have solid evidence that vaccination against HPV has high rates of efficacy, effectiveness, efficiency and safety and that the current recommendation of secondary preventive methodology –early diagnosis, screening– of the CC is well established[8], taking its joint action –vaccine, screening– to what we have called "Integral Cervical Cancer Prevention", aimed at responding positively to the call made by the World Health Organization to eradicate CC[9] from our world, the first cancer in which this health action of so much draft is possible.

But we did not have any strategy that, applied to women who are carriers of HPV, a significant fraction of the female population, as previously noted, would facilitate the clearance of the virus and the regression of the initial lesion caused in the epithelium by its presence, the low-grade squamous intraepitelial lesión (LG.SIL). We did not have it, but the recent publication of the results of the PALOMA study has filled this gap[10], a study preceded by the demonstration that the application of Papilocare®, a vaginal administration gel that basically contains Coriolus versicolor, a fungus containing polysaccharidopeptides, Polysaccharide-K / Krestin (PSK) and Polysaccharidopeptide (PSP), caused a very intense normalization of the vaginal ecosystem and, in addition, very clearly improved the epithelialization of the cervix[11]. The PALOMA trial was designed as a phase IIb - III, prospective, randomized to a Papilocare® treatment group versus routine clinical practice, that is, follow-up without further ado, clinical practice for which the expected results are known, HPV clearance at 6 months of 29%[12], and a regression of the LG.SIL at 2 years of 59%[13]. Papilocare® significantly demonstrated to cause a 63% clearance of high-risk HPV 16 after 6 months of treatment and to re-epithelialize the neck of uterus of women carrying high-risk strains of HPV in 87.8% of cases, percentages markedly higher than those obtained, as indicated above, with current clinical practice. The PALOMA results, which were confirmed by two independent studies carried out in parallel[14,15], open a door until now closed, that of being able to intervene in the day-to-day care in the treatment of the presence of HPV in the lower genital tract and in that of LG.SIL.

Papilocare® also showed a very high tolerability, expressed in that there were no serious adverse effects related to the treatment and only two dropouts due to mild intolerance were noted.

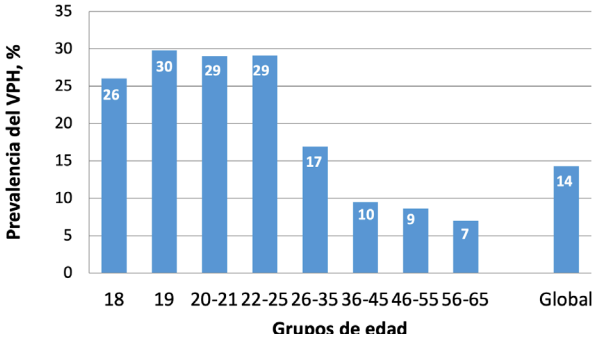
The research group was also interested in sub-analyzing whether these high efficacy data from Papilocare® were reproduced in women over 40 years of age, a group that, being a carrier of HPV, is at a clear high-risk of developing CC, given its immunosenescence[17], a concept coined a few years ago, related to the gradual deterioration of the immune system caused by the natural advancement of age and that involves both the host's ability to respond to infections and the development of long-term immune memory. The analysis of this group of women over 40 years of age has concluded[18] that the data obtained in the PALOMA study are improved: 90.5% regression of the LG.SIL in the treated group versus 33% in the control group; 66.7% clearance of high-risk HPV in the treated group versus 44.4% in the control group.

We believe that all these results are of great importance, since they provide a solid basis for a therapeutic indication lacking evidence so far.

As a consequence of these excellent results, the research group has considered two new projects:

- Apply Papilocare® post-conization to explore if a normalization of the vaginal microbiota is obtained, usually altered by the presence of HPV: modifications of the microbiota play a decisive role in the development of CC[19].
- To test whether the anal application of Papilocare® obtains the same results as its vaginal application in women with rectal HPV: there is evidence that a high fraction of women with HPV in the lower genital tract also present it in anus[20], a relevant fact and that together with the lack of agreements and application of early diagnosis techniques and programs[21,22] could explain the tendency to increase the incidence of anal cancer, 90% causal HPV[23], which the registries note[24]

Figure 1: Prevalence of VPH according age (%).



Conflict of interests

JaC has received travel and / or research grants and / or conference and / or consulting fees from Genomics, GSK, Merck, Procare Health, Qiagen, Roche, and SPMSD.
DD has received conference and / or consulting fees from Sanofi Pasteur, MSD, and Procare Health.
ACL has received consulting fees from Procare Health.LS ha recibido honorarios por conferencias y/o asesorías de Shionogi, Iprad y Procare Health.
FL has received travel and / or research grants and / or conference and / or consulting fees from Bayer, Boiron, Novonordisk, Iprad, and Procare Health.
JoC has a professional relationship with Procare Health for medical advice.
CE has an employment relationship with Procare Health.
YG has an employment relationship with Procare Health.
SP has received research grants and / or fees for conferences and / or consultancies and / or for being a member of the advisory committee from Pfizer, Amgen, MSD, Sandoz, Procare Health, Bayer, MSD, Serelys, Shionogi, Servier, Abbott, Novo Nordisk, Theramex and Gedeon Richter.

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ORIGINAL

Estimación del nivel de riesgo cardiometabólico en trabajadores con sobrepeso/obesidad durante la pandemia Covid-19. Estilo de vida y variables sociodemográficas

Cardiometabolic risk level estimated in workers with overweight/obesity. Lifestyle and sociodemographic variables

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Resumen

Introducción: La obesidad se ha convertido en una pandemia mundial de origen multifactorial y puede ser más común de lo que se diagnostica considerando únicamente el Índice de Masa Corporal (IMC).
Metodología: Estudio descriptivo transversal en 815 trabajadores de edades entre 18-66 años, datos recogidos en los reconocimientos periódicos de vigilancia de la salud de las empresas participantes desde marzo de 2020 hasta junio de 2021.
Se estima el Nivel de Riesgo Cardiometabólico (NR) desde 0 a 3 en función de la presencia de: síndrome metabólico, riesgo cardiovascular elevado y valores fuera de rango de, al menos, dos parámetros de adiposidad. Se establecen relaciones con variables sociolaborales y con hábitos de vida (dieta y actividad física).
Resultados: Más del 70% de la población estudiada presenta algún grado de riesgo y se relaciona significativamente con el IMC (<0.0001), es mayor en varones y aumenta con la edad. Los indicadores de adiposidad son el factor que más se asocia con el NR en hombres y en mujeres, en el NR2 destaca la mayor presencia de Síndrome metabólico en mujeres y de Riesgo cardiovascular en hombres (<0.0001). El nivel de actividad física se relacionan con el NR en ambos sexos, pero en la adherencia a la dieta mediterránea se observan diferencias estadísticamente significativas entre hombres y mujeres.
Conclusión: El NR estimado guarda relación con el IMC, se relaciona con la edad, género, nivel cultural y actividad física realizada. Su estratificación facilita actuaciones preventivas, de control y seguimiento coordinado en trabajadores españoles.

Palabras clave: obesidad; riesgo cardiometabólico; cuestionario PREDIMED; cuestionario IPAQ.

Abstract

Introduction: Obesity has become a worldwide pandemic of multifactorial origin and may be more common than is diagnosed considering Body Mass Index (BMI) alone.
Methodology: Cross-sectional descriptive study in 815 workers aged 18-66 years, with data collected in the periodic health surveillance examinations of the participating companies from March 2020 to June 2021.
The Cardiometabolic Risk Level (CRL) of each participant is estimated from 0 to 3 according to the presence of: metabolic syndrome, elevated cardiovascular risk and values outside the range of at least two adiposity parameters. Relationships were established with sociolaboral variables and lifestyle habits (diet and physical activity).
Results: More than 70% of the population studied presented some degree of risk and this was significantly related to BMI (<0.0001), which was higher in men and increased with age. Adiposity indicators are the factor most associated with NR in men and women; in NR2 there is a greater presence of Metabolic Syndrome in women and Cardiovascular risk in men (<0.0001). The level of physical activity was related to NR in both sexes, but statistically significant differences were observed between men and women in adherence to the Mediterranean diet.
Conclusion: The estimated NR is related to BMI, age, gender, cultural level and physical activity. Its stratification facilitates preventive actions, control and coordinated follow-up in Spanish workers.

Key words: Obesity; cardiometabolic risk; PREDIMED questionnaire; IPAQ questionnaire.

Introducción

La prevalencia de la obesidad, como enfermedad de origen multifactorial y pandemia mundial, se ha duplicado desde 1980. Actualmente, casi un tercio de la población mundial presenta sobrepeso u obesidad, independientemente de la residencia, origen étnico o nivel socioeconómico.

Algunos estudios epidemiológicos recientes sugieren que diagnosticar la obesidad solo en base al Índice de Masa Corporal (IMC) puede suponer infradiagnóstico, dificultando su prevención y control poblacional[1].

La enfermedad cardiovascular (ECV), directamente relacionada con la obesidad, es la causa más común de morbilidad y mortalidad mundial, particularmente en presencia de síndrome metabólico (SMet). Su prevención incluye actuar sobre los factores de riesgo cardiovascular (RCV), e invenciones dirigidas a diagnosticar, tratar y prevenir el SMet y la obesidad grave[2].

La presencia de SMet con prevalencia en torno al 31%, duplica el riesgo de desarrollar enfermedad coronaria o cerebrovascular y aumenta[1,5] veces el riesgo de mortalidad por todas las causas[3]. Tras contraer la enfermedad por COVID-19 se observa peor evolución en pacientes obesos lo que, junto a las complicaciones cardiometabólicas relacionadas con la obesidad, incrementa el riesgo de muerte en estos pacientes[4].

Es objetivo de este trabajo establecer unos niveles de riesgo cardiometabólico que faciliten actuaciones preventivas, control y seguimiento coordinado en trabajadores españoles, valorando la presencia de RCV, SMet e indicadores de adiposidad, de forma independiente al grado de sobrepeso u obesidad que presenten.

Metodología

Estudio descriptivo transversal en población laboral española, con muestra de 815 trabajadores (481 hombres y 334 mujeres), de edades entre 18-66 años, durante los reconocimientos periódicos de vigilancia de la salud de las empresas participantes desde marzo de 2020 hasta junio de 2021, con participación voluntaria y consentimiento informado para el uso epidemiológico de los resultados.

El estudio fue aprobado por el Comité Ético de Investigación Clínica del Área de Salud de Baleares (IB 4383/20).

El peso y la altura se midieron con báscula SECA 700 y tallímetro SECA 220. El IMC se calculó como el peso en kg dividido por el cuadrado de la altura en metros. Se utilizaron los rangos para IMC considerados por la OMS: normopeso <25; sobrepeso >25-<30; obesidad grado 1 >30-<40; obesidad grado 2 >40[5].

El perímetro de cadera y el perímetro de cintura fueron determinados con cinta métrica modelo SECA 20.

La composición corporal se determinó con el analizador TANITABC-420MA, estimando el porcentaje de grasa corporal y grasa visceral.

Como **indicadores de adiposidad** (IA) se han calculado los siguientes:

- Perímetro de cintura (PCI): normal en el hombre un valor <94 cm y en la mujer <80 cm.
- El índice cintura/cadera (ICC): normal en hombres si es <0,94 y en mujeres si es <0,84.
- El índice cintura/altura (ICA): normal si es <0,5 tanto para hombres como para mujeres.
- El porcentaje de grasa corporal (GC): normal en hombre si es <10 y en la mujer si es <20.
- La grasa visceral (GV): normal si es <10 para ambos, hombres y mujeres.

Se considera riesgo la presencia de al menos 2 de los IA valorados alterados.

Las **variables sociales y laborales** incluidas en el estudio han sido:

- Edad- rangos: 18-39 años; 40-50 años; 51-66 años.
- Género: mujer u hombre.
- Clase social y tipo de trabajo: a partir de la Clasificación Nacional de Ocupaciones del año 2011 (CNO-11), según propuesta del grupo de determinantes sociales de la Sociedad Española de Epidemiologia[6]. Para el tratamiento estadístico de nuestros datos se ha utilizado la clasificación reducida a tres categorías:
  - Clase I. Directores/gerentes, profesionales universitarios, deportistas y artistas.
  - Clase II. Ocupaciones intermedias y trabajadores por cuenta propia sin asalariados.
  - Clase III. Trabajadores/as no cualificados/as.
- El tipo de trabajo, según la simplificación de estos mismos autores, se distingue como manual (blue collar) y no-manual (white collar).
- Nivel de estudios: se categorizaron en tres niveles, de acuerdo con el sistema educativo vigente en España:
  - Elementales: Si el participante realizó los seis niveles básicos, desde primero a sexto de primaria.
  - Medios: haber cursado la educación secundaria obligatoria (E.S.O)
  - Superiores: se incluyen todos aquellos que hubieran realizado alguna enseñanza universitaria o de formación profesional en grado superior.
- Características del puesto de trabajo: se incluyó manipulación manual de cargas y conducción de vehículos (al menos 1/3 de la jornada laboral) y trabajos sedentarios (al menos el 50% de la jornada sentados).

Se valoró la adherencia a dieta mediterránea (MedDiet) mediante el cuestionario PREDIMED, con puntuación:< 9 baja adherencia > 9 buena adherencia[7] y la actividad física (AF) semanal mediante el cuestionario IPAQ reducido: actividad física moderada como mínimo 600 MET y alta, al menos 3000 MET[8].

Se consideraron pacientes con RCV elevado a los que obtuvieron un riesgo de muerte cardiovascular ≥ 5% en las tablas del SCORE y/o un riesgo ≥ 10% en las tablas de Framingham-REGICOR[9].

El síndrome metabólico se calculó con la aplicación disponible on line y validada en pacientes españoles que incluye: sexo, perímetro abdominal, triglicéridos, tensión arterial máxima y mínima y glucemia basal, considerando presencia de SMet con tres o más parámetros alterados[10].

Se propone en este estudio calcular el Nivel de Riesgo Cardiometabólico (NR), valorando la presencia o no de: SMet, RCV elevado (medido con Score o Regicor) y valores anómalos en 2 o más de los indicadores de adiposidad (IA). Estos valores se relacionaron de forma independiente con el valor del IMC clasificado por la OMS con los parámetros anteriormente referidos.

Se establecen así 4 niveles de Riesgo Cardiometabólico en función de la presencia de ninguno, 1, 2 ó 3 aspectos alterados: NR 0= ninguno de los aspectos valorados alterados; NR1= 1 de los 3 aspectos valorados en límites de no-normalidad; NR 2= 2 de los 3 aspectos valorados en límites de no-normalidad y NR 3= los 3 aspectos valorados alterados (**Tabla I**).

Se establecen actuaciones preventivo/asistenciales en función del NR estimado:

NR-0. No repercusión en ningún apartado: Control regular
NR-1. Repercusión en 1 parámetro: Vigilancia y control con medidas iniciales
NR-2. Repercusión en 2 parámetros –Intervención desde medicina del trabajo y/o derivación especializada y coordinada.
NR-3. Repercusión en 3 parámetros - derivación especializada y coordinada y control y seguimiento por medicina del trabajo

Análisis estadístico

Se realizó un análisis descriptivo de las variables categóricas, calculando la frecuencia y la distribución de las respuestas para cada una de ellas. Para las variables cuantitativas se calculó la media y la desviación estándar y para las cualitativas el porcentaje. Se realizó un análisis de asociación bivariante mediante el test de 2 (con una corrección con el test estadístico exacto de Fisher, cuando las condiciones lo requerían) y una prueba t de Student para muestras independientes. El análisis estadístico se realizó con el programa SPSS 27.0, considerando valor p de <0,05 estadísticamente significativo.

Resultados

Las características de la muestra poblacional se recogen en la **tabla II**.

Población de 48 años de edad media global, con IMC en valores de sobrepeso, más en hombres (27,49) que en mujeres (26,33), y diferencias significativas entre ambos en todos los IA, teniendo en cuenta los distintos valores de referencia en algunos de ellos según género: el perímetro de cintura está elevado en la mujer (84.5 cm) pero es casi normal en el hombre (94.6 cm). El ICA y el ICC están en los límites de la normalidad tanto en hombres como en mujeres. La grasa corporal está elevada en ambos géneros, (24,7 en hombres y 36,08 en mujeres). La grasa visceral está elevada en hombres (11,35) pero es normal en mujeres (7,5).

No se observan diferencias significativas en el nivel educacional entre géneros. En ambos géneros predomina la clase social tipo III y realizar un tipo de trabajo manual, encontrando valores más elevados en hombres en ambos casos, con diferencias también estadísticamente significativas. Se observan, asimismo, diferencias significativas en las características del puesto de trabajo: en los varones predomina la conducción de vehículos (al menos 1/3 de la jornada) con manipulación manual de cargas (MMC) y en las mujeres los trabajos con sedentarismo (al menos el 50% de la jornada).

Refieren mayor adherencia a la dieta mediterránea las mujeres, con resultados significativos, pero es mayor el porcentaje de hombres que realiza un nivel alto de actividad física.

La distribución porcentual del Nivel de Riesgo Cardiometabólico (NR) estimado se muestra en la **figura 1** y refleja que más del 70% de la población estudiada presenta algún grado de riesgo, si bien el más prevalente es el NR1 con un 43,5% (al menos 1 de los 3 factores estudiados alterados) frente al 23.3 % y 8.7%, respectivamente, de los trabajadores que presentan un NR2 o NR3 (2 ó 3 de los factores estudiados alterados).

