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MEDICINA BALEAR

Variables that influence the values of 7 scales that determine the risk of nonalcoholic fatty liver disease and liver fibrosis in 219,477 spanish workers

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Relationship between values of 7 NAFLD scales and different RCV scales in 219,477 Spanish workers

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Hyperbilirubinemia is a predictor of appendiceal perforation in children: A meta-analysis

Cancer and vaccines. Present and future

Multicentric study on the effect of rectal Ozone on COVID-19: the Spanish and Slovakian experience

Concordance between non-invasive tests for the implementation of liver fibrosis screening algorithms in high-risk patients

Relationship between nonalcoholic fatty liver disease and liver fibrosis risk scales with overweight and obesity scales in 219,477 spanish workers

Comparing the effect of three trigger methods (human HCG, combination of recombinant HCG with GnRH agonist, and double recombinant HCG) on the fertility outcome of patients with poor ovarian response in ovulation stimulation cycle (IVF/ICSI)

Evaluation of the Antibacterial Effects of the Various Nanoparticles Coated Orthodontic Brackets: A Systematic Review and Meta-analysis

What happens with the health system: Medical mistrust

Systematic review of the relationship between pain due to herpes zoster infection and the quality of life of subjects living in the community

Evaluation of dietary habits and nutritional needs in women treated for breast cancer in the Balearic Islands

Variables influencing the appearance of metabolic syndrome with three different definitions in 418.343 spanish workers

Prevalence of adverse drug effects of anti-retroviral drugs on hiv-positive patients receiving anti-retroviral treatment in General Hospital Onitsha, Anambra, Nigeria

A Quantitative Assessment of Coping Strategies among Jamaican Males 18+ years old: Post-COVID-19

Association between different cardiometabolic risk scales and metabolic syndrome scales in 418.343 Spanish workers

Effects of a personalized medical educational intervention on the perception of the risk of gynecological cancer and attitudes to control it: a healthcare research model

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Surgical treatment of a patient with hemangiopericytoma and subsequent abdominoplasty: a clinical case

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CONTENTS

VOLUME 38 NUM. 4
JULY - AUGUST 2023

ORIGINALS ARTICLES

Variables that influence the values of 7 scales that determine the risk of nonalcoholic fatty liver disease and liver fibrosis in 219,477 spanish workers 9-16
Emilio Martínez-Almoyna Rifá, Pilar Tomás-Gil, Josep Lluis Coll Villalonga, José Ignacio Ramírez-Manent, Katrina Riera Routon, Ángel Arturo López-González

Knowledge, attitude and practice towards antibiotic use and resistance among non-medical university students: A cross sectional survey in the United Kingdom 17-23
Shruti Malik

Development of professional skills to prevent aggression through virtual simulation in nursing students: experimental study 24-30
M. Raquel Caballero, Guillermo Moreno, Juan Vicente Beneit, Mercedes Gómez del Pulgar, Encarnación Caballero, L. Iván Mayor-Silva

Challenges of Adhering to Hand Washing Protocols as a COVID-19 Prevention Measure Among Slum Dwellers in Nairobi, Kenya 31-40
Kelly Oluoch, John Muthuka, Francis Wambura, Muthoka Mirrium, Edwin Dede

Comparion between General and Spinal Anesthesia for Lumbar Disc Surgery: A Randomized Clinical Trial 41-46
Molouk Jaafarpour, Masoud Hatefi, Aminollah Vasigh, Ali Khani, Fatemeh Njafi, Elham Shafiei

The efficiency of artificial neural network (ANN) for diagnosis of obesity and hypertension 47-51
Somayeh Ebrahimi, Farshid Haghi

Relationship between values of 7 NAFLD scales and different RCV scales in 219,477 Spanish workers 52-59
Emilio Martínez-Almoyna Rifá, Pilar Tomás-Gil, Josep Lluis Coll Villalonga, José Ignacio Ramírez-Manent, Pau Martí-Lliteras, Ángel Arturo López-González

Prevalence of sacroiliac joint dysfunction in patients with chronic low back pain 60-63
Hossein Karimiyarandi, Khalil Komlakh

Hyperbilirubinemia is a predictor of appendiceal perforation in children: A meta-analysis 64-68
Mustafa Azizoğlu, Mehmet Hanifi Okur, Bahattin Aydoğdu, Tuğçe Merve Orbay, Ayten Ceren Bakir, Sergey Alexandrovich Klyuev, Salim Bilici, Salih Bayram, Fikret Salik, Toni Risteski