Se muestra en la **tabla III-A** la distribución individualizada en hombres y mujeres de los 3 aspectos cuantificados para estimar el NR (presencia de síndrome metabólico, RCV elevado y al menos 2 indicadores de adiposidad alterados): se observan mayores porcentajes de valores alterados en hombres en todos los aspectos, con significación estadística, siendo especialmente amplia esta diferencia en RCV elevado (41,85 % en hombres frente a 11.34% en mujeres).

Las relaciones entre el NR estimado y el IMC calculado se muestran en la **tabla III-B**. Encontramos relación estadísticamente significativa entre IMC elevado y NR altos (p>0.001). Los trabajadores con normopeso

presentan de forma predominante NR0 (62%); el NR1 es el más frecuente en los que tienen sobrepeso, pero es de destacar que un porcentaje moderado de ellos presenta NR 2 (27.5%); y en los trabajadores con obesidad (tipo 1 ó 2) más del 43% se encuentra en NR 2 y más del 23% en NR 3, aunque llama la atención que el 33.5 % de los que presentan obesidad tienen NR1 (bajo).

En la **tabla III-C** se recogen las relaciones del NR estimado con los tres factores de riesgo valorados. En NR1 (un parámetro alterado) lo más frecuente, en ambos géneros, es tener al menos 2 índices de adiposidad alterados (88.83% y 96.36% respectivamente). En NR2 (2 parámetros alterados), el 100% de los trabajadores valorados presentan al menos 2 IA alterados, pero en el

Tabla I: Estimación del nivel de riesgo cardiometabólico y relación con el IMC.

IMC	Presencia de SMet SÍ/NO	RCV alterado Score/Regicor SÍ /NO	IA (Señalar los que estén alterados)						Nivel de Riesgo Cardiometabólico			
			1. GV	2. GC	3. PCi	4. ICA	5. ICC	Resultado: >2 IA alterados Sí/No				
normopeso (<25)									NR0	NR1	NR2	NR3
sobrepeso (>25-<30)									NR0	NR1	NR2	NR3
obesidad tipo 1 (>30-<40)									NR0	NR1	NR2	NR3
obesidad tipo 2 (>40)									NR0	NR1	NR2	NR3

IMC= Índice de masa corporal; SMet = síndrome metabólico; RCV= riesgo cardiovascular
IA=indicadores de adiposidad: GV=grasa visceral ;GC=grasa corporal ;PCi=perímetro de cintura
ICA= índice cintura/altura;ICC= índice cintura/cadera

Tabla II: Características de la muestra. Comparativa hombres-mujeres.

Variables analizadas			Hombres n=481	Mujeres n=334	P
			Media (dt)	Media (dt)	
Variables antropométricas y de adiposidad (medias)	Edad		48,25 (8,35)	48,89 (8,16)	0.277
	Peso		82,79 (13,93)	67,97 (11,98)	<0.0001
	Altura		173,42 (6,81)	160,72 (5,98)	<0.0001
	IMC		27.49 (4,01)	26,33 (4,47)	<0.0001
	Cintura		94,61 (10,96)	84,35 (11,43)	<0.0001
	Cintura/altura		0,55 (0,06)	0,53 (0,07)	<0.0001
	Cadera		106,22 (58,83)	99,00 (10,13)	0.027
	Cintura/cadera		0,92 (0,07)	0,85 (0,06)	<0.0001
	Grasa corporal		24,70 (6,58)	36,08 (7,78)	<0.0001
	Grasa visceral		11,35 (4,53)	7,53 (2,65)	<0.0001
			Hombres %	Mujeres %	
Clasificación IMC (porcentajes)	Normopeso		29.11	41.62	0.001
	Sobrepeso		48.86	39.52	
	Obesidad		22.04	18.86	
Variables sociales y culturales (porcentajes)	Nivel estudios	Básicos	49,06	41,92	0.116
		Intermedios	32,43	35,63	
		Superiores	18,50	22,46	
	Clase social	Clase I	3,33	2,40	<0.0001
		Clase II	20,58	36,83	
		Clase III	76,09	60,78	
	Tipo de trabajo	Trabajo no manual	23,91	39,22	<0.0001
		Trabajo manual	76,09	60,78	
Características de su puesto de trabajo (porcentajes)	Trabajo sedentario (Sentado > 50%)		25,16	41,92	<0.0001
	Conducción de vehículos (al menos 1/3 de la jornada) + MMC		71,93	53,29	<0.0001
Hábitos de vida: Dieta mediterránea-PREDIMED	Adherencia dieta mediterránea alta		43,87	56,89	<0.0001
Hábitos de vida: Actividad Física-IPAQ	Ejercicio bajo		1,87	3,29	0.041
	Ejercicio moderado		40,33	47,31	
	Ejercicio alto		57,80	49,40	

dt= desviación típica, magnitud en que se desvían las diversas puntuaciones obtenidas de su valor medio. Se considera significativo un valor de p<0.005; IMC: normopeso <25; sobrepeso >25-<30; obesidad grado 1 >30-<40; obesidad grado 2 >40; PREDIMED: < 9 baja adherencia a MedDiet, >= 9 alta adherencia; IPAC: actividad física moderada al menos 600 SMet , alta actividad física al menos 3000 SMet .

Tabla III: Distribución porcentual de los factores incluidos en la valoración del nr estimado. Relación con IMC y factores de riesgo valorados. Diferencias por género.

A. Distribución porcentual de los factores incluidos en la valoración del NR. Diferencias por género			
	Hombres %	Mujeres %	P
Presencia de SMet	20.88	16,82	<0.0001
Presencia de RCV elevado	41,85	11,34	<0.0001
Presencia de ≥ 2 IA alterados	75,05	68.26	0.001

B. Relación del NR estimado con el IMC y los factores de riesgo valorados							
Relación del nivel de riesgo estimado y relación con el IMC							
NR estimado	Normopeso		Sobrepeso		Obesidad		P
	n	%	n	%	n	%	
NR 0	173	62.0	26	7.1	0	0	<0.0001
NR 1	89	31.9	207	56.9	57	33.9	<0.0001
NR 2	16	5.7	100	27.5	72	42.9	<0.0001
NR 3	1	0,4	31	8,5	39	23.2	<0.0001

C. Relación del NR estimado y relación con los 3 factores valorados. Diferencias por género									
NR estimado*	Presencia de SMet			Presencia de RCV elevado (Score/Regicor)			Presencia de ≥ 2 IA elevados		
	hombres	mujeres	p	hombres	mujeres	p	hombres	mujeres	P
Nivel de Riesgo 1	1.06	0		11.73	4.03		88.83	96.36	
Nivel de Riesgo 2	30.37	77.78	<0.0001	73.28	25	<0.0001	100	100	0.006
Nivel de Riesgo 3	100	100		100	100		100	100	

*Se excluye el NR 0 por no presentar ninguno de los factores valorados alterados. Se considera significativo un valor de p<0.005. IMC: normopeso <25; sobrepeso >25-<30; obesidad grado 1 >30-<40; obesidad grado 2 >40; Se considera alto riesgo Score ≥ 5% y Framingham-REGICOR ≥10%. Se considera la presencia de Síndrome metabolic (SMet) con tres o más parámetros alterados

Tabla IV: Relación entre el nivel de riesgo estimado con variables sociales y laborales.

Relación entre el Nivel de Riesgo Estimado con: edad, género, clase social, tipo de trabajo y nivel cultural																	
	Edad				Género			Clase social				Tipo de trabajo			Nivel cultural			
	18-39	40-50	51-66	p	hombre	mujer	p	I	II	III	p	manual	No manual	p	Bajo	medio	alto	p
NR-0	54.26	25.19	14.66	<0.0001	20.58	29.94	<0.0001	20.83	22.52	25.31	0.483	25.31	22.36	0.582	19.41	27.27	31.10	0.015
NR-1	38.76	55.18	37.03		39.09	49.40		58.33	40.55	43.76		43.76	42.28		43.35	43.27	43.29	
NR-2	6.98	15.93	33.65		28.48	16.47		12.50	26.58	22.85		22.85	25.20		25.80	22.91	19.51	
NR-3	0.00	3.70	14.66		11.85	4.19		8.33	10.36	8.08		8.08	10.16		11.44	6.55	6.10	

Relación del NR estimado con las características del puesto de trabajo desempeñado												
Nivel de riesgo estimado	Tareas sedentarias						Conducción de vehículos+MMC					
	hombres			mujeres			Hombres			mujeres		
	sí	no	p	Sí	no	p	sí	no	p	sí	no	p
NR-0	11.57	23.61	0.221	30.00	29.90	0.448	23.99	11.85	0.112	30.34	29.49	0.339
NR-1	40.50	38.61		46.42	51.55		38.14	41.48		50.00	48.72	
NR-2	30.57	27.78		19.29	14.43		27.75	30.37		14.60	18.58	
NR-3	17.36	10.00		4.29	4.12		10.12	16.30		5.06	3.21	

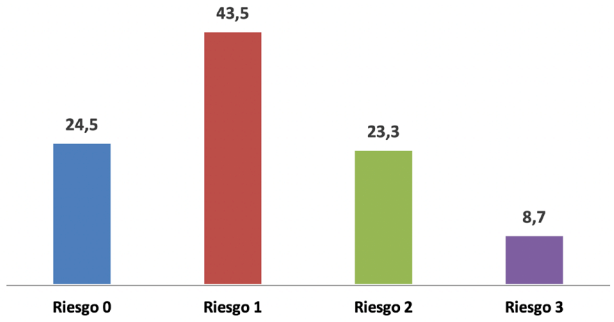
MMC= manipulación manual de cargas; Se considera significativo un valor de p<0.005.

Tabla V: Relación entre el nivel de riesgo estimado y los hábitos de vida: alimentación mediterránea y actividad física.

Relación de los resultados del cuestionario PREDIMED con el NR estimado						
Nivel de riesgo estimado	Adherencia alta			Adherencia baja		
	hombres	mujeres	p	hombres	mujeres	P
NR-0	25.12	31.58	<0.0001	17.04	27.78	<0.0001
NR-1	31.75	47.36		44.81	52.08	
NR-2	31.75	16.32		25.93	16.67	
NR-3	11.38	4.74		12.22	3.47	
Relación de los resultados del cuestionario IPAC con el NR estimado						
	Actividad física / Ejercicio bajo/moderado			Actividad física / Ejercicio alto		
	hombres	mujeres	p	hombres	mujeres	P
NR-0	10.34	24.26	<0.0001	28.06	35.75	<0.0001
NR-1	41.38	49.11		37.41	49.70	
NR-2	32.02	21.30		25.90	11.52	
NR-3	16.26	5.33		8.63	3.03	

Se considera significativo un valor de p<0.005; PREDIMED: < 9 baja adherencia a MedDiet, >= 9 alta adherencia; IPAC: actividad física moderada al menos 600 SMet, alta actividad física al menos 3000 SMet .

Figura 1: Distribución porcentual de nivel de riesgo cardiometabólico estimado (NR).



segundo factor, en hombres predomina, el RCV elevado (73.28%), mientras que en las mujeres destaca la presencia de SMet (77.78%). En el NR3, por definición, los tres parámetros valorados se encuentran alterados.

En la relación entre el NR estimado y las variables socio-demográficas: edad, género, clase social, tipo de trabajo y nivel cultural (**Tabla IV**), se ha encontrado significación estadística con la edad (la prevalencia de NR 2 y 3 aumenta con la edad), el género (mayor presencia de NR elevados, 2-3, en varones) y nivel cultural (prevalencia más alta de NR 2-3 en estudios bajos). No se observan diferencias significativas en el NR en relación con clase social, tipo de trabajo o características del puesto desempeñado.

Al relacionar el NR estimado con el grado de actividad física (AF), tanto en hombres como en mujeres encontramos mayor prevalencia de NR elevados (2-3) en aquellos que realizan ejercicio bajo/moderado. Se observan, sin embargo, resultados paradójicos en relación con el grado de adherencia a la dieta mediterránea: los hombres que refieren adherencia baja presentan menor porcentaje de NR 2 y las mujeres menor prevalencia de NR3. Existen diferencias estadísticamente significativas entre géneros: en los hombres encontramos NR más elevados (NR 2 y 3) que en las mujeres en relación con bajo nivel de ejercicio y baja adherencia a dieta mediterránea (**Tabla V**).

Discusión

Los resultados de nuestro trabajo muestran que más del 70% de la población estudiada presenta algún nivel de riesgo cardiometabólico y que el NR se asocia a distintos factores relacionados con obesidad. Cerca de una cuarta parte presenta NR 2, esto es, dos factores alterados, siendo los más coincidentes en hombres el SMet y el RCV. El NR aumenta a medida que lo hace el IMC.

En este trabajo se ha simplificado la clasificación de la OMS del IMC con el objetivo de no subdividir la muestra en exceso, si bien esto puede suponer un sesgo ya que, en la actualidad, la categorización se basa en una clasificación en seis grupos, tanto en la clasificación ampliada de la OMS como por trabajos más recientes[11] que han servido para documentos de consenso de manejo de la obesidad, como el recientemente publicado por la SEEN[12].

Respecto al RCV, el informe de 2019 del Atlas de la Sociedad Europea de Cardiología, muestra un aumento progresivo en los últimos 30 años de la prevalencia de obesidad y diabetes, que supone un desafío para lograr mayores reducciones en la carga de ECV intensificando iniciativas que permitan reducir el riesgo y priorizar la prestación de atención de salud cardiovascular[13].

El SMet definido por la OMS como una condición patológica caracterizada por obesidad abdominal, resistencia a la insulina, hipertensión e hiperlipidemia, se asocia con un aumento del riesgo de enfermedad coronaria, enfermedad cerebrovascular y de mortalidad por todas las causas con un elevado costo por atención médica y pérdida de actividad económica potencial[14].

En nuestro trabajo, tanto hombres como mujeres presentan con frecuencia al menos dos IA fuera de los rangos de normalidad. En todos los casos, el NR es mayor en los hombres y aumenta con la edad, por lo que las estrategias han de tener en consideración esta visión de género, tanto más cuando el 65% de la población estudiada está en niveles de sobrepeso/obesidad tipo 1 y que el NR aumenta según lo hace la obesidad cuantificada en función del IMC.

El NR se relaciona con los hábitos de vida: dieta mediterranea recogidos con el cuestionario PREDIMED y Actividad Física recogido con el cuestionario IPAQ reducido. Si bien en algunos estudios se apunta que la evidencia que respalda el uso del IPAQ-SF como indicador de actividad física relativa o absoluta es débil[15], el debate en torno a este cuestionario sigue abierto[16] y en otros estudios se afirma que los instrumentos IPAQ tienen propiedades de medición aceptables, y propiedades de medición razonables para monitorizar los niveles de actividad física de adultos de 18 a 65 años en diversos entornos. El formulario corto de se recomienda para el seguimiento y el formulario largo para investigaciones que requieren una evaluación más detallada[17]. En nuestro caso, su uso ha sido sencillo y bien aceptado, haciéndolo recomendable para estudios epidemiológicos en entorno laboral.

En las mujeres encontramos mayor adherencia a dieta mediterránea, mientras que los hombres refieren más actividades físicas intensas y en ambos el NR es menor al aumentar la Actividad Física. Estudios realizados en este tema en países como EE. UU. afirman que la obesidad se asocia con mayor prevalencia de FRCV y la actividad física y el entrenamiento se relacionan con factores de riesgo cardiometabólico mejorados y pérdida de peso por creación de un balance energético negativo[18]. Por el contrario, el sedentarismo se encuentra entre los

principales factores de riesgo modificables relacionados con las enfermedades cardiovasculares y la mortalidad por todas las causas. Los autores recomiendan la práctica de ejercicio habitual para la prevención de enfermedades crónicas no transmisibles, incluida la obesidad y la enfermedad cardiovascular[19]. Estudios realizados en población coreana muestran que la actividad física regular se asocia con baja prevalencia de enfermedades cardiovasculares, independientemente de la composición corporal y de los factores de riesgo convencionales, con una dosis-respuesta positiva[20].

En estudios realizados sobre adherencia a dieta mediterránea, los autores destacan que el consumo de fruta reduce el riesgo cardiovascular y síndrome metabólico, especialmente en personas de mayor edad[21]. También diversos estudios epidemiológicos y ensayos clínicos proporcionan evidencias que respaldan el efecto beneficioso de la dieta mediterránea tradicional (MedDiet) sobre el riesgo de diabetes mellitus tipo 2 y síndrome metabólico[22]. Los resultados obtenidos en nuestro trabajo no son totalmente coincidentes con esta evidencia, ya que encontramos trabajadores con baja adherencia a MedDiet que tienen NR bajos (0-1). Esta divergencia podría explicarse porque, para calcular el nivel de riesgo cardiometabólico (NR) se tienen en cuenta otros factores de riesgo, además de la presencia de síndrome metabólico.

Nuestro estudio se ha desarrollado en periodo de pandemia COVID-19, lo que puede suponer un sesgo en los resultados ya que ha supuesto una modificación de los hábitos de vida en nuestro país, hecho este que se refleja también en otros estudios en Europa (Italia y España) y América Latina (Brasil, Chile y Colombia) durante este período pandémico del SARS-CoV-2 y que han observado mayor prevalencia de inactividad en la población y modificaciones en la dieta, con mayor consumo de ultraprocesados, especialmente en América Latina[23]. Nuestros hallazgos refuerzan la importancia de promover un estilo de vida saludable, con ejercicio y dieta mediterránea, aún más durante los períodos de aislamiento social.

Destacamos como fortalezas de este trabajo su tamaño muestral, el hecho de que recoja datos del periodo de pandemia COVID en España y la aportación de un cálculo global en obesidad que se extiende al riesgo tanto metabólico como cardiovascular (SMet + RCV) y a los IA, que dan una idea global que permite anticiparse al riesgo en algunos casos y actuar precozmente en otros.