Cancer and vaccines. Present and future 69-75
Mª Teófila Vicente-Herrero, José Lorenzo Bravo-Grande, Mª Victoria Ramírez-Iñiguez de la Torre

Multicentric study on the effect of rectal Ozone on COVID-19: the Spanish and Slovakian experience 76-84
Marcos Fernández-Cuadros, Olga Pérez-Moro, María Jesús Albaladejo-Florín, Javier Rodríguez-de-Cía, Alberto Hernández, Sandra Álava-Rabasa, Mohammed Darraj, Alžbeta Gondžúrová, Martin Molnár, Monika Kulinova, Juraj Vyletelka

Concordance between non-invasive tests for the implementation of liver fibrosis screening algorithms in high-risk patients 85-91
Cristina Gómez Cobo, Daniel Morell García, Francisco Berga Montaner, Antonia Barceló Bennasar

Relationship between nonalcoholic fatty liver disease and liver fibrosis risk scales with overweight and obesity scales in 219,477 spanish workers 92-100
Emilio Martínez-Almoyna Rifá, Pilar Tomás-Gil, Josep Lluis Coll Villalonga, José Ignacio Ramírez-Manent, Pau Martí-Lliteras, Ángel Arturo López-González

Comparing the effect of three trigger methods (human HCG, combination of recombinant HCG with GnRH agonist, and double recombinant HCG) on the fertility outcome of patients with poor ovarian response in ovulation stimulation cycle (IVF/ICSI) 101-106
Hatav Ghasemi Tehrani, Nasrin Heidari, Farahnaz Mardanian, Ferdous Mehrabian, Elham Naghshineh, Narges Motamedi

Evaluation of the Antibacterial Effects of the Various Nanoparticles Coated Orthodontic Brackets: A Systematic Review and Meta-analysis 107-114
Navid Kerayechian, Arkia Mardany, Faezeh Bahraini, Fatemeh Teimoori, Maryam Ahmadi, Ali Amiri

What happens with the health system: Medical mistrust 115-118
Selman Kızılkaya

Systematic review of the relationship between pain due to herpes zoster infection and the quality of life of subjects living in the community 119-124
Fátima Madrona Marcos, Antonio Moya Moya, Loreto Tárraga Marcos, Jose Ignacio Ramirez-Manent, Pilar Tomás-Gil, Pere Riutord Sbert, Pedro J. Tarraga López

Evaluation of dietary habits and nutritional needs in women treated for breast cancer in the Balearic Islands 125-128
Mar Nafría, Antoni Aguiló-Pons, Dora Romaguera, Alice Chaplin, Javier Cortés Bordoy

Variables influencing the appearance of metabolic syndrome with three different definitions in 418.343 spanish workers 129-135
Andrés Martínez Jover, Ángel Arturo López González, Pilar Tomás Gil, Josep Lluis Coll Villalonga, Pau Martí Lliteras, José Ignacio Ramírez Manent

Prevalence of adverse drug effects of anti-retroviral drugs on hiv-positive patients receiving anti-retroviral treatment in General Hospital Onitsha, Anambra, Nigeria 136-144
Emmanuella Chidimma Ofoelo, David Chinaecherem Innocent, Ifeoma Lucy Ofoelo, Advait Vasavada, Stanley Chinedu Eneh

A Quantitative Assessment of Coping Strategies among Jamaican Males 18+ years old: Post-COVID-19 145-151
Paul Andrew Bourne, Raveena Blake, Serena Braham, Betonia Chisholm, Janeil Deer, Patrina Royal, James Fallah, Calvin Campbell, Clifton Foster, Caroline McLean, Tabitha Muchee, Advella L. Meikle

Association between different cardiometabolic risk scales and metabolic syndrome scales in 418.343 Spanish workers 152-157
Andrés Martínez Jover, Ángel Arturo López González, Pilar Tomás Gil, Josep Lluis Coll Villalonga, Pau Martí Lliteras, José Ignacio Ramírez Manent

Effects of a personalized medical educational intervention on the perception of the risk of gynecological cancer and attitudes to control it: a healthcare research model 158-159
Gabriel Ferret, Gabriela Capllonch, Javier Cortés

SPECIAL ARTICLE

Elimination of cervical cancer 160-162
Javier Cortés, Ana Forteza, José Reyes

CASE REPORT

Acute pancreatitis due to diverticular compression of the gland 163-165
Alexey V. Shabunin, David D. Dolidze, Serghei Covantsev, Ivan N. Lebedinsky, Andrei I. Evsikov, Andrei A. Kolotilshchikov

Surgical treatment of a patient with hemangiopericytoma and subsequent abdominoplasty: a clinical case 166-169
Alexey V. Shabunin, David D. Dolidze, Ivan N. Lebedinsky, Zurab A. Bagatelia, Anna S. Sukhotko, Maria V. Kovaleva, Serghei Covantsev

Possible benefit of intra- articular ozone in advanced osteonecrosis of the knee: two case reports 170-174
Marcos Edgar Fernández-Cuadros, Olga Susana Pérez-Moro, Javier Rodríguez de Cía, María Jesús Albaladejo-Florín

Drug-Induced Stevens Johnson's Syndrome; 4 case Series in Tertiary Hospital in Somalia 175-177
Oznur Sari, Ahmed Muhammad Bashir

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SUMARIO

VOLUMEN 38 NUM. 4
JULIO - AGOSTO 2023

ORIGINALES

Variables que influyen en los valores de 7 escalas que determinan el riesgo de hígado graso no alcohólico y fibrosis hepática en 219.477 Trabajadores españoles 9-16
Emilio Martínez-Almoyna Rifá, Pilar Tomás-Gil, Josep Lluis Coll Villalonga, José Ignacio Ramírez-Manent, Katrina Riera Routon, Ángel Arturo López-González

Conocimiento, actitud y práctica hacia el uso de antibióticos y la resistencia entre los estudiantes universitarios no médicos: Una encuesta transversal en el Reino Unido 17-23
Shruti Malik

Desarrollo de competencias profesionales para prevenir las agresiones a través de la simulación virtual en estudiantes de enfermería: estudio experimental 24-30
M. Raquel Caballero, Guillermo Moreno, Juan Vicente Beneit, Mercedes Gómez del Pulgar, Encarnación Caballero, L. Iván Mayor-Silva

Desafíos de la adhesión a los protocolos de lavado de manos como medida de prevención del COVID-19 entre los habitantes de los barrios marginales de Nairobi, Kenia 31-40
Kelly Oluoch, John Muthuka, Francis Wambura, Muthoka Mirrium, Edwin Dede

Comparación entre anestesia general y raquídea para la cirugía discal lumbar: Un ensayo clínico aleatorizado 41-46
Molouk Jaafarpour, Masoud Hatefi, Aminollah Vasigh, Ali Khani, Fatemeh Njafi, Elham Shafiei

La eficacia de la red neuronal artificial (RNA) para el diagnóstico de la obesidad y la hipertensión 47-51
Somayeh Ebrahimi, Farshid Haghi

Relación entre valores de 7 escalas de NAFLD y diferentes escalas de RCV en 219.477 trabajadores españoles 52-59
Emilio Martínez-Almoyna Rifá, Pilar Tomás-Gil, Josep Lluis Coll Villalonga, José Ignacio Ramírez-Manent, Pau Martí-Lliteras, Ángel Arturo López-González

Prevalencia de disfunción de la articulación sacroilíaca en pacientes con dolor lumbar crónico 60-63
Hossein Karimiyarandi, Khalil Komlakh

La hiperbilirrubinemia es un factor predictivo de perforación apendicular en niños: Un metaanálisis 64-68
Mustafa Azizoğlu, Mehmet Hanifi Okur, Bahattin Aydoğdu, Tuğçe Merve Orbay, Ayten Ceren Bakir, Sergey Alexandrovich Klyuev, Salim Bilici, Salih Bayram, Fikret Salik, Toni Risteski

Cáncer y vacunas. Presente y futuro 69-75
Mª Teófila Vicente-Herrero, José Lorenzo Bravo-Grande, Mª Victoria Ramírez-Iñiguez de la Torre

Estudio multicéntrico sobre el efecto del Ozono rectal en COVID-19: la experiencia española y eslovaca 76-84
Marcos Fernández-Cuadros, Olga Pérez-Moro, María Jesús Albaladejo-Florín, Javier Rodríguez-de-Cía, Alberto Hernández, Sandra Álava-Rabasa, Mohammed Darraj, Alžbeta Gondžúrová, Martin Molnár, Monika Kulinova, Juraj Vyletelka

Concordancia entre pruebas no invasivas para la implementación de algoritmos de cribado de fibrosis hepática en pacientes de alto riesgo 85-91
Cristina Gómez Cobo, Daniel Morell García, Francisco Berga Montaner, Antonia Barceló Bennasar

Relación entre escalas de riesgo de hígado graso no alcohólico y fibrosis hepática con escalas de sobrepeso y obesidad en 219.477 Trabajadores españoles 92-100
Emilio Martínez-Almoyna Rifá, Pilar Tomás-Gil, Josep Lluis Coll Villalonga, José Ignacio Ramírez-Manent, Pau Martí-Lliteras, Ángel Arturo López-González