Como sesgos considerar que el estudio se ha llevado a cabo en población en edad laboral, excluyendo menores de 18 y mayores de 66 lo que impide extrapolar resultados a población general, no poder calcular el RCV en menores de 40 años y la desigual distribución en los grupos de riesgo (pocos incluidos en los NR3 lo que puede desvirtuar el resultado).

Conclusiones

El nivel de riesgo cardiometabólico guarda relación significativa con el IMC, aumenta con la edad, niveles educativos bajos y es más alto en hombres. En el NR 2, el factor más prevalente es la alteración de Índices de Adiposidad, el RCV es más prevalente en hombres y la presencia de SMet en mujeres. El NR se relaciona directamente con bajos niveles de actividad física y muestra resultados contradictorios con la adherencia a la dieta mediterránea, con diferencias entre hombres y mujeres.

La estratificación del NR puede ser un apoyo en actuaciones preventivas, de control y seguimiento coordinado en trabajadores valorando, junto con el IMC, la presencia de RCV, síndrome metabólico, indicadores de adiposidad y la influencia de la dieta mediterránea y el ejercicio físico realizado.

Conflicto de intereses

Los autores declaran no tener conflicto de intereses.

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ORIGINAL

Digitization with 3D haptic technology in dental training

Digitalización con tecnología háptica 3D en la formación dental

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Abstract

Introduction: 3D haptic technology stands out in the field of dentistry as a tool that allows preclinical practice, which is very close to reality. The objective of this study is to collect the assessments of teachers, students, and other groups related to dentistry, on the use of this technology in the teaching-learning process.
Methodology: Exploratory, non-probabilistic study. A survey and interviews are given to 865 subjects from different fields of dentistry to collect assessments on the use of 3D haptic technology in teaching.
Results: The evaluation of different interest groups related to the teaching of the Dentistry degree, both in the interviews and in the surveys carried out, show a high degree of user satisfaction and the conviction that this tool can help in the learning of dentistry professionals.

Key words: virtual reality, dental health, education.

Resumen

Introducción: La tecnología háptica 3D se destaca en el campo de la odontología como una herramienta que permite una práctica preclínica, muy cercana a la realidad. El objetivo de este estudio es recoger las valoraciones de docentes, estudiantes y otros colectivos relacionados con la odontología, sobre el uso de esta tecnología en el proceso de enseñanza-aprendizaje.
Metodología: Estudio exploratorio, no probabilístico. Se realiza una encuesta y entrevistas a 865 sujetos de diferentes campos de la odontología para recopilar valoraciones sobre el uso de la tecnología háptica 3D en la enseñanza.
Resultados: La evaluación de diferentes grupos de interés relacionados con la docencia de la carrera de Odontología, tanto en las entrevistas como en las encuestas realizadas, muestran un alto grado de satisfacción de los usuarios y el convencimiento de que esta herramienta puede ayudar en el aprendizaje de los profesionales de la odontología.

Palabras clave: realidad virtual, salud dental, educación.

Introduction

A fundamental part of the teaching-learning process in the field of dentistry involves acquiring procedural knowledge, that is, it involves "knowing how" to do something, or knowledge in action[1] . The automation of certain motor and executive skills is necessary to be able to carry out interventions in any of the treatments that current dentistry students will have to enact in their professional work.

To move from declarative knowledge, that is, having ideas and knowledge of how things should be done (theoretical knowledge) to procedural knowledge or knowing how to do them (practical application), the most important thing is to carry out practical activities continuously, habitually, and consciously to be able to acquire the necessary skills with a high level of automation. This is how, by doing things many times with the aim of acquiring the skills involved, the student will be able to reduce the cognitive load required to develop the activity.

In the field of health sciences in general and in dentistry in particular, where carrying out internships implies carrying out treatments with real patients, being able to exercise the necessary skills for learning is, in most cases, truly complex, and the same time, it entails a great responsibility, which is why it is necessary to use methods that allow the acquisition of preclinical skills with the maximum guarantees to face clinical application[2].

At the Adema University School, a center attached to the University of the Balearic Islands, we have state-of-the-art 3D haptic technology, which allows training through virtual practices in different oral and dental treatments. This technology is capable of transferring realistic sensations, allowing one to see and to feel at a tactile and auditory level, a high degree of similarity to reality, while performing multiple dental treatments[3].

During the process of incorporating 3D haptic technology into dentistry degree studies, the opinion of the different users of the aforementioned technology has been collected in order to know their assessment. After using the simulators, they were administered a questionnaire and an interview was conducted through which their assessments were collected.

Material and method

Study is exploratory, qualitative, not probabilistic

1. Poll

The survey was conducted in autofill format through the Google Forms application , voluntarily and anonymously. A question was included in which the participants expressed consent for the use of the data collected for research purposes. No identification data was collected except for differences in interest groups: teachers, students, dentists and others.

The questionnaire was administered after using the 3D haptic simulators and included questions directed, first of all, to assess the degree of use that participants had in handling the computer devices. That is, if they used them on a daily basis and if they had had any previous experience with 3D haptic technology. The next questions assessed the use of 3D haptic tools in preclinical practice and their possible usefulness for practicing treatments of complex cases before treating real patients. Finally, they were asked about the degree to which it helped in their training, to use 3D haptic technology as a tool to acquire skills during the learning process.

2. Interviews

An undirected interview with open questions focused on assessing the experience of using the simulators, and the degree of application to the teaching of dentistry.

3. Selection of participants

The sample for both the questionnaire and the interview is a deliberate selection or intentional sample, since it takes into account the relationship of dentistry studies with the use of 3D haptic technology at the Adema University School during the academic years 2018-19 and 2019-20 (ceasing to collect information during a period in which access to the center was not possible due to a state of alarm due to covid-19).

Included in the sample are dental degree and undergraduate students, professors from the Adema University School, professors who visited the school and who teach the Degree in Dentistry at other Universities, Dentists in professional practice and representatives of dental brands. Likewise, taking advantage of other visiting professionals; politicians, directors and teachers from other centers were asked to assess the 3D haptic technology.

A total of 865 subjects distributed as follows: 90 Dentistry Students, 550 Undergraduate Students (includes Oral Hygiene Superior Technician, Dental Prosthesis Superior Technician and Baccalaureate students), 50 Dentists, 40 Dentistry professors of the School Adema University and 25 from other Universities, 30 dentistry visitors and 40 representatives of dental brands, 15 politicians, 5 school directors and 20 school teachers.

4. Target

The objective pursued was to assess, after the experience of using 3D haptic technology, its use-value as a tool to improve learning during undergraduate studies, and if it was considered that virtual simulation could be an element to improve the training of our students.

Results

The assessment and opinion collected by applying interviews and surveys to different interest groups related to

the field of oral health and the teaching of the Dentistry degree have provided the following results.

1. Poll

In relation to the level of knowledge regarding the use of computing devices, most of the respondents valued their level as medium or medium-high (**Figure 1**). Of the sample, only 3.5% indicated that they used digital technology little, or not on a daily basis, while 65.5% indicated that they had medium use.

56.7% indicated that they did not know 3D haptic technology before using it in Adema, while 40% indicated that they had known it before. When asked how long they had known it, 40% indicated that it was less than two years ago, 36.7% less than a year and 20% for six months.

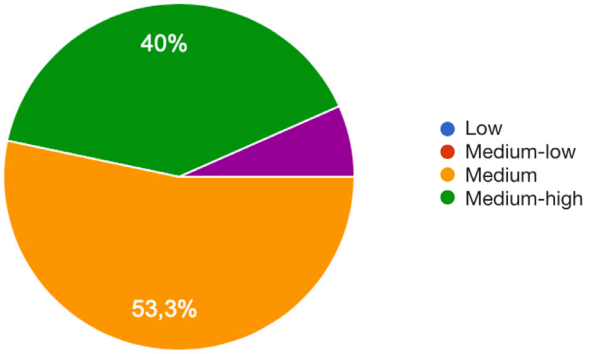

Figure 1: Level of knowledge in the use of computing devices.

They were asked about the degree to which the simulation was close to reality (**Figure 2**), to which the majority responded medium high and high.

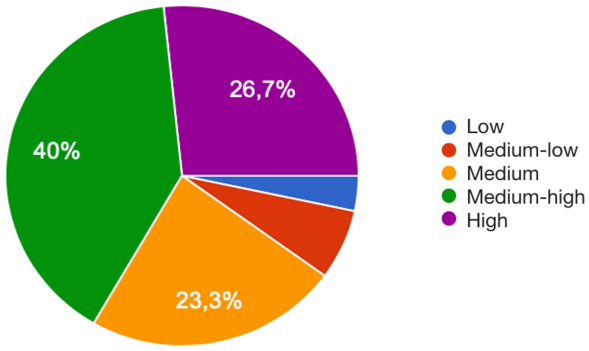

Figure 2: Degree to which simulators approximate to reality.

The foregoing implies the level of validity that this technology can have for the preclinical practice that all students must carry out during their training. Most respondents consider the validity to be medium-high or very high (**Figure 3**). They also consider that it can be a useful tool for training in complex cases, for testing treatments before carrying them out with patients (**Figure 4**).

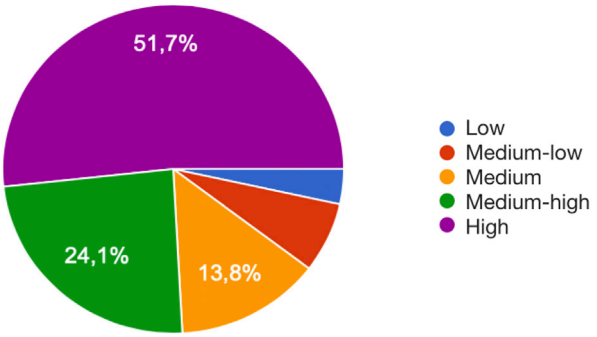

Figure 3: The level of validity that 3D haptic technology has for learning in preclinical practice.

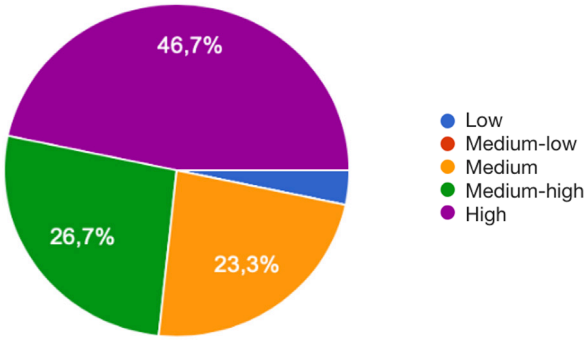

Figure 4: Usefulness of the technology for training before dealing with real cases.

When asked if our respondents would have liked to have had 3D haptic technology earlier in their learning process, and whether it would have helped them advance their obtaining skills, the answer was positive (**Figure 5**), in fact 86.7% indicated that they would have liked this technology earlier.

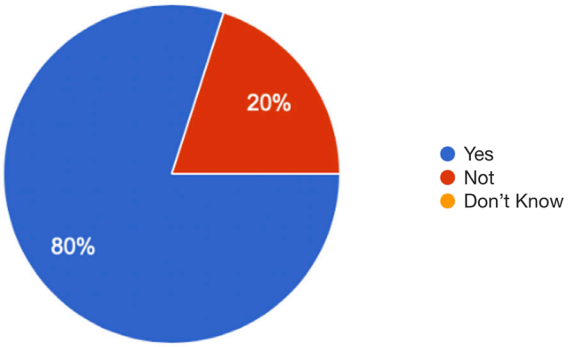

Figure 5: Degree to which 3D Haptic Technology would have allowed them to advance in obtaining skills.

Finally, we wanted to know if they considered it appropriate to use this technological innovation in our university school, to which the respondents answered affirmatively (**Figure 6**).

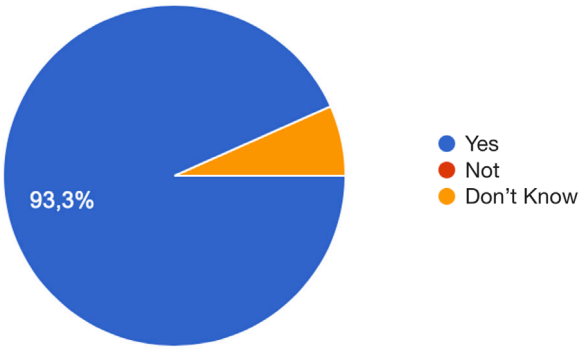

Figure 6: Assessment of the uses of technological innovations at the Adema University School.

2. Interview

After analyzing the content of the answers obtained after the interviews, the results are specified by interest groups, differentiating between students, teachers, other interested parties, and dentists.

Dentistry and undergraduate students:

- They enjoy playing and learning
- They feel new sensations
- They are having fun

Teachers from the Adema University School and from other universities where the Degree in Dentistry is taught:

- They find it a great tool for teaching-learning
- Students will be better able to acquire skills
- Students can improve learning outcomes.
- Teachers will have to update
- Teachers need training to prepare their classes using simulators

Other stakeholders including medical visitors, teachers, center directors and politicians:

- It is an advance in the methodology of teaching students.
- They see many possibilities

Dentists in professional practice:

- The benefit that they would have had at the beginning of their learning if they had had this technology at their fingertips.

Conclusions

Haptic technology is occupying an increasingly prominent place in the teaching and learning process of dentistry. It is a new technology that for a few years has been incorporated into undergraduate dentistry studies worldwide[4,5].

The Adema University School has been implementing the use of the aforementioned technology in Dentistry Degree studies for two years. It is a fundamental tool for learning and work, since it allows the future dentist to enter the operative field from different perspectives, without time limitations, and being able to change the types and complexity of treatment. It is therefore positioned as a tool that simulates the real treatment process in a reliable way.

Throughout this process of incorporating technology into teaching, contributions have been collected from different interest groups on its use as a method for acquiring skills and generating procedural knowledge in the teaching-learning process.

From the results collected through the interviews and surveys, a high degree of user satisfaction and the conviction that 3D haptic technology can help dental professionals learn, is inferred.

In all cases, the great similarity of the simulation with real practice and its validity in preclinical practice stands out, alongwith the positive assessment of the tools as a method for training in interventions and case studies prior to carrying them out in clinical practice.

Equally, it seems a good way to solve some of the shortcomings that teaching within the degree of dentistry has had until now, thanks to the great similarity that the technology has with real exercises, and the possibility of unlimited practice that is allowed.

Throughout the interviews, the students have highlighted the most playful, dynamic, attractive and entertaining component of the technology, while the teachers emphasize the potential they represent for better acquiring skills and improving learning results.

We can conclude that haptic technology can be a fundamental tool for learning and work in the University Faculties and that the data obtained show that it is well received by students, teachers and other professionals related to the world of dentistry.

Discussion

In the review of studies we have verified that 3D haptic technology presents itself as an option in the teaching of dentistry at an international level and that it allows preclinical practices to be carried out in degree level training[6].

The assessment in our study has been very positive and all the participants have seen the potential of this technology in the teaching process. We have not received negative evaluations regarding the use of the simulators. Presumably there are critical voices in relation to their application for student training, but perhaps the site in which the survey and interviews took place, the Adema university school, which has opted for the incorporation of technology, has inhibited this kind of

negative assessment. However, given the diversity of students, teachers and other professionals who have participated, we believe we are in a position to support a positive view of the incorporation of 3D haptic technology as a learning tool.

We have collected contributions from the teachers on the implications that incorporating this technology means for them when the need arises to train and master the technology to be able to use it in teaching. Certainly, the incorporation of technology supposes the modification of the teaching-learning model and requires a change in the conception of practices in the field of dentistry, providing a new scenario to which centers, teachers and students will have to adapt.

It should be noted that this work is a first approach to learn about simulators and their use in the dentistry degree. It will be their practice and use in teaching in the different subjects, and the learning results that are generated, which will finally confirm the value of their use as indicated by the data described in this study.

Conflict of interests

The authors have no conflict of interest.

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ORIGINAL

On the psychological levels of general population of Saudi Arabia amidst the second wave of COVID 19: a cross sectional study

Sobre los niveles psicológicos de la población general de Arabia Saudí en medio de la segunda ola de COVID 19: un estudio transversal

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Abstract

Introduction and aim: The Covid- 2019 pandemic has caused serious threats to the life of people all over the world, including Saudi Arabia, leading to a more alarming concern of public health. This maiden pandemic to most of the century's inhabitants has also raised a wide range of psychological problems, such as distress, panic disorder, anxiety and depression, which could be long lasting and more devastating. The main purpose of the present questionnaire based study was to measure the prevalence and severity of distress in the population of six major regions of Saudi Arabia to have an idea of the impact of the second wave of Covid-19.

Methods: This initial analysis, is an important large-scale study of psychological distress among the Saudi population during the second wave of COVID-19 epidemic, as few reports exist in literature in the area. An online cross sectional study was conducted from 24th March 2021 to 15 April 2021 in important regions of KSA where bilingual questionnaires with both Arabic and English versions were circulated to volunteers. Sample size calculation was based on WHO recommended criteria, minimum sample size being 385 based on 95% confidence interval with 5% significance level.

Results: Among the total participants, 33.5% showed mild level of anxiety, followed by moderate (25.5%) and severe (14.3%) anxiety levels. A total of 230 out of 525 (43.8%) showed depression symptoms and among the total participants, females expressed more depressive symptoms compared to the male participants.

Conclusion: The findings of the study can be used for developing better and improved care and provision for people with psychological burden and mental illness, as it is necessary to offer targeted treatment, such as online psychotherapy in particular for the distressed.

Key words: distress, anxiety, Covid-19 second-wave.

Resumen

Introducción y objetivo: La pandemia de Covid- 2019 ha provocado graves amenazas para la vida de las personas en todo el mundo, incluida Arabia Saudí, lo que ha llevado a una preocupación más alarmante de la salud pública. Esta pandemia inaugural para la mayoría de los habitantes del siglo también ha planteado una amplia gama de problemas psicológicos, como la angustia, el trastorno de pánico, la ansiedad y la depresión, que podrían ser duraderos y más devastadores. El objetivo principal del presente estudio basado en un cuestionario era medir la prevalencia y la gravedad de la angustia en la población de seis grandes regiones de Arabia Saudí para tener una idea del impacto de la segunda oleada de Covid-19.

Metodología: Este análisis inicial, es un importante estudio a gran escala de la angustia psicológica entre la población saudí durante la segunda ola de la epidemia de COVID-19, ya que existen pocos informes en la literatura en el área. Se llevó a cabo un estudio transversal en línea desde el 24 de marzo de 2021 hasta el 15 de abril de 2021 en importantes regiones de KSA donde se distribuyeron cuestionarios bilingües con versiones en árabe e inglés a los voluntarios. El cálculo del tamaño de la muestra se basó en los criterios recomendados por la OMS, siendo el tamaño mínimo de la muestra de 385 basado en un intervalo de confianza del 95% con un nivel de significación del 5%.

Resultados: Del total de participantes, el 33,5% mostraba un nivel de ansiedad leve, seguido de niveles de ansiedad moderados (25,5%) y graves (14,3%). Un total de 230 de 525 (43,8%) mostraron síntomas de depresión y, entre el total de participantes, las mujeres expresaron más síntomas depresivos en comparación con los hombres.

Conclusión: Los resultados del estudio pueden servir para desarrollar una mejor atención y provisión para las personas con carga psicológica y enfermedades mentales, ya que es necesario ofrecer un tratamiento específico, como la psicoterapia en línea, en particular para los angustiados.

Palabras clave: angustia, ansiedad, Covid-19 segunda ola.

Introduction

The COVID-19 epidemic has caused serious threats to the physical health and life of people as a whole including Saudi Arabia. Originating in China, the disease has a rapid progression to other countries. Research suggests remarkable genomic resemblance of 2019-nCoV with Severe Acute Respiratory Syndrome (SARS) which has a history of a pandemic in 2002, resulting in a return of more serious global public health emergency, (WHO 2020, Gralinski and Menachery, 2020).

As the Corona Virus -19 has been reported to spread faster than its two ancestors the SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), but has lower fatality. Since the WHO, declared the New SARS-CoV-2 in China, in late 2019, a public health emergency of international followed in every continent, with several data based and review articles flooding the scientific literature. The global impact of this new epidemic is yet uncertain, (WHO, 2020, Singhal 2020), though with concentrated international efforts and better preparedness for such pandemics at the global levels, the caused scars on human race will fade and humanity will carry on with each other's healing touches, (Shaima Miraj 2020 and Miraj & Miraj 2021).

This has led to a more alarming concern of public health with war footing attempts to curtail its impact on global health and economy, including human health and wellness of mind and body. This pandemic has also raised a wide range of psychological problems, such as fear, panic disorder, anxiety and depression, which are long lasting and more devastating. Several studies conducted recently after the pandemic and during its onset as well have reported serious psychological distress due to the pandemic in human subjects analyzed in several countries, (Feng et al (2020), Costantini & Mazzotti, (2020), Horesh and Brown 2020, Jahanshahi et al (2020) and Jiménez et al., (2021).

The main purpose of the present questionnaire based study was to measure the prevalence and severity of distress for the population of the important regions of Kingdom of Saudi Arabia to have an idea of the impact of the second wave of CORONA viral disease 2019, consequent to the more serious first wave in the kingdom. The initial analysis, is an important large-scale study of psychological distress among the Saudi population during the second wave of COVID-19 epidemic, as few reports exist in literature in the area. The findings of the study can be used for developing better and improved care and provision for people with psychological burden and mental illness, as it is necessary to offer targeted treatment, such as online psychotherapy in particular for the distressed.

Methodology

An online cross sectional study was conducted in March and April 2021 in six major regions of Saudi Arabia during the 2nd wave of Covid-19 pandemic, where about 1251 daily confirmed cases with 7347 deaths, been reported by May end 2021. The bilingual questionnaires with both Arabic and English versions were circulated to the volunteers with the help of social platforms like emails and WhatsApp to reach all different categories and major regions of general population in KSA. The eligibility criteria was defined as the participants should be residents of KSA, aged 18 years and above to participate in the study by answering the questionnaires. Participation in the study was completely voluntary, and the participants were requested to give their informed consent and endorse their eligibility for participation. Sample size calculation was based on WHO recommendation's criteria. The minimum sample size required for this study is 385 based on 95% confidence interval with 5% significance level. The study was approved by the Institutional Review Board (IRB approval number: SEUREC-CHS21102).

The reliability and validity pretested questionnaire from the pilot study (Cronbach's alpha > 8) was used for the data collection. The study questionnaire composed of four major parts which included socio demographic information, information of health related factors, anxiety measurement scales a (DAD-7, 7 item generalized anxiety severity scale) and depression measurement scales (CESD-10).

The questionnaire was provided to 1105 individuals and out of which 728 (65.8 %) initiated to fill the questionnaire and among those 624 full filled the eligibility criteria. A total 84% (525 out of 624) completed all domains of the questionnaire including the baseline and demographic details, GED-7 and CESD 10 items.

Results and discussion

The results of the present study point out towards increasing levels of distress anxiety and fear among the participants indicating that the second wave of the pandemic is more distressful and is a significant causative factor of sustained stress among all sections of the studied volunteers, both males and females, being higher in females than the males. Recent studies also show that there are increasingly comprehensive data on recognition of the psychological impact of the coronavirus disease 2019 (COVID 19) pandemic on global populations. In most regions of the world, the economic and psychological burden on the general population and persons with mental disorders has risen sharply over the course of the pandemic, (Liu et al 2021).

Table I: Socio demographic information.

Variable	Frequency	%
Age		
< 25 years	148	28.2
25- 34 years	220	41.9
35 - 44 years	140	26.7
45 years and older	17	3.2
Nationality		
Saudi	461	87.8
Non Saudi	64	12.2
Gender		
Female	356	67.8
Male	169	32.2
Marital status		
Single	221	42.1
Married	265	50.5
Divorced/ widowed	39	7.4
Education		
Diploma	64	12.2
High school or less	175	33.3
Post graduate and above	53	10.1
Undergraduate	233	44.4
Occupation		
Student	160	30.5
Government	177	33.7
Private	94	17.9
Self employed	4	0.8
Retired	3	0.6
Not working	87	16.6
Regions		
Central	214	40.8
Eastern	122	23.2
Northern	1	0.2
Southern	53	10.1
Western	110	21.0
Others	25	4.8

The demographic features of the participants studied in the present investigation are summarized in **table I**, showing that majority of participants being female (67.8%) and nearly half of the participants (41.9%) were under 25 -34 years of age group, followed by less than 25 years (28.2%), 35- 44 years (26.7%), 45 years older (3.2%) respectively. About, 87.8% were from Saudi nationalities and half of the participants were married (50.5%). Most of the participants were from central region (40.8%), followed by eastern (23.2%) and western regions (21.0%). Most of the participants had completed undergraduate level of education (44.4 %) and one third of the participants were working in government sector (33.7%).

The anxiety and depression levels of the studied samples are illustrated in **figure 1.1**. Among the total participants, 33.5% showed mild level of anxiety, followed by moderate (25.5%) and severe (14.3%) anxiety levels. A total of 230 out of 525 (43.8%) showed depression symptoms and

Table II: Showing the levels of Anxiety and Depression.

Anxiety	Frequency	%
None /Minimal	140	26.7
Mild	176	33.5
Moderate	134	25.5
Severe	75	14.3
Depression		
Present	230	43.8
Absent	295	56.2

Table III: Association between *anxiety and demographic variables*.

Variables	Levels of anxiety				P value
	No/ Minimal	Mild	Moderate	Severe	
Gender					
Male	52(30.8%)	81(47.9%)	15(8.9%)	21(12.4%)	0.000*
Female	88(24.7%)	95(26.7%)	119(33.4%)	54(15.2%)	
Age group					
18- 24	30(20.3%)	36(24.3%)	39(26.4%)	43(29.1%)	0.000*
25-34 years	65(29.5%)	56(25.5%)	81(36.8%)	18(8.2%)	
35-44 years	37(26.4%)	77(55.0%)	12(8.6%)	14(10.0%)	
45 years and above	8(47.1%)	7(41.2%)	2(11.8%)	0(0.00)	
Marital status					
Married	60(22.6%)	103(38.9%)	79(29.8%)	23(8.7%)	0.000*
Single	48(21.7%)	71(32.1%)	52(23.5%)	50(22.6%)	
Divorced/ widowed	32(82.0%)	2(5.12%)	3(7.69%)	2(5.12%)	
Education					
High school or less	25(14.3%)	59(33.7%)	74(42.3%)	17(9.7%)	0.000*
Diploma	43(67.2%)	18(28.1%)	1(1.6%)	2(3.1%)	
Undergraduate	54(23.2%)	75(32.2%)	53(22.7%)	51(21.9%)	
Post graduate and above	18(34.0%)	24(45.3%)	6(11.3%)	5(9.4%)	
Occupation					
Government	78(44.1%)	73(41.2/%	13(7.3%)	13(7.3%)	0.000*
Private / self employed	14(14.28%)	56(57.1%)	11(11.2%)	17(17..3%)	
Student	37(23.12%)	39(24.37%)	47(29.37%)	37(23.12%)	
Not working /retired	11(12.2%)	8(8.88%)	63(70%)	8(8.88%)	
Region					
Central	56(26.2%)	85(39.4%)	28(13.1%)	45(21.0%)	0.000*
Eastern	18(14.8%)	55(45.1%)	29(23.8%)	20(16.4%)	
Southern	40(75.5%)	7(13.2%)	4(7.5%)	2(3.8%)	
Western	15(13.6%)	24(21.8%)	66(60.0%)	5(4.5%)	
Northern / Others	11(42.30%)	5(19.2%)	7(26.9%)	3(11.5%)	

*P<0.005, statistically significant at 5% significance level.

Table III: Association between *depression and demographic variables*.

Variables	Depression		P value
	Yes	No	
Gender			
Male Female	51(30.2.%) 179(50.2%)	118(69.8%) 177(49.7)%	0.000*
Age group			
18- 24 25-34 years 35-44 years 45 years and above	101(68.2%) 77(35.0%) 46(32.9%) 6(35.3%)	47(31.8%) 143(65.0%) 94(67.1%) 11(64.7%)	0.000*
Marital status			
Married Single Divorced/ widowed	77(29.1%) 147(66.5%) 6(15.38%)	188(70.9%) 74(33.5%) 33(84.61%)	0.000*
Education			
High school or less Diploma Undergraduate Post graduate and above	47(26.9%) 18(28.1%) 137(58.8%) 28(52.8%)	128(73.1%) 46(71.9%) 96(41.2%) 25(47.2%)	0.000*
Occupation			
Government Private / self employed Student Not working /retired	70(39.5%) 39(39.7%) 106(66.2%) 15(16.6%)	107(60.5%) 59(60.2%) 54(33.8%) 75(83.33%)	0.000*
Region			
Central Eastern Southern Western Northern / Others	119(55.6%) 59(48.4%) 9(17.0%) 27(24.5%) 16(61.53%)	95(44.4%) 63(51.6%) 44(83.0%) 83(75.5%) 10(38.46%)	0.000*

*P< 0.05 statistically significant at 5% significance level

among the total participants, female expressed more depressive symptoms compared to male participants.

With reference to the demographic distribution related to age, it was observed that 33.5% of the sample population had mild anxiety as compared to 39.8% of the population which had moderate to severe anxiety. On further gender wise evaluation it was observed that females had more moderate to severe anxiety (44.9%) as compared to males(9.35%), found to be statistically significant (**Table III**). 17% of the sample population had symptoms of mild anxiety between 18-34 years as compared to 16% observed between age group of 35 years and above. However, with respect to moderate to severe anxiety, it was observed that 34.47% of the population in the age group of 18-34 years complained of the symptoms in comparison to 5.3% in the age group of 35 years or above found to be statistically significant (p=0.00*) (**Table III**).

With relation to the effect of marital status to anxiety, it was observed that 38.9% of the married population had mild symptoms in comparison to single (32.1%). Likewise, 19.4% of the married showed moderate to severe symptoms as compared to 20.3% who were single/ widowed (**Table III**). Comparing in terms of education with relation to anxiety levels it was found that 14.6% of the sample having education high school/diploma or less had mild symptoms in comparison to 18.8% who had qualification undergraduate or above. In comparison 17.9% of the married population showed moderate to severe anxiety with respect to 21.9% who were single, found to be statistically significant (p=0.00*) (**Table III**). Evaluating Occupation status with anxiety levels it was observed that 24.5% of the population showing mild anxiety symptoms were employed either in government, private or self. It is in comparison to 8.9 % of population who were unemployed (either students/ retired professionals). This was in contrast to 10.2% of the employed professionals who showed moderate to severe anxiety in comparison to unemployed population (29.5%), found to be statistically significant (p=0.008) (**Table III**).

Evaluating the association between various demographic factors with reference to depression, it was observed that females were depressed more(50.2%) as compared to males, found to be statistically significant (p=0.00*) (**Table IV**). Likewise, 68.2% of the population was found to be depressed between the age group of 18-24 years. Recent studies conducted in Italy and Spain, have also demonstrated that women showed a higher level of distress, as well as in the Spanish sample (Magomed-Eminov et al., 2020; Jiménez et al., 2021), similar to the present investigation. It has been also observed in these previous studies that the survivors of the COVID-19 contraction are characterized by higher indicators of the index of distress than for those who are not ill and have not encountered the disease in their family environment, (Costantini & Mazzotti, 2020).

Univariate analysis showed the association of different demographic factors namely age group, gender, marital status, education level, occupational status with anxiety and depressive symptoms ($p<0.05$) at 5% significance level. Detailed analysis is depicted in **tables III** and **IV**. The mean and SD of anxiety score was 8.08 ±5.62 on GED 7 scale and depression score was 10.41± 6.21on CESD-on a 10 scale. There is significant positive correlation showed ($r=0.680$, $p= 0.000$) between anxiety and depression score at 5% significance level and p value <0.05.

Conclusion

Among the total participants, 33.5% showed mild level of anxiety, followed by moderate (25.5%) and severe (14.3%) anxiety levels. A total of 230 out of 525 (43.8%) showed depression symptoms and among the total participants, females expressed more depressive symptoms compared to the male participants. The findings of the study can be used for developing better and improved care and provision for people with psychological burden and mental illness, especially in a current scenario like present when the world is gearing for a new omicron third wave as it is necessary to offer targeted treatment, such as online psychotherapy in particular for the distressed.

Data Availability Statement

The datasets generated and/or analysed during the current study are not publicly available due to privacy and confidentiality agreements as well as other restrictions but are available from the corresponding author on reasonable request.

Author Contributions

All authors made substantial contributions to conception, design, acquisition of data, analysis and interpretation of data, drafting the article or revising it critically for intellectual content and reasoning, provided final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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Conflict of interests

The authors have no conflict of interest.

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ORIGINAL

La pandemia de gripe rusa en las Islas Baleares (1889-1892)

The Russian flu pandemic in the Balearic Islands (1889-1892)

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Resumen

La llamada gripe rusa que afectó a distintos países de Europa a partir de noviembre de 1889, llegó a Baleares los últimos días del año, vinculándose los primeros casos con la aduana de Palma. Los médicos de la época señalaron que la mitad de la población enfermó presentando, por lo general, cuadros clínicos leves. La epidemia no produjo un incremento significativo de las tasas brutas de mortalidad en el conjunto de las Islas Baleares ni en ninguna de las tres principales capitales que hemos estudiado. Señalamos que la ausencia de fallecimientos podría ser debida a la avanzada transición demográfica de Mallorca.

Palabras clave: Pandemia, 1889, gripe rusa, higiene, aislamiento, transición demográfica.

Abstract

The so-called Russian flu pandemic, which affected different European countries from November 1889, reached the Balearic Islands in the last days of the year. The first cases were linked to the Palma customs office. The doctors of the time pointed out that half of the population fell ill, generally presenting mild clinical symptoms. However, the epidemic did not produce a significant increase in the crude mortality rates in the Balearic Islands or in any of the three main capitals we have studied. We note that the absence of deaths could be due to the advanced demographic transition in Mallorca.

Key words: Pandemic, 1889, russian flu, hygiene, Isolation, demographic transition.

Introducción

La llamada pandemia de "gripe rusa" constituye un hito importante en la historia de las enfermedades porque, tras un siglo XIX marcado por epidemias de cólera y fiebre amarilla, y en el caso concreto de la isla de Mallorca por una epidemia de peste en 1820, la pandemia de 1889 inició un nuevo ciclo. Es la primera de las pandemias víricas de los últimos 130 años que han afectado de una manera grave y generalizada a Europa y a todo el mundo, culminando el 2020 con la llegada de la Covid-19.

El origen de la pandemia de 1889 seguramente estuvo en China, tras las inundaciones de 1888. La tenemos documentada en Asia Central, concretamente en Tomsk (Siberia) y Bukhara (Uzbekistan) en octubre de 1889. A finales de ese mes aparece en San Petersburgo, extendiéndose rápidamente por toda Europa gracias al ferrocarril. El 17 de noviembre de 1889 ya hay casos documentados en París; el 30 de noviembre en Berlín y Viena; a mediados de diciembre en Londres y, a finales de ese mes en los países del sur de Europa, desde Italia hasta Portugal. Por vía marítima a mediados de diciembre de 1889 llegó a América; en enero de 1890 a Suez y África del Sur; en febrero a la India y en abril hasta Australia. Es decir, la expansión del nuevo virus por todo el mundo ocurrió a una velocidad increíble y desconocida hasta ese momento.