Comparación del efecto de tres métodos desencadenantes (HCG humana, combinación de HCG recombinante con agonista de GnRH y HCG recombinante doble) en el resultado de la fertilidad de pacientes con respuesta ovárica deficiente en el ciclo de estimulación de la ovulación (FIV/ICSI) 101-106
Hatav Ghasemi Tehrani, Nasrin Heidari, Farahnaz Mardanian, Ferdous Mehrabian, Elham Naghshineh, Narges Motamedi

Evaluación de los efectos antibacterianos de los diversos brackets de ortodoncia recubiertos con nanopartículas: Una revisión sistemática y metanálisis 107-114
Navid Kerayechian, Arkia Mardany, Faezeh Bahraini, Fatemeh Teimoori, Maryam Ahmadi, Ali Amiri

Lo que ocurre con el sistema sanitario: Desconfianza médica 115-118
Selman Kızılkaya

Revisión Sistemática de la relación entre el dolor por infección herpes zóster y la calidad de vida de los sujetos que viven en la comunidad 119-124
Fátima Madrona Marcos, Antonio Moya Moya, Loreto Tárraga Marcos, Jose Ignacio Ramirez-Manent, Pilar Tomás-Gil, Pere Riutord Sbert, Pedro J. Tarraga López

Evaluación de los hábitos dietéticos y las necesidades nutricionales en mujeres tratadas por cáncer de mama en las Islas Baleares 125-128
Mar Nafría, Antoni Aguiló-Pons, Dora Romaguera, Alice Chaplin, Javier Cortés Bordoy

Variables que influyen en la aparición del síndrome metabólico con tres definiciones diferentes en 418.343 trabajadores españoles 129-135
Andrés Martínez Jover, Ángel Arturo López González, Pilar Tomás Gil, Josep Lluis Coll Villalonga, Pau Martí Lliteras, José Ignacio Ramírez Manent

Prevalencia de los efectos adversos de los medicamentos antirretrovirales en pacientes seropositivos que reciben tratamiento antirretroviral en el Hospital General de Onitsha, Anambra, Nigeria 136-144
Emmanuella Chidimma Ofoelo, David Chinaecherem Innocent, Ifeoma Lucy Ofoelo, Advait Vasavada, Stanley Chinedu Eneh

Una evaluación cuantitativa de las estrategias de afrontamiento entre los varones jamaicanos mayores de 18 años: Post-COVID-19 145-151
Paul Andrew Bourne, Raveena Blake, Serena Braham, Betonia Chisholm, Janeil Deer, Patrina Royal, James Fallah, Calvin Campbell, Clifton Foster, Caroline McLean, Tabitha Muchee, Advella L. Meikle

Asociación entre diferentes escalas de riesgo cardiometabólico y escalas de síndrome metabólico en 418.343 trabajadores españoles 152-157
Andrés Martínez Jover, Ángel Arturo López González, Pilar Tomás Gil, Josep Lluis Coll Villalonga, Pau Martí Lliteras, José Ignacio Ramírez Manent

Efectos de una intervención educativa médica personalizada sobre la percepción del riesgo de padecer un cáncer ginecológico y de las actitudes para controlarlo: un modelo de investigación asistencial 158-159
Gabriel Ferret, Gabriela Capllonch, Javier Cortés

ARTÍCULO ESPECIAL

Eliminación del cáncer de cérvix 160-162
Javier Cortés, Ana Forteza, José Reyes

ESTUDIO DE CASOS

Pancreatitis aguda por compresión diverticular de la glándula 163-165
Alexey V. Shabunin, David D. Dolidze, Serghei Covantsev, Ivan N. Lebedinsky, Andrei I. Evsikov, Andrei A. Kolotilshchikov

Tratamiento quirúrgico de una paciente con hemangiopericitoma y posterior abdominoplastia: un caso clínico 166-169
Alexey V. Shabunin, David D. Dolidze, Ivan N. Lebedinsky, Zurab A. Bagatelia, Anna S. Sukhotko, Maria V. Kovaleva, Serghei Covantsev

Posible beneficio del ozono intraarticular en la osteonecrosis avanzada de la rodilla: informe de dos casos 170-174
Marcos Edgar Fernández-Cuadros, Olga Susana Pérez-Moro, Javier Rodríguez de Cía, María Jesús Albaladejo-Florín

Síndrome de Stevens Johnson inducido por fármacos; serie de 4 casos en un hospital terciario de Somalia 175-177
Oznur Sari, Ahmed Muhammad Bashir