La aparición y el desarrollo de la epidemia en París está bien estudiada por Bertillon[2] (1), apareciendo los primeros casos benignos, a mediados de noviembre, en empleados de grandes almacenes, de Correos y Telégrafos, ministerios, etc. A partir del 15 de diciembre, el virus se volvió extremadamente virulento empezando a provocar un gran número de defunciones. Entre el 16 de diciembre de 1889 y el 31 de enero de 1890 fallecieron en Paris 5.042 personas por esta causa. La mayoría fueron mayores de 50 años y más hombres que mujeres. La tasa de mortalidad de esta primera ola fue,

según Bertillon, de 2,1 por 1000 habitantes (hombres 2,5 por 1000 y mujeres 1,7 por 1000 habitantes).

La presentación clínica de esta enfermedad en París fue muy bien estudiada por el Dr. Proust[3], distinguiendo en su informe, publicado por la *Académie de Médecine* de Paris, tres formas definidas de la enfermedad (2): lo que llamó "gripe nerviosa" de comienzo brusco, con cefalea y fuertes dolores articulares y musculares; una "forma pulmonar" con los mismos síntomas además de una gravísima neumonía; y una tercera "forma gástrica" en la que prevalecían los trastornos digestivos con vómitos, diarrea, etc.

La pandemia llegó a España por diferentes vías en el mes de diciembre de 1889. A través del Mediterráneo se encontraron los primeros casos en ciudades portuarias como Valencia o Málaga desde comienzos de mes, en ambos casos la prensa se hizo eco de la llegada de una "epidemia de dengue" (3). Paralelamente, por vía ferroviaria y a través de los Pirineos la pandemia llegó a Barcelona y a Irún (4). A lo largo de este mes la difusión por el resto de territorios peninsulares fue muy rápida y los efectos comenzaron a ser visibles en las tasas de mortalidad desde finales de diciembre pero, especialmente, en enero de 1890.

Material y método

Nuestra investigación se fundamenta en el estudio de distintas fuentes relativas a la mortalidad en las islas Baleares a finales del siglo XIX. En un primer nivel, hemos trabajado los datos generales relativos a España y a las Islas Baleares en base a la información del Movimiento Natural de Población (MNP). Esta fuente ha permitido el cálculo de las tasas brutas de mortalidad generales de las tres principales ciudades del archipiélago: Palma, Mahón (Maó) y la ciudad de Ibiza (Eivissa). Estas tasas se han calculado para los años más próximos a la pandemia estudiada, 1886-1892. A partir de la información agregada del MNP también hemos estimado las tasas de mortalidad a nivel nacional y las observadas en el conjunto del Archipiélago Balear. Desgraciadamente la información del MNP no permite la realización de estudios desagregados de la mortalidad por edades.

En un segundo nivel, hemos consultado información epidemiológica más concreta para estos años a través de los resúmenes estadísticos de mortalidad publicados en la *Revista Balear de Ciencias Médicas*[4]. En esta fuente se recogen datos demográficos como la natalidad y, especialmente, los resúmenes de mortalidad por edades, meses del año y causas de defunción. Paralelamente también hemos estudiado los discursos y noticias sobre la gripe rusa aparecidas en esa Revista. En dichas fuentes, médicos y especialistas de la época relatan de primera mano la llegada de la pandemia a las islas y como va discurriendo a lo largo del tiempo. Se trata de textos de elevado valor histórico que ponen de manifiesto el desconcierto y desconocimiento de los profesionales de la época a la hora de hacer frente a la propagación de un nuevo agente patógeno. En este tipo de trabajos los especialistas del momento relatan, principalmente, la sintomatología observada en diferentes pacientes, la expansión de la pandemia y debaten en torno a los tratamientos más eficaces.

Resultados

El archipiélago balear a lo largo del siglo XIX y especialmente en los años previos a la llegada de la pandemia de 1889-1892 destaca por sus reducidas tasas de mortalidad en comparación con las cifras peninsulares. Somos conscientes de que la comparación de las tasas brutas de mortalidad entre diferentes poblaciones puede estar afectada por la estructura por edades de estas. En la década de 1880 las tasas brutas de Baleares se mantuvieron siempre muy por debajo del promedio nacional (ver **tabla I**). Algunos autores ya se han hecho eco de esta realidad y han tratado de ofrecer diferentes explicaciones en torno a la menor mortalidad general e infantil del archipiélago (5). Incluso, hemos recogido opiniones de especialistas de la época, higienistas como el Dr. Fajarnés Tur[5] (6) que hablan de la "bondad" del clima balear para justificar las reducidas tasas de mortalidad observadas.

Lo cierto es que, más allá de esta mejor situación epidemiológica balear en comparación con las cifras peninsulares, en los dos años inmediatamente anteriores a la llegada de la pandemia estudiada, 1887 y 1888, se aprecia un notable incremento de las tasas de mortalidad. En el conjunto del archipiélago se pasa de cifras inferiores a los 20 fallecidos por 1000 habitantes en los años previos a un 25,94 y un 27,24 por 1000 en 1887 y 1888 respectivamente. El incremento es especialmente elevado

Tabla I: Tasa bruta de mortalidad (TBM) en Palma, Ibiza, Mahón, Baleares y España, 1886-1892.

Localidad	1886	1887	1888	1889	1890	1891	1892
Palma	21,54	30,27	26,53	24,38	22,61	22,31	23,39
Ibiza	25,65	27,62	32,34	21,28	19,97	25,28	19,58
Mahón	19,23	19,52	20,02	17,04	19,07	22,93	20,42
Baleares	19,06	25,94	27,24	21,86	21,34	21,24	22,88
España	29,12	32,68	30,09	30,88	32,62	31,87	31,02

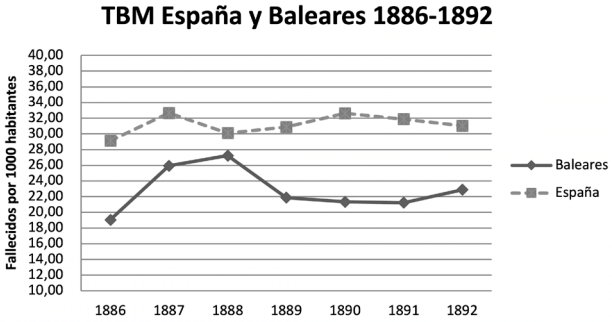
Elaboración propia a partir de datos del Movimiento Natural de Población, MNP.

en las capitales de Palma e Ibiza, en las que se llegaron a sobrepasar las 30 defunciones por 1000 habitantes. La causa de este mayor incremento en las principales ciudades la podemos localizar en una cierta penalización urbana o "Urban penalty", a la vez que un posible mejor registro en las ciudades como consecuencia de una mayor institucionalización como se ha demostrado en otras zonas de España (7), ya que la mortalidad en zonas rurales baleares era aún más reducida (8). Con respecto al agente patógeno que provocó esta epidemia en los años 1887 y 1888, los datos observados nos llevan a hablar de la coexistencia de dos enfermedades que incrementaron especialmente la mortalidad infantil: viruela (9) y, especialmente, sarampión. Fajarnés Tur describió también los efectos de esta última afección que, a modo de ejemplo, entre los meses de marzo y septiembre de 1887 supuso más del 20% de las defunciones totales de Palma, con 237 decesos (6).

Para el año 1889 la situación epidemiológica balear retornó a la realidad previa, aunque, tal y como se aprecia en las cifras estadísticas ofrecidas por la *Revista Balear de Ciencias Médicas* siguieron apareciendo nuevos casos de viruela. En diciembre de 1889 la pandemia conocida históricamente como "gripe rusa" comenzó a disparar las cifras de mortalidad en diversas ciudades europeas (10). Sin embargo, esta pandemia no llegó a afectar de verdad a las Islas Baleares hasta mediados de enero de 1890, cuando ya todo el territorio peninsular estaba afectado por la misma.

A la hora de valorar el impacto de esta pandemia en los datos demográficos de Baleares observamos una realidad inesperada y totalmente opuesta a lo observado en otras zonas de la geografía española. La pandemia de 1889-1892 no produjo un incremento significativo de las tasas brutas de mortalidad de Baleares. De hecho, se prosiguió con un descenso de las cifras de mortalidad observadas en los años anteriores. No se aprecia, por lo tanto, una mortalidad en exceso durante estos años, ni en el conjunto de las Islas Baleares ni en ninguna de las tres principales capitales, tal y como puede apreciarse en el **gráfico 1** y en la **tabla I**.

Tabla I: Tasa bruta de mortaldad (TBM) en España y Baleares, 1886-1892.



Estos datos confirman el escaso impacto que tuvo la pandemia en las tasas de mortalidad de las Islas Baleares. Es cierto que el pico de mortalidad observado en el conjunto de España tampoco es muy elevado, ya que la pandemia no afectó por igual a todas las zonas y las principales tasas de mortalidad las podemos encontrar en los grandes núcleos urbanos e industriales, más afectados por la penalización urbana. Madrid es un ejemplo de esto, con una mortalidad en exceso del 5,8 por 1000 (11) o el caso de Bilbao, en el que en los varios años de afección de la pandemia, se sobrepasaron las 10,6 defunciones en exceso por 1000 habitantes (4).

Sin embargo, en Baleares el impacto de la pandemia es mínimo, lo que nos podría llevar a plantear que no se propagó el virus o que tuvo una menor afección. Las fuentes primarias consultadas confirman que el virus sí llegó a las islas y que se extendió por ellas afectando a una buena parte de la población con cuadros que, aparentemente, no fueron muy graves. Así lo atestiguan los siguientes testimonios de facultativos que vivieron la pandemia de primera mano y publicaron sus impresiones en la *Revista Balear de Ciencias Médicas*:

Uno de los mejores testimonios disponibles al respecto corresponde al Dr. Pere Mas Oliver, que describió a la perfección la llegada y propagación del virus por la ciudad de Palma. En sus "Notas para el estudio de la epidemia gripal en Palma" publicadas en la citada *Revista Balear de Ciencias Médicas*, Mas constata que tuvo noticias de la epidemia a través de las informaciones de la prensa relativas a Madrid. La pandemia no llegó a la isla hasta el 25 de diciembre de 1889, y empezó en una mujer de 35 años que presentaba la siguiente sintomatología:

> *"El día anterior había sentido un violento escalofrío seguido de una cefalea frontal intensa, lumbago, dolores articulares más acentuados en las extremidades inferiores y fiebre alta. Por la noche le fue imposible conciliar el sueño y, a la mañana, en mi primera visita pude apreciar el extraño cuadro sindrómico, para mi clínicamente desconocido con el que describen los patólogos la Influenza."*

El doctor dudó en realizar un diagnóstico al no existir precedentes en la isla. Lo cierto es que el virus posiblemente infectó primero a su marido, trabajador de la aduana de Palma, aunque los primeros síntomas los experimentó el hijo de ambos que presentó la misma sintomatología de la madre. Poco a poco enfermaron 8 de los 10 miembros de la familia y, con posterioridad, vecinos de la casa contigua. Posteriormente, ya en enero, se generaron otros focos con casos importados desde Madrid. Para esta fecha la pandemia se había extendido y los nuevos casos surgían por toda la isla con sintomatologías similares. El 15 de febrero los médicos dieron por finalizada la pandemia.

Pese a que el Dr. Mas estimó que prácticamente la mitad de la población se contagió, el número de defunciones tanto por gripe como por patologías respiratorias vinculadas con la epidemia fue muy limitado. Al contrario que en otras poblaciones, la enfermedad no causó cuadros muy graves: *"Los cuadros graves fueron excepcionales, no solo en personas jóvenes y robustas sino en viejos y enfermos"* no generando una gran preocupación entre la población y las autoridades.

Estos apuntes recogidos por el Dr. Mas se ven confirmados y complementados por los escritos del Dr. Guillem Serra y Bennàssar[6] desde Barcelona nuevamente en la *Revista Balear de Ciencias Médicas* en 1890. En estos textos, el doctor se refirió a la pandemia como *"El dengue"*, contando así cómo tuvo noticia de la enfermedad:

> *"A últimos de noviembre el telégrafo nos sorprendió con la noticia de haberse desarrollado esta enfermedad en San Petesburgo, contándose unas 150.000 invasiones en pocos días y continuando de manera que pocos habitantes de la capital se han librado del contagio, sin exceptuar a la familia imperial, cuyos miembros, en su mayor parte lo han pasado".*

Otros lo definieron como una fiebre catarral *"no contagiosa"*. El Dr. Serra y Bennàssar consideró inaceptables estas definiciones, poniendo de manifiesto que es una enfermedad infecciosa aunque no se conozca *"el microbio"* que la produce. España, en palabras del doctor, bautizó a la pandemia como *"trancazo"*, Francia y Alemania hablaron de *"grippe"*, Italia como *"pantomima"* y *"fiebre polka"*. En el Reino Unido fue conocida como *"dandy fever"* o *"break bones"* (quebranta huesos) y en Rusia *"influenza"*.

Respecto a los tratamientos, se hace eco de los dictámenes de la Junta de Sanidad de Madrid. En todo momento se buscó favorecer la sudoración del paciente permaneciendo abrigados, mantener en la habitación un mínimo de 16 grados y recomendación de permanecer en la cama, con botellas de agua caliente a los pies. También el tratamiento con sustancias como antipirina, polvos de Dover[7], tintura de acónito o salicilato de Sosa.

Por último, el Dr. Federico Farinos Delhom[8] también publicó sus apuntes sobre la última epidemia relativos a la isla de Menorca en la *Revista Balear de Ciencias Médicas*. Según este doctor, la gripe apareció en Menorca a finales de enero, cuando ya había alcanzado su mayor incremento en el litoral mediterráneo y en Mallorca. En la segunda decena de enero se extendió por Maó. El doctor calcula que la tercera parte de sus habitantes padecieron la epidemia con mayor o menor intensidad. Comenzó a disminuir la afección a finales de mes y comienzos de febrero. A mediados de este mes dieron por finalizada la pandemia. Hacen referencia a que más de la mitad de la población sufrió la enfermedad, aunque de forma benigna en la mayor parte de los casos y sin incrementos significativos de mortalidad. En los individuos sanos el pronóstico fue, por lo general, leve. La mortalidad, en palabras del doctor, se incrementó en los casos con patologías preexistentes, siendo mayor en niños y ancianos. Se recomendó el aislamiento de los afectados, pero las *"necesidades de la vida moderna lo hacen impracticable; los perjuicios y los males que acarrearía serían, quizás, más temibles que la misma enfermedad (…)"*.

Por último, el doctor expone el caso del Hospital Militar de Maó, en el que ejercía como médico y donde, entre el día 16 de enero y el 10 de febrero, ingresaron un total de 62 militares. Su presentación clínica fue muy leve en casi todos los enfermos y de mediana intensidad en unos pocos. Tan solo hubo 4 casos graves. En total enfermaron 197 soldados y un enfermero que, a la postre, fue el único fallecido. El Dr. Farinós Delhom expone finalmente su opinión de que la enfermedad se propagó menos dentro de esta unidad militar que en el resto de la isla.

En conclusión, podemos observar que, aunque las cifras de mortalidad no revelen un impacto de la pandemia en el territorio balear, los testimonios de la época confirman que la epidemia llegó a las Islas Baleres y se propagó afectando a la mayor parte de sus habitantes. En cualquier caso, los cuadros fueron muy leves y no incrementaron las cifras de fallecidos.

Discusión

La pandemia de gripe rusa no presentó un modelo de afección y mortalidad homogéneo a lo largo de la geografía española. Tal y como hemos comentado, las mayores tasas de mortalidad en exceso parecen concentrarse en regiones industriales, que se caracterizaban, en esta época, por presentar déficits en materias de higiene, servicios asistenciales, por hacinamiento, etc. Las Islas Baleares no experimentaron un incremento de la mortalidad a causa de la pandemia, aunque su nivel de industrialización era importante sobre todo centrado en su capital la ciudad de Palma, aspecto que podría ser explicado desde una doble hipótesis: la no propagación de la pandemia o una menor afección de esta a las tasas de mortalidad. La primera hipótesis no se sostiene ya que los testimonios médicos de la época estudiados en este artículo atestiguan que la gripe rusa llegó a las Islas Baleares y que la mayor parte de la población se vio afectada.

Por tanto, dado que la pandemia sí se propagó por el archipiélago y que la cronología de los contagios (enero de 1890) es similar a la observada en los territorios

peninsulares, descartamos la posible existencia de una cepa del virus menos letal, debiendo buscar la causa de la baja mortalidad en otros factores. Los médicos de la época destacaron que los cuadros clínicos observados rara vez revistieron gravedad y que los fallecimientos fueron algo extraordinario en este territorio. Las causas de esta diferente afección pueden ser múltiples, pero destaca el avanzado proceso de transición demográfica observado en Baleares, tal y como se refleja en las conclusiones del proyecto de investigación de Francesc Bujosa, Bernat Sureda, e Isabel Moll (12). Este territorio se encontraba en un estadio demográfico más avanzado, con tasas de mortalidad inferiores a las peninsulares sobre todo en cuanto a la mortalidad infantil y juvenil (Pujadas-Mora, 2009). Los habitantes baleares dispondrían ya de una mejor salud, que se reflejaba en la mayor esperanza de vida y una afección más leve por las pandemias como la gripe rusa.

A esta más avanzada transición demográfica hay que añadirle otros factores muy relacionados con el control de la mortalidad: mejores condiciones higiénicas, alimentación de los habitantes, una clase médica muy preparada para la época y unas infraestructuras sanitarias avanzadas, como la Casa de Socorro o una red de conventos religiosos que se preocupó por el desarrollo de normas básicas de higiene (Pujadas-Mora & Salas-Vives, 2021).

En cualquier caso, el resultado es claro: la pandemia de gripe rusa llegó a Baleares a finales de diciembre de 1889, se extendió rápidamente en enero del 1890 hasta afectar a la mayor parte de la población y posiblemente alcanzar cifras cercanas a la inmunidad de rebaño para, posteriormente, remitir en febrero. La pandemia, sin embargo, no revistió gravedad, aspecto que los estudiosos de la época achacaban a la "benignidad del clima", pero que debe estar más relacionado con la propia estructura demográfica balear y su avanzada transición de la mortalidad.

Conflicto de intereses

Ninguno

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ORIGINAL

Distribution of the antibiotic resistance genes amongst methicillin-resistant *Staphylococcus aureus* bacteria isolated from human clinical infections

Distribución de los genes de resistencia a los antibióticos en las bacterias Staphylococcus aureus resistentes a la meticilina aisladas de infecciones clínicas humanas

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Abstract

Background: Methicillin-resistant *Staphylococcus aureus* (MRSA) strains are important causes of human clinical infections in the hospital environment. The present survey was performed to assess the distribution of antibiotic resistance genes amongst the MRSA strains isolated from human clinical infections.

Methods: Thirty-five MRSA strains were isolated from human clinical infection samples. All isolates were confirmed using culture, biochemical tests and cefoxitin (30 µg) and oxacillin (1 µg) susceptibility testing. DNA was extracted from isolates and subjected to PCR for detection of antibiotic resistance genes.

Results: Prevalence of MRSA in isolates collected from sputum, urine, pus, and blood samples was 23.68%, 26.31%, 31.57%, and 10.52%, respectively. MRSA bacteria harbored the highest distribution of *blaZ* (100%), *msrA* (68.42%), and *tetK* (57.89%). Distribution of *ermB* (31.57%) and *aacA-D* (42.10%) antibiotic resistance genes were lower than others. Statistically significant differences were obtained between the distribution of *emrA* and *ermB* (*P* value <0.05), and *msrA* and *msrB* (*P* value <0.05). Distribution of ermA and msrB antibiotic resistance genes were 55.26% and 39.47%, respectively.

Conclusion: Regarding the high prevalence of MRSA and antibiotic resistance encoding genes among isolates in the hospitals, special health-based measures should be taken to reduce the use of antibiotics and control infections in the hospital.

Keywords: Methicillin-resistant *Staphylococcus aureus* (MRSA), antibiotic resistance genes, hospital infections, distribution.

Resumen

Antecedentes: Las cepas de *Staphylococcus aureus* resistentes a la meticilina (SARM) son causa importante de infecciones clínicas humanas en el entorno hospitalario. El presente estudio se realizó para evaluar la distribución de los genes de resistencia a los antibióticos entre las cepas de SARM aisladas de infecciones clínicas humanas.

Métodos: Se aislaron 35 cepas de SARM de muestras de infecciones clínicas humanas. Todos los aislados se confirmaron mediante cultivo, pruebas bioquímicas y pruebas de susceptibilidad a la cefoxitina (30 µg) y la oxacilina (1 µg). Se extrajo el ADN de los aislados y se sometió a la PCR para detectar los genes de resistencia a los antibióticos.

Resultados: La prevalencia de SARM en los aislados recogidos de muestras de esputo, orina, pus y sangre fue del 23,68%, 26,31%, 31,57% y 10,52%, respectivamente. Las bacterias MRSA albergaban la mayor distribución de *blaZ* (100%), msrA (68,42%) y *tetK* (57,89%). La distribución de los genes de resistencia a los antibióticos *ermB* (31,57%) y *aacA-D* (42,10%) fue menor que la de los demás. Se obtuvieron diferencias estadísticamente significativas entre la distribución de *emrA* y *ermB* (valor *P* <0,05), y *msrA* y *msrB* (valor *P* <0,05). La distribución de los genes de resistencia a los antibióticos *ermA* y *msrB* fue del 55,26% y del 39,47%, respectivamente.

Conclusiones: En relación con la alta prevalencia de SARM y de genes codificadores de resistencia a los antibióticos entre los aislados en los hospitales, deben tomarse medidas especiales de carácter sanitario para reducir el uso de antibióticos y controlar las infecciones en el hospital.

Palabras clave: *Staphylococcus aureus* resistente a la meticilina (SARM), Genes de resistencia a los antibióticos, Infecciones hospitalarias.

Introduction

Despite all advances created in the medical sciences, infectious diseases become an important life-threating issue among people of developed and developing countries[1-8]. Among them, the methicillin-resistant Staphylococcus aureus (MRSA) accounted for severe cases of infections in the hospitals and healthcare units[9]. MRSA strains are Gram-positive, catalase positive, and cocci-shaped bacteria originate from both hospital and the community[10]. They are mostly responsible for plain nosocomial and community-acquired infections, particularly Respiratory Tract Infections (RTIs), soft tissue infections, Urinary Tract Infection (UTIs), wound and burn infections, endocarditis, blood infections, and etc[11].

MRSA strains are mainly resist toward all types of penicillins and cephalosporins, simultaneously[12]. Treatment of infections caused by these strains are mostly difficult, because they are resist toward some other types of antimicrobial agents[13]. MRSA bacteria are the chief causes of around 100,000 morbidity with 20% mortality yearly in the United States[14]. MRSA bacteria harbored significant resistance toward penicillins, cephalosporins, tetracyclines, aminoglycosides, phenicols, fluoroquinolones, lincosamides, macrolides, and glycopeptides[15].

According to the high important of antibiotic resistant-MRSA strains, it is essential to signify the main source for the occurrence of resistance among MRSA strains. Some researches showed the role of antibiotic resistance genes for the occurrence of antibiotic resistance among bacterial strains[16]. In this regard, tet (*K* and *M*), *aacA-D*, *blaZ, erm* (*A, B,* and *C*), and *msr* (*A* and *B*) are the genes that responsible for the occurrence of resistance against tetracyclines, aminoglycosides, penicillins, macrolides, and macrolides antimicrobial agents, respectively[17].

MRSA strains have been tested in hospital infections to assess their role as a definitive cause of nosocomial infections. High pathogenicity of MRSA strains and general weakness of hospitalized patients make it necessary to assess their antimicrobial resistance in human clinical infections. Thus, the present survey was done to assess the prevalence rate and distribution of antibiotic resistance genes amongst the MRSA strains isolated from human clinical infections.

Materials and methods

Bacterial strains and confirmation

Thirty-five MRSA strains were isolated from different human clinical specimens. Strains were isolated from Al-Zahra and Shariati Hospitals, Isfahan, Iran. For confirmation, all isolates were cultured in blood agar (BA, Merck, Darmstadt, Germany) and incubated aerobically at 37°C for 48 h. Additionally, colonies were subjected to morphological analysis including Gram-staining, microscopical morphology, catalase and coagulase production tests. Furthermore, pigment production, glucose O/F test, resistance to bacitracin (0.04 U) and novobiocin, oxidase test, mannitol fermentation on Mannitol Salt Agar (MSA, Merck, Darmstadt, Germany), nitrate reduction, phosphatase, urease activity, deoxyribonuclease (DNase) test and carbohydrate (sucrose, xylose, maltose, trehalose, mannose, lactose, and fructose) fermentation tests were applied to confirm isolates (18). For MRSA identification, cefoxitin (30 µg) and oxacillin (1 µg) susceptibility testing was performed[18].

DNA extraction and quality assessment

MRSA isolates were sub-cultured on TSB media and further incubated for 48 h at 37ºC. Genomic DNA was extracted from bacterial colonies using the DNA extraction kit (Thermo Fisher Scientific, St. Leon-Rot, Germany) according to manufacturer's instruction. Purity (A260/A280) and concentration of extracted DNA were then checked (NanoDrop, Thermo Scientific, Waltham, MA, USA). The quality of the DNA was assessed on a 2% agarose gel stained with ethidium bromide (0.5 µg/mL) (Thermo Fisher Scientific, St. Leon-Rot, Germany)[19-25].

Detection of antibiotic resistance genes

Table I represents the list of primers and PCR conditions used for amplification of antibiotic resistance genes in the MRSA strains. A programmable DNA thermo-cycler (Eppendorf Mastercycler 5330, Eppendorf-Nethel-Hinz GmbH, Hamburg, Germany) was used in all PCR reactions. Ten microliters of PCR product were exposed to electrophoresis in a 2% agarose gel in 1X TBE buffer at 80 V for 30 min, stained with SYBR Green. The UVI doc gel documentation systems (Grade GB004, Jencons PLC, London, UK) was applied for analysis of images[26].

Data analysis

Statistical analysis was done using the SPSS 21.0 statistical software (SPSS Inc., Chicago, IL, USA). Chi-square test and Fisher's exact two-tailed test were used to assess any significant relationship between data obtained from the present study. P value <0.05 was considered as statistical significant level[27,28].

Results

Among all 38 isolates, sputum, urine, pus, and blood samples were harbored 9 (23.68%), 10 (26.31%), 12 (31.57%), and 4 (10.52%) MRSA isolates, respectively.

Table II shows the distribution of antibiotic resistance genes amongst the MRSA strains isolated from human clinical infections. According to obtained data, MRSA bacteria harbored the highest distribution of *blaZ* (100%), *msrA* (68.42%), and *tetK* (57.89%). Distribution of *ermB*

(31.57%) and *aacA-D* (42.10%) antibiotic resistance genes were lower than others. Statistically significant differences were obtained between the distribution of *emrA* and *ermB* (*P* value <0.05), and *msrA* and *msrB* (*P* value <0.05). Distribution of *ermA* and *msrB* antibiotic resistance genes were 55.26% and 39.47%, respectively.

Discussion

S. aureus is considered as an important bacterium responsible for hospital infections and food poisoning[29-32]. The most important issue regarding infections caused by MRSA strains is the occurrence of antibiotic resistance in bacterial strains. High resistance rate of the MRSA strains harden the procedure of treatment and faced patients with high economic burden. Thus, it is essential to found all epidemiological aspects of MRSA infections in the hospital environment.

One of the most important epidemiological aspects of the MRSA strains is presence of antibiotic resistance genes amongst the bacteria. The present survey showed that human clinical infections harbored the high distribution of MRSA strains harbored antibiotic resistance genes. Widespread and unauthorized administration of antimicrobials and excessive using of disinfectant solutions in hospital environment have been considered to be a major factor in the emergence of antibiotic resistance amongst MRSA strains.

High prevalence of resistance of MRSA bacteria isolated from diverse kinds of clinical infectious

Table I: Target genes, oligonucleotide primers and PCR conditions used for detection of antibiotic resistance genes amongst MRSA strains.

Target gene	Primer sequence (5'-3')	PCR product (bp)	PCR programs	PCR volume (50µL)
AacA-D	F: TAATCCAAGAGCAATAAGGGC R: GCCACACTATCATAACCACTA	227	1 cycle: 94 ^{0C} ---------- 5 min.	5 µL PCR buffer 10X
ermA	F: AAGCGGTAAACCCCTCTGA R: TTCGCAAATCCCTTCTCAAC	190	25 cycles: 94 ^{0C} ---------- 60 s 55 ^{0C} ---------- 70 s	1.5 mM $Mgcl_2$
tetK	F: GTAGCGACAATAGGTAATAGT R: GTAGTGACAATAAACCTCCTA	360	72 ^{0C} ---------- 60 s 1 cycle: 72 ^{0C} ---------- 10 min	200 µM dNTP 0.5 µM of each primers F & R
ermB	F: CCGTTTACGAAATTGGAACAGGTAAAGGGC R: GAATCGAGACTTGAGTGTGC	359		1.25 U Taq DNA polymerase 2.5 µL DNA template
msrA	F: GGCACAATAAGAGTGTTTAAAGG R: AAGTTATATCATGAATAGATTGTCCTGTT	940	1 cycle: 94 ^{0C} ---------- 6 min.	5 µL PCR buffer 10X
msrB	F: TATGATATCCATAATAATTATCCAATC R: AAGTTATATCATGAATAGATTGTCCTGTT	595	34 cycles: 95 ^{0C} ---------- 60 s 50 ^{0C} ---------- 70 s 72 ^{0C} ---------- 70 s 1 cycle: 72 ^{0C} ---------- 8 min	2 mM $Mgcl_2$ 150 µM dNTP 0.75 µM of each primers F & R 1.5 U Taq DNA polymerase 3 µL DNA template
blaZ	F: TGAACCGTATGTTAGTGC R: GTCGTGTTAGCGTTGATA	681	1 cycle: 94 ^{0C} ---------- 6 min. 30 cycles: 95 ^{0C} ---------- 60 s 59 ^{0C} ---------- 60 s 72 ^{0C} ---------- 60 s 1 cycle: 72 ^{0C} ---------- 10 min	5 µL PCR buffer 10X 2 mM $Mgcl_2$ 150 µM dNTP 0.75 µM of each primers F & R 1.5 U Taq DNA polymerase 3 µL DNA template

Table II: Distribution of antibiotic resistance genes amongst the MRSA strains isolated from human clinical infections.

Clinical specimens) (N. MRSA	N. isolates harbored each gene (%)						
	aacA-D	*tetK*	*balZ*	*ermA*	*ermB*	*msrA*	*msrB*
Sputum (9)	4 (44.44)	5 (55.55)	9 (100)	5 (55.55)	2 (22.22)	6 (66.66)	3 (33.33)
Urine (10)	5 (50)	6 (60)	10 (100)	6 (60)	4 (40)	7 (70)	4 (40)
Pus (12)	6 (50)	9 (75)	12 (100)	8 (66.66)	5 (41.66)	10 (83.33)	6 (50)
Blood (4)	1 (25)	2 (50)	4 (100)	2 (50)	1 (25)	3 (75)	2 (50)
Total (38)	16 (42.10)	22 (57.89)	38 (100)	21 (55.26)	12 (31.57)	26 (68.42)	15 (39.47)

specimens have been described toward penicillins (33-38), cephalosporins[33-35,39], tetracyclines[33-35,40], macrolides[33-35,41], and aminoglycosides[33-35,42]. Abdolmaleki et al. (2019)[43] reported that *BlaZ, aacA-D, tetK, msrA, dfrA, ermA, gyrA, grlA* and *rpoB* were the most commonly detected antibiotic resistance genes amongst the MRSA strains with a distribution rate between 11 to 100%. Rahi et al. (2020)[44] reported that the most frequently distinguished antibiotic resistance markers were *blaZ* (100%), *tetK* (85.71%), *dfrA1* (71.42%), *aacA-D* (67.85%), *ermA* (50%) and *gyrA* (42.85%). Akanbi et al. (2017)[45] reported that *blaZ, mecA, rpoB, ermB* and *tetM* were the most generally identified antibiotic resistance genes amongst the *S. aureus* bacteria recovered from food samples in South Africa which was relatively similar to our findings. In this regard, Momtaz and Hafezi (2014)[46] reported that the distribution of *mecA, tetK, ermA, ermC, tetM, aacA-D, linA, msrA, vatA, vatC* and *vatB* antibiotic resistance genes in the *S. aureus* strains isolated from human clinical infections were 80.30%, 34.84%, 30.30%, 25.75%, 24.24%, 19.69%, 7.57%, 7.57%, 6.06%, 3.03% and 1.51%, respectively.

Conclusion

Sum it up, we recognized boost incidence of MRSA bacteria in human clinical infections on top of boost incidence of the genes encode resistance toward antibiotic agents. High prevalence of MRSA bacteria and high distribution of *blaZ, tetK, aacA-D ermA* and *msrA* antibiotic resistant genes may pose a possible menace regarding the MRSA human infections in hospitals.

Interests conflict

The authors declare no conflict of interest.

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Generalized anxiety disorder among saudi university medical students

Trastorno de ansiedad generalizada en estudiantes de universitarios saudíes

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Abstract

Background: Generalized Anxiety Disorder is a common mental health problem associated with high morbidity and mortality. The disorder is highly prevalent among undergraduate medical students. The objectives of the current study were to determine the prevalence of Generalized Anxiety Disorder and its relation to socio-demographic characteristics among medical students at Majmaah University, Saudi Arabia.

Methods: This is a cross-sectional study conducted on medical students at the Medical Colleges of Majmaah University, Saudi Arabia. The colleges were Colleges of Medicine, Dentistry, and Applied Medical Sciences. The medical students of both sexes who were registered for the current academic year performed the sample frame of the study. The sample was calculated as 369. The data collection was performed by a pre-tested questionnaire. The data analysis was performed using SPSS version 24.

Results: Students with mild, moderate, and severe Generalized Anxiety Disorder were 49.6%, 21.7%, and 13.8% respectively. Male students who had mild, moderate, and severe GAD were 55.4%, 17.4%, and 7.1 % respectively. Female students who had mild, moderate, and severe GAD were 47.0%, 24.9%, and 15.1% respectively. Students of the College of Medicine who had severe Generalized Anxiety Disorder were 14.7%. Students of the College of Dentistry and the College of Applied Medicine Sciences who had severe GAD were 6.3% and 5.6% respectively.

Conclusion: Generalized Anxiety Disorder among medical students at Majmaah University, Saudi Arabia is high and the severe form of the disease is higher compared with other studies. The rate of the disorder is higher in females than male students.

Keywords: Generalized anxiety disorder, medical students.