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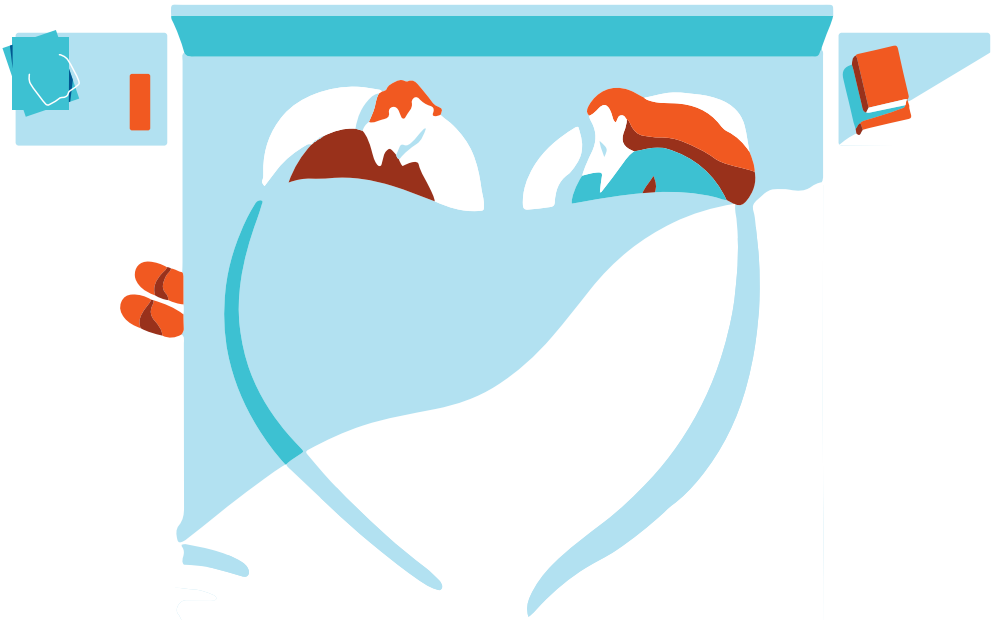

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ORIGINAL

Variables that influence the values of 7 scales that determine the risk of nonalcoholic fatty liver disease and liver fibrosis in 219,477 spanish workers

Variables que influyen en los valores de 7 escalas que determinan el riesgo de hígado graso no alcohólico y fibrosis hepática en 219.477 Trabajadores españoles

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Abstract

Introduction: Non-alcoholic fatty liver disease (NAFLD) is a very frequent and multifactorial pathology that can lead to liver fibrosis (LF). The aim of the present study was to assess the influence of sociodemographic variables such as age, sex, social class and tobacco consumption on the increased risk of NASFLD and HF.

Material and methods: Descriptive and cross-sectional study in 219.477 Spanish workers in which the influence of age, sex, social class and tobacco consumption on the increased risk of presenting NASH and FH determined with 7 different scales was assessed. We also assessed the concordance and correlation between the different scales using Pearson's and Cohen's kappa indices, respectively.

Results: All the EHGNA and FH risk scales have increased values as age increases and as one moves down the social scale. These values are also higher in men. Smoking does not seem to show any effect on the risk of NASH and FH. The degree of correlation of the different scales is high.

Conclusions: Age, sex and social class all have an influence on the increased risk of NASH and FH, while smoking has no effect.

Keywords: non-alcoholic fatty liver disease (NAFLD), sociodemographic variables, tobacco consumption, social class.

Resumen

Introducción: La enfermedad del hígado graso no alcohólico (EHGNA) es una patología muy frecuente y multifactorial que puede terminar en fibrosis hepática (FH). El presente estudio tiene como objetivo valorar la influencia de variables sociodemográficas como edad, sexo y clase social y el consumo de tabaco en el incremento del riesgo de presentar EHGNA y FH.

Material y métodos: Estudio descriptivo y transversal en 219.477 trabajadores españoles en los que se valora la influencia de la edad, el sexo, la clase social y el consumo de tabaco en el incremento del riesgo de presentar EHGNA y FH determinadas con 7 escalas diferentes. También se valora la concordancia y correlación entre las diferentes escalas empleando los índices de Pearson y kappa Cohen respectivamente.

Resultados: Todas las escalas de riesgo de EHGNA y FH ven incrementados sus valores a medida que aumenta la edad y a medida que se desciende en la escala social. Estos valores también son más elevados en los hombres. El tabaco no parece mostrar ningún efecto en el riesgo de EHGNA y la FH. El