Resumen

Antecedentes: El Trastorno de Ansiedad Generalizada es un problema de salud mental común asociado a una alta morbilidad y mortalidad. Este trastorno tiene una alta prevalencia entre los estudiantes de medicina. Los objetivos del presente estudio fueron determinar la prevalencia del Trastorno de Ansiedad Generalizada y su relación con las características sociodemográficas entre los estudiantes de medicina de la Universidad de Majmaah, Arabia Saudí.

Métodos: Se trata de un estudio transversal realizado en estudiantes de medicina de las facultades de medicina de la Universidad de Majmaah (Arabia Saudí). Las facultades eran las de Medicina, Odontología y Ciencias Médicas Aplicadas. Los estudiantes de medicina de ambos sexos inscritos en el curso académico actual constituyeron el marco muestral del estudio. La muestra se calculó en 369. La recogida de datos se realizó mediante un cuestionario previamente probado. El análisis de los datos se realizó con el programa SPSS versión 24.

Resultados: Los estudiantes con Trastorno de Ansiedad Generalizada leve, moderado y grave fueron el 49,6%, el 21,7% y el 13,8% respectivamente. Los estudiantes varones que presentaban un TAG leve, moderado y grave eran el 55,4%, el 17,4% y el 7,1% respectivamente. Las alumnas que presentaban un TAG leve, moderado y grave eran el 47,0%, el 24,9% y el 15,1%, respectivamente. Los estudiantes de la Facultad de Medicina que presentaban un trastorno de ansiedad generalizada grave eran el 14,7%. Los estudiantes de la Facultad de Odontología y de la Facultad de Ciencias Médicas Aplicadas que padecían TAG grave eran el 6,3% y el 5,6% respectivamente.

Conclusiones: El Trastorno de Ansiedad Generalizada entre los estudiantes de medicina de la Universidad de Majmaah (Arabia Saudí) es elevado y la forma grave de la enfermedad es mayor en comparación con otros estudios. La tasa del trastorno es mayor en las mujeres que en los estudiantes varones.

Palabras clave: Trastorno de ansiedad generalizada, estudiantes de medicina.

Introduction

Generalized Anxiety Disorder is a mental condition characterized by excessive or unrealistic anxiety about two or more aspects of life such as work, social relationships, and financial matters. The condition is often accompanied by symptoms such as palpitations, shortness of breath, or dizziness. Extreme worrying almost every day for six months or more may suggest generalized anxiety disorder[1].

Generalized Anxiety is associated with high morbidity and mortality. According to a report by the World Health Organization, about 264 million people live with anxiety disorder[2]. Mental disorders are increasing in the East Mediterranean Region (EMR), Generalized disorders rank number two after Depression as a cause of mental illness in the region.[3] It was estimated that the prevalence of the condition is 10.4% and females have a higher prevalence compared to males[4]. The average age of GAD onset is the typical college age ranging from 18 to 24 years, 75 percent of all individuals with an anxiety disorder will experience symptoms before the age of 22 years[5].

The estimated prevalence of generalized anxiety disorder for undergraduate students is 15.6%. Studies showed that students with financial constraints were at higher risk for anxiety disorders[6]. The medical field is one of the most demanding undergraduate degrees, and mental health problems are more frequently encountered among medical students than is generally recognized. Anxiety disorder is one of the issues frequently addressed in the medical education field[7].

In Medical college life students experience different types of stress such as new lifestyle, exposure to new cultures, difficult lessons, language barriers, quizzes, and exams. If students are not adequately prepared to cope with the new challenges of a college environment, they could easily become susceptible to many psychological disorders including anxiety. In college life, competition is more significant and there is continuous pressure on students to do better and the demands usually come from family and the student[8]. It is more likely for medical students to develop generalized anxiety disorder due to the fact that they tend to link symptoms and signs of serious medical conditions they are studying with body sensations[9].

The objectives of the current study were to determine the prevalence of Generalized Anxiety Disorder among medical students at the Medical Colleges of Majmaah University, Saudi Arabia and to determine its relationship to socio-demographic characteristics.

Materials and methods

This is a cross-sectional study conducted among medical students at the Medical Colleges, Majmaah University, Saudi Arabia. The colleges were the College of Medicine, the College of Dentistry, and the College of Applied Medical Sciences (AMS). The medical students of both sexes registered for the current academic year performed the sample frame of this study. The size of the sample, which was calculated as 369, was collected by stratified sampling.

The data collection was performed by a pre-tested questionnaire after acquiring the ethics approval from Majmaah University IRB. Informed consent was obtained from the students. Cronbach's alpha was employed to confirm the reliability of the questionnaire. The reliability of the questionnaire was Cronbach's alpha = 0.835. The questionnaire included questions related to socio-demographic characteristics of the sample and questions to determine the presence or absence of Generalized Anxiety Disorder. The pretest of the questionnaire was conducted on medical students at the College of Applied Medical Sciences at Qassim University. The revision took place for ambiguous and difficult questions. Generalized Anxiety Disorder Assessment (GAD-7) was used to assess GAD. The GAD-7 score is calculated by assigning scores of 0, 1, 2, and 3, to the response categories of 'not at all, 'several days', 'more than half the days', and 'nearly every day, respectively. A summation of the scores for the seven questions took place. Scores of 5, 10, and 15 are taken as the cut-off points for mild, moderate, and severe anxiety, respectively. Data analysis was conducted using SPSS version 24. The Chi-square test was used to compare qualitative data. The p-value of less than 0.05 was considered significant.

Results

Table I shows the social characteristics of the sample. Female and male students were 50.1% and 49.1% respectively. Students from colleges of Medicine, Dentistry and Applied Medical

Table II shows the response to some questions related to Generalized Anxiety Disorder. One hundred and sixty-eight (45.5%) of the students were not aware of their dryness of mouth while 26.5% and 10.3% had some degree and very much degree of awareness. Two hundred and ten (56.9%) students experienced breathing difficulty while 20.7% and 11.4% showed some degree and very much

Table I: Gender and college distribution of the students.

Item	Frequency	%
Gender		
Female	185	50.1
Male	184	49.9
Total	369	100.0
College		
Medicine	218	59.1
Dentistry	80	21.7
Applied Medical Sciences	71	19.2
Total	369	100

Sciences were 59.1%, 21.7% and 19.2% respectively

Table II: Generalized Anxiety Disorder among university students.

Item	No n (%)	Some degree n (%)	Considerable degree n (%)	V. much n (%)
I was aware of dryness of my mouth	168(45.5)	98(26.6)	65(17.6)	38(10.3)
I experienced breathing difficulty	210(56.9)	77(20.7)	40(10.8)	42(11.4)
I experienced trembling (e.g. in the hands)	180(49)	97(26.4)	46(12.5)	44(11.9)
I was worried about situations in which I might panic and make a fool of myself	167(45.3)	95 (25.7)	59(16.0)	48 (13.0)
I felt I was close to panic	209(59.6)	75(20.3)	42(11.4)	41(11.1)
I was aware of the action of my heart in the absence of physical exertion	180(49.0)	83(22.6)	51(13.9)	53(14.4)
I felt scared without any good reason	205(55.7)	74(20.1)	38(10.3)	51(13.9)

Table III: Relation between Generalized Anxiety Disorder and social characteristics.

Social characteristics	Anxiety					
	No n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)	p
Gender:						
Male	37(20.1)	102(55.4)	32(17.4)	13(7.1)	184(100)	0.008
Female	24(13.0)	87(47.0)	46(24.9)	28(15.1)	185(100)	
College:						
Medicine	37(17.0	99(45.4)	50(22.9%)	32(14.7)	218(100)	
Dentistry	11(13.8)	51(63.7)	13(16.3%)	5(6.3%)	80(100)	0.063
AMS	13(18.3)	39(54.9)	15(21.1%)	4(5.6%)	71(100)	

Rate of disease in males= 79.9%. Rate of disease in females=87%

degree of breathing difficulty. One hundred and eighty (49.0%) students were aware of the action of their hearts in the absence of physical exertion while 22.6%,13.9%, and 14.4% had some degree, considerable degree, and very much consideration of awareness respectively. Two hundred and five students (55.7%) feel scared without any good reason while 20.1%, 10.3%, and 13.9% show some degree, considerable degree, and very much degree of scaring without reason.

Table III shows the relation between Generalized Anxiety Disorder and social characteristics. Male students who had mild, moderate, and severe GAD were 55.4%, 17.4%, and 7.1 % respectively. Female students who had mild, moderate, and severe GAD were 47.0%, 24.9%, and 15.1 % respectively.

Discussion

This study was conducted to determine the level of Generalized Anxiety Disorder among 369 students of Majmaah University, Saudi Arabia. Three hundred and fourteen students (85.1%) had simple, moderate and, severe GAD. This rate is higher compared with the rate of the disorder among medical students in different parts of the world: 45.3% in Nepal[10], 66% in Turkey[11], 25% in Spain[12], and 62.4% in Egypt[13]. This rate of Generalized anxiety disorder is also higher than the findings of studies conducted among medical students in Saudi Arabia which found that 17% and 31.7% of students were suffering from the disease[2,14]. Our study revealed that 13.8% of students had a severe level of GAD. This finding is lower than the finding of a study conducted in Saudi Arabia which found that 14.3% of the students had a severe form of the disorder[14]. Our finding is higher than that reported among medical students in Taibah University, Saudi Arabia in which only 4% of the students were suffering from the severe form of the disease[15].

Our study found that the rate of GAD is higher among females compared to male students (87.0% and 79.9%, p= 0.008). This is finding is consistent with studies conducted among Turkish, Spanish, and Egyptian medical students[11-13]. This finding is also consistent with studies conducted among medical students in different parts of Saudi Arabia[14,16,17].

The prevalence of Generalized Anxiety Disorder is higher among the students of the College of Dentistry followed by the students of the College of Medicine. The students of the Applied Medical Sciences had the least level of GAD (86.2%, 83.0%, 81.7%; p=0.063), but the relation between the prevalence of GAD and type of college is not significant.

This finding is consistent with a study conducted in KSA, which showed that the students of the College of Medicine reported lower levels of anxiety compared to students from the College of Dentistry: However, during their clinical rotations, the students of the College of Medicine used to have higher levels of Generalized Anxiety Disorder[18].

Conclusion

This study concluded that Generalized Anxiety Disorder among medical students at Majmaah University, Saudi Arabia is high and the severe form of the disease

is higher compared with other studies. The rate of Generalized Anxiety Disorder is higher in females than in male students. The disorder is higher among students of the college of Dentistry while the severe form is higher among the students of the College of Medicine.

Student counseling programs emphasizing coping techniques are advised to be implemented, especially in the College of Medicine and the College of Dentistry. This urges periodic mental health screenings, providing individual guidance and psychological counseling services for medical students could be beneficial.

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Conflict of interest

The researcher declares that he has no conflict of interest in this study.

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SPECIAL ARTICLE

Vaccination against human papilloma virus in men: situation and proposals

Vacunación contra el virus del papiloma humano en hombres: situación y propuestas

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Abstract

The causal epidemiology of papillomavirus pathology in man and its incidence and the status of its preventive activity in Spain are described, which does not conform to the recommendation that scientific evidence has formulated and that many countries in our environment are following. Lines of action are detailed in this regard that are considered preferred from the point of view of health political action.

Keywords: Vaccination, human papilloma virus, prevention.

Resumen

Se describe la epidemiología causal de la patología papiloma virus causal en el hombre y su incidencia y la situación de su actividad preventiva en España, no conforme con la recomendación que la evidencia científica ha formulado y que numerosos países de nuestro entorno sí están siguiendo. Se detallan líneas de acción al respecto que se consideran preferentes desde el punto de vista de acción político – sanitaria.

Palabras clave: Vacunación, virus papiloma humano, prevención.

Introduction

The human papillomavirus (HPV) is a transmission virus associated with sexual activity, not necessarily coital: transmission by skin-to-mucosal contact is an essential condition for contagion to occur[1]. The World Health Organization[2] reports that In the world more than 290 million women are infected with HPV. Actually, it is a universal pathogenic microorganism, since it affects both men and women: around 80-85% of sexually active individuals will be in contact with HPV at some point in their lives. Most of these infections will be controlled by the infected person's immune system, but in general, in 1 or 2 cases out of 10, the infection will persist and put the carrier at risk of developing HPV-dependent disease. At the time, the CLEOPATRE[3] study reported that in Spain 14% of women over 30 years of age were positive for HPV. Right now, the prevalence of HPV DNA in Spanish women is estimated to range between 1.3 and 5%,[4] which represents a number of female carriers between 350,000 and 900,000.

Knowledge of the structure of HPV and the mechanisms of its oncogenic action[5] have allowed the development of very effective, safe, effective and efficient strategies for primary and secondary prevention of the pathology it causes, cervical cancer in women –also of the vulva and vagina–, of the penis in men and of the oro-pharynx and anus in both, in addition to skin warts and recurrent respiratory papillomatosis.

This volume of disease constitutes a significant oncological burden[6]. For the National Health System, its treatment represents an annual cost of slightly more than €150 million[7]. Consequently, establishing guidelines and recommendations for population application for its prevention must be a priority. The World Health Organization (WHO) has declared cervical cancer –caused in 100% of cases by HPV[8]– as the first eradicable cancer in our world[9]. To achieve this, implement preventive action in women –very consolidated and in majority application in clinical practice[10]– with actions also in men seems absolutely essential.

This work updates and summarizes the evidence in this regard and, in its conclusions, establishes recommendations for preventive action.

Epidemiology of HPV in men

The evidence indicates that the prevalence of genital HPV infection in healthy men is relatively higher than in women, with very important differences published that reach 73% in reference works[11], differences attributable to the different populations studied, to the anatomical sites used for the determination and the different HPV detection methods used. Everything shows that the study of HPV infection in men is far from having obtained the solidity of the data obtained in women: we cannot at this time offer a man a solid recommendation on how and in what way to detect HPV.

In prospective multinational studies, it has been observed that up to 50.5% of the men studied were positive for at least 1 type of HPV, oncogenic or not. HPV type 16 was the most commonly detected, up to 6.5%[12], a relevant fact since it is the type most involved in oncological damage[13]. In asymptomatic heterosexual men, the penis and scrotum were the sites in which almost 95% of genital HPV[11] infections were detected.

An important aspect is that in men the risk of acquiring an HPV infection does not change with age. This lack of association with age suggests that the prevalence of male HPV infection is relatively constant and may be due to the continual acquisition of new infections throughout life. The good news is that infections in men are less likely to persist than in women: the median time to clearance of an infection in men is 5.9 months, with 75% of infections cleared within[12] months post infection[14], a risk of persistence that decreases more among circumcised men[15].

In relation to the most important locations of causal HPV cancer mentioned above in men, anus and oropharynx, it should be noted that in the "HPV Infection in Men" study, the prevalence of anal HPV in heterosexual men was 12% and the rate of the incidence of anal cancer was 8.1%, a prevalence that was markedly higher –47.2%– among men who had sex with men[11].

The incidence of oral HPV infection is higher in adults aged between 31-50 years, and, as in other locations, the persistence of HPV infection in the oral cavity increases with age[16], with a prevalence of HPV infection in the oropharynx in men between 18 and 65 years of 11.5%. It is noted that oral infection is more prevalent in men than in women, with a bimodal distribution throughout life in men, higher in adulthood.

Another characteristic of HPV infection in men is that only 7.7% have antibodies against HPV 6-11-16-18 at 36 months post-infection, with titers 4 to 10 times lower than those of women. This weak seroconversion does not protect against subsequent infections, a protection that is manifested in women[17].

HPV disease in men

A recent publication[15] reports that HPV causes 118 penile cancers in Spain each year and, in men, 522 high-grade intraepithelial lesions of the anus or anal cancers, 603 oropharyngeal cancers, and 28,047 genital warts.
The estimate for Europe is that 325,700 cases of genital warts and 12,700 of oropharyngeal, 1,700 anal, and 1,090 penile cancers are diagnosed annually in men[18]. There are no secondary prevention programs against any of these cancers, so primary prevention, vaccination against HPV, is the only possible alternative.

Vaccines against HPV

Once the infectious cause of a disease is known, the primary preventive measure to apply preferentially if available is vaccination against the causal agent. The two HPV vaccines currently available, Cervarix® and Gardasil9®, do not include a gender difference in the indication for their administration in their technical data sheet approved and disseminated by the European Medicines Agency: both are said to be vaccines indicated for immunization of people from the age of 9 years[19,20]. Consequently, male vaccination against HPV is approved by all European national regulatory agencies.

The degrees of efficacy of both vaccines against pre-cancerous lesions of the cervix, vulva, vagina and anus are very high, always greater than 90-95%[19, 20]. In addition, on June 15, 2020, the Food and Drug Administration of the United States specifically approved the indication of Gardasil9® for the primary prevention of oropharyngeal cancers caused by HPV[21].

We therefore have highly effective vaccines against cancers caused by HPV, but are they safe? Is their application to men efficient?

Although it is true that at some point adverse reactions occurred that initially seemed associated and only initially raised some doubts, the safety of HPV vaccines is unquestionable after more than 15 years of use and hundreds of millions of doses administered. The latest review by the WHO is forceful in its report[22]: its vaccine safety review committee reaffirms that no doubt should be raised about the safety of HPV vaccines and that political decisions based on unverified data that induce doubt about its safety and that consequently lower the quality of the recommendation for its use can cause considerable damage to the health of the affected community.

The most recent reports on the cost/benefit of the application of HPV vaccines in population-based Public Health programs for boys, from France[23] and the Netherlands[24] and from other countries and scenarios[25], demonstrate their high efficiency: to the benefit of Prevention of HPV lesions in them adds to the impact on transmission to girls. Collecting this evidence, already 53 countries from the five continents – 28 Europeans – include financed vaccination against HPV in children in the vaccination schedules of their Public Health programs[25]. An associated benefit that has been highlighted of male vaccination is that HPV could be eradicated even in conditions of low coverage in female vaccination[26].

In Spain, the vaccination calendar published by the Ministry of Health 27 includes HPV vaccination for adolescent women according to the following guideline:

- Vaccination at 12 years of age: 2 doses will be administered at least 5-6 months apart (depending on the vaccine used).
- Vaccination between 13 and 18 years: Only adolescents who have not been vaccinated, or who have not received the complete schedule, will be vaccinated. Two doses will be administered at least 5-6 months apart (depending on the vaccine used).
- If vaccination is started after 14 or 15 years of age, 3 doses will be administered with a schedule of 0, 1-2, 6

The Advisory Committee on Vaccines of the Spanish Association of Pediatrics states that vaccinating boys within the current Spanish vaccination calendar should be an immediate recommendation, in line with the proposal of the European Center for Diseases Prevention and Control[27]. This recommendation has not been collected, however, in the latest edition of the "Cancer Strategy of the National Health System"[28], unlike the European plan against Cancer, published in the same year, which not only includes the indication of male vaccination, but also establishes vaccination against HPV in girls and boys as one of the emblematic initiatives of plan[29].

HPV vaccination coverage in Spain

A crucial aspect of all vaccination procedures in Public Health is to achieve sufficient coverage to, in addition to protecting the vaccinated, achieve herd immunity and block and perhaps prevent the circulation of the virus. Coverage greater than 70% would be required to achieve these objectives[30]. In Spain, the latest report available from the Ministry of Health[31] details that in 2019 a satisfactory coverage of 79% was achieved in the administration of the second dose of the HPV vaccine to girls born in 2006, with a range that goes from 75.4% in Andalusia to 91% in La Rioja, although it should be noted that the table does not include the data on the coverage achieved in Aragon, Asturias, the Balearic Islands and the Canary Islands. Working to maintain or improve this coverage when –as soon as possible– the boys are included in the program, constitutes a priority and a victory for equality[32], as Kevin Pollock titled in his very recent article communicating the inclusion of the males in the UK vaccination programme. Along these lines is the publication of the Evaluation Service of the Canary Islands Health Service, supported by the Spain Ministry of Health[33], in which it is stated verbatim that "it would be advisable to introduce the universal vaccination strategy against HPV with a vaccination schedule of two dose at 12 years of age for both sexes in Spain, with the condition of reviewing its cost-effectiveness with new evidence on the effectiveness, costs or alternative guidelines".

A review of the vaccination calendar in execution in all the Spanish Autonomous Communities and the two Autonomous Cities carried out in September 2021, was able to document that only in Euskadi[34], Cantabria[35], Catalonia[36] and Castilla y León[37] is it implemented, with different age indications and circumstances, vaccination of males.

Conclusions

1. The human papillomavirus is the most common sexually transmitted infection, and is considered a universal pathogen, since it affects both women and men.
2. In recent years, progress has been made in understanding the burden of disease associated with HPV: it is currently estimated that HPV is responsible for 5% of cancer that occurs in humans.
3. Men can develop cancers of the anus, penis, head, and neck that are related to HPV.
4. The prevalence of genital warts is high and similar in both sexes.
5. Unlike what happens with cervical cancer, cancers that affect men lack secondary prevention methods (screening).
6. The available vaccines against HPV have proven to be effective, safe, effective and efficient in their application to women and men.

7. A gender-independent HPV vaccination program would be more equitable than the situation that currently exists in access to this vaccine in our country, it could provide direct health benefits not only for women, but also for men and women, it would maximize the prevention of cervical cancer, accelerating the global control of HPV infection, in addition to helping to mitigate the negative impact on the prevention of possible low female vaccination coverage.

Definitely, the WHO has formally requested[38] that HPV vaccination be extended immediately to all eligible populations, saying that "…there is also a clear risk in terms of missed opportunities for the expansion of other immunization services, for example, the safe and effective implementation of HPV vaccines. Low-income countries need timely access to vaccines at sustainable prices and timely financial support", a position also defended by the European Center for Disease Control and Prevention in a recent publication[39]. On the other hand, international reference sources[40] call for a global solidarity policy aimed at the elimination of HPV-dependent pathology.

The authors of this work formally align themselves with these requests and make them their own, hoping that the Spanish Health Institutions will take the appropriate measures to comply with them.

Conflict of interests

JC has received travel and/or research grants and/or speaking and/or consulting fees from Genomics, GSK, Merck, Procare Health, Qiagen, Roche, and SPMSD.

AG has received grants for travel and/or fees for conferences and/or sponsorship of projects and/or consultancies from Sanofi Pasteur, MSD, GSK, Seqirus and Pfizer.

FM has received fees from Biofabri, GSK, Pfizer, Sanofi Pasteur, MSD, Segirus, Novavax and Janssen as advisor, consultant or speaker outside the scope of this work and has worked as principal investigator in clinical trials promoted by the aforementioned pharmaceutical companies and , in addition, Ablynx, Regeneron, Roche, Abbott and MedImmune, with fees paid to the Institution. FXB is International Consultant of MSD.

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CASE REPORT

Desmopressin as treatment of anemizing hematuria secondary to platelet dysfunction in the setting of uremia

Desmopresina como tratamiento de la hematuria anemizante secundaria a la disfunción plaquetaria en el contexto de la uremia

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Abstract

Uremia is a condition that eases bleeding in patients with chronic kidney disease. We present the case of a 68-year-old male in current predyalisis situation, who was admitted for transurethral resection of a bladder tumor, suffering from hematuria in the postoperative period, which stopped after treatment with desmopressin.

Key words: Desmopressin, anemizing hematuria, platelet dysfunction, uremia.

Resumen

La uremia es una condición que facilita el sangrado en pacientes con enfermedad renal crónica. Presentamos el caso de un varón de 68 años en situación actual de predilección, que ingresó para resección transuretral de un tumor vesical, sufriendo hematuria en el postoperatorio, que cesó tras el tratamiento con desmopresina.

Palabras clave: Desmopresina, hematuria anemizante, disfunción plaquetaria, uremia.

Introduction

Hematuria is a common complication in the postoperative period of endoscopic surgery. Anemia is considered an independent predictor of high postoperative morbidity and mortality[1]. The possible risk of transmission of infections as well as the reactions associated with the transfusion of blood products has aroused interest in agents that reduce blood loss, such as tranexamic acid or desmopressin (DDAVP)[2].

Case presentation

68-year-old male, former smoker, with a history of hypertension, type 2 diabetes mellitus and diabetic nephropathy for which he received a kidney transplant 7 years ago, in current pre-dialysis situation with residual diuresis of 1.5 liters, baseline creatinine of 3.5 mg/dl and estimated glomerular filtration rate of 17 mL/min /1.73m^2 according to the Modification of Diet in Renal Disease (MDRD). On antiplatelet therapy with acetylsalicylic acid 100 mg because of a coronary stent implantation 24 years ago due to ischemic heart disease. He has received a follow-up from 2008 onwards because of a recurrent low-grade pTa urothelial transitional cell carcinoma.

He was admitted for a scheduled surgical intervention of a new bladder tumor recurrence, endoscopically observed as extensive papillary areas at the bladder fundus, dome and left lateral side. According to the physical examination, the abdomen was soft and depressible, with no masses or megalies, and digital rectal examination was normal. Transurethral resection of the described bladder lesions was carried out without intraoperative complications, after a previous interruption of antiplatelet treatment for 7 days.

In the first postoperative hours the patient came up with gross hematuria without hemodynamic repercussion and associating few clots which were manually evacuated. Despite achieving clearing up of the urine by continuous bladder irrigation, hematuria reappeared once and again after its withdrawal.

Blood test showed progressive anemization, up to a minimum hemoglobin of 6.8 g/dl and hematocrit of 20% in a few days, requiring red blood cell transfusion during admission. Likewise, an exacerbation of his basal thrombopenia was observed, presenting 93,600/µL platelets on the first postoperative day. His renal function also got worse presenting a creatinine of 5.3 mg/dl and uremia increased up to 218 mg/dl. Renal ultrasound described absence of hydronephrosis in the kidney graft. Regarding coagulation parameters, a slight initial alteration was observed - prothrombin time (PT) being 62% and an international normalized ratio (INR) of 1.37 - returning

to normal values after administration of a dose of 10 mg phytomenadione.

Given the persistence of hematuria refractory to bladder irrigation withdrawal, and due to platelet dysfunction in the setting of a patient with chronic renal failure, a single dose of desmopressin 0.3 mcg/kg solution was administered in 30 minutes, being this effective, after which hematuria definitely stopped. The first postoperative cystoscopy ensured the absence of tumor recurrence. The patient has not suffered from new episodes of hematuria so far.

Discussion

Bleeding and hemostasis defects are two common complications of uremia. This bleeding may be associated with ineffective binding of the von Willebrand Factor (a component of factor VIII) to platelet membranes, acquired storage-pool deficiency, and anemia. In relation to this, alterations in the synthesis of prostaglandins, defects in platelet aggregation or platelet retention have been reported. These defects can contribute to prolonged bleeding times in patients with uremia. Uremic patients may develop epistaxis, purpura, and bleeding from the gastrointestinal tract or urinary tract. The standard treatment for bleeding derived from uremia is dialysis, however, it does not completely correct platelet dysfunction and so, it is sometimes ineffective. Therefore, both cryoprecipitates and desmopressin (DDAVP) have been studied as alternatives when an immediate effect is desired[3,4].

Desmopressin is a synthetic analog of the antidiuretic hormone vasopressin, the first clinical use of which was established in 1977 as a treatment for diabetes insipidus. Its mechanism of action is based on the increase in plasma levels of von Willebrand factor (vWF), coagulation factor VIII and activation of tissue plasminogen (t-PA), shortening the activated partial thromboplastin time (aPTT) and bleeding time. In addition, it exerts a vasodilator effect which is explained by a direct action on the endothelium, from the activation of endothelial vasopressin receptors (V2R) and and cAMP-mediated signaling[5].

Desmopressin can be administered intravenously (0.3 micrograms / kg diluted in 50-100 ml of isotonic saline by infusing over 30 minutes), subcutaneously, or intranasally. It takes approximately 30 minutes to reach its peak concentration and this effect lasts for about 8 hours[6]. Tachyphylaxis is to be considered after the second dose due to the depletion of multimers from endothelial storage.

Despite not being an agent commonly used in the treatment of hematuria, it has the advantages of being an inexpensive drug with a good safety profile, and also avoids the risk of transmission of viral infections related to transfusion. Because of that, it has already proved useful in the prevention of bleeding from minor procedures such as kidney or liver biopsy, where the risk of bleeding is below 1%[2].

Von Willebrand Factor is essential for forming normal clots through platelet adhesion and the aggregation that follows endothelial damage. Increasing vWF levels in patients undergoing interventional or surgical procedures may reduce or even prevent bleeding loss, therefore reducing the need for red blood cell transfusion. Prevention of bleeding in patients with platelet dysfunction is of particular interest. Uremia, which associated with platelet dysfunction, can result in a major bleeding event after an invasive procedure or surgery that may be aggravated by antiplatelet agents. In this setting, a single infusion of desmopressin before invasive procedures in uremic patients on antiplatelet drugs appeared to be well tolerated and improved platelet dysfunction measured by collagen/epinephrine-closure time[7]. Moreover, as a result of its quick response in these patients and its high availability, desmopressin is a cheap drug that should be beared in mind when managing bleeding complications such as gross hematuria in a postoperative setting.

Conclusions

Platelet disfunction caused by uremia can ease the onset of hematuria after a minor procedure or surgical intervention. Desmopressin proved an effective agent in the treatment of persistent and anemizing gross hematuria in this setting.

Conflict of interests

The authors have no conflict of interest.

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CASE REPORT

Neumonia meningocócica: un nuevo caso

Meningococcal pneumonia: a new case

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Resumen

La *Neisseria meningitidis* (N. m.) es un gérmen que se halla en la nasofaríngе de los portadores, generalmente asintomáticos, y se transmite por la saliva y las gotitas de Flügge. Su diseminación hematógena origina meningitis y eventualmente meningococemia. La diseminación al aparato respiratorio puede causar neumonía, que es muy infrecuente.
Presentamos un caso que reúne las características típicas de la neumonía por N.m., una entidad posiblemente infradiagnosticada.

Palabras clave: Neumonía, Neisseria meningitidis.

Abstract

Neisseria meningitidis (N. m.) is a germ found in the nasopharynx of carriers, who are generally asymptomatic, and is transmitted via saliva and Flügge droplets. Its hematogenous dissemination causes meningitis and eventually meningococcemia. In case of dissemination to the respiratory tract it can cause pneumonia, but very rarely.
We present a case that meets the typical characteristics of N.m. pneumonia, possibly an underdiagnosed entity.

Key words: Pneumonia, Neisseria meningitidis.

Caso clínico

Mujer de 70 años de edad con antecedentes de cifoplastia, hipertensión arterial y enfermedad pulmonar obstructiva crónica, por la que precisa oxigenoterapia domiciliaria.

Acudió al hospital por empeorar su disnea con febrícula de 37.7ºC, sin tos ni expectoración.

En la exploración clínica se apreciaba evidente disnea con acrocianosis (Sat. O2 82%) y ausencia de edemas. La auscultación respiratoria mostraba roncos y sibilancias bilaterales con crepitantes y discreta matidez en la base pulmonar derecha. La radiografía de tórax evidenció una silueta cardíaca normal y una condensación con patrón alveolar en el lóbulo inferior derecho. (**Figuras 1** y **2**)

Las determinaciones analíticas sanguíneas practicadas fueron normales, resaltando un recuento leucocitario normal sin desviación a la izquierda. Únicamente la proteína C reactiva (CRP) estaba elevada: 105.9 mg/L (Inf. 5.0).

Se practicaron dos hemocultivos con crecimiento de N. m. y PCR (Protein Chain Reaction) positivo para meningococo. Así mismo se realizaron tomas para PCR de SARS –CoV-2 y patógenos respiratorios que resultaron negativas.

Se instauró tratamiento con oxigenoterapia con *Ventimask* y Ceftriaxona a dosis de 2gr/24h. La evolución clínica fue satisfactoria y fue dada de alta a los 11 días de la hospitalización.

Figura 1: Radiografía postero anterior: Condensación basal derecha.

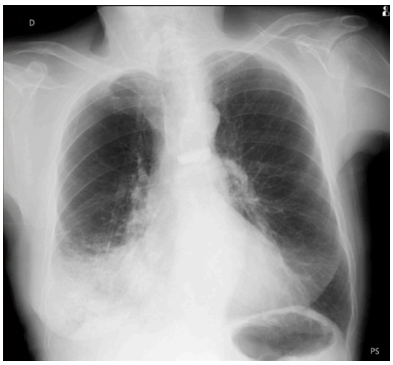

Figura 2: Radiografía lateral: Además de la condensación de lóbulo inferior derecho, se aprecia vertebroplastia dorsal.

Discusión

La *Neisseria meningitidis* o meningococo posee una cápsula de polisacáridos que permiten clasificarlo en 13 serogrupos, de los que el A, B, C, W, e Y son los de más importancia patológica. El gérmen se mantiene en la nasofaringe de los portadores con una prevalencia media del 10% que se eleva mucho durante las epidemias. La infección orofaríngea suele ser asintomática y la enfermedad se transmite por la saliva o las gotitas de Flügge al toser o estornudar; la diseminación hematógena predomina en los jóvenes y puede originar meningitis y en ocasiones meningococemia. En los casos de neumonía por N.m, propia de adultos, el serogrupo más frecuente es el Y, seguido del W.

La neumonía por meningococo tiene una prevalencia tan escasa que los tratados de Medicina Interna le dedican solo unas líneas[1]. El primer caso se describió en 1907 y posteriormente continuaron publicándose otros casos esporádicos, con un evidente incremento durante la pandemia gripal de los años 1918-1919[2]. En la actual pandemia de la COVID-19 no parece que se haya producido nada semejante, ya que solamente hemos localizado un caso de meningitis meningococica en un paciente infectado por el SARS-CoV-2[3]. De la neumonía por N.m. se han comunicado casos aislados en todos los continentes[4,5,6].

En el año 2000 se publicó una revisión de 78 casos[7] que ha permitido perfilar mejor las características de este cuadro neumónico. Afecta por igual a pacientes de ambos sexos, con edad superior a los 50 años, que presentan los clásicos factores de riesgo de estos procesos respiratorios: Tabaquismo, diabetes, inmunodepresión, etc. El comienzo suele ser con tos y fiebre, ocasionalmente dolor pleurítico, y habitualmente disnea. La exploración física y radiológica es indistinguible de otras neumonías bacterianas y por esto puede tratarse de un proceso infra diagnosticado, ya que el meningococo solo se aísla en el esputo en el 30% de los casos. Es llamativo que los hemocultivos pueden ser positivos hasta en el 79% de los pacientes. La mortalidad es del 8.2% y solo 2 pacientes sufrieron shock séptico.

No hay un tratamiento establecido para este proceso neumónico, pero la creciente resistencia del meningococo a la Penicilina, determina que el tratamiento de elección sean las cefalosporinas de 3ª generación. Se acepta que la mejor elección es la Ceftriaxona a dosis de 50mg/kg durante 7 días. En caso de alergia a los betalactámicos puede usarse el Aztreonam 30mg/kg/6h.[1]. No hay evidencia de que el uso de corticosteroides en los casos graves sea beneficioso[2].

Ethical approval

Patient´s consent has been obtained before writing this manuscript.

Declaration of interest

The authors of this manuscript has not conflict of interest

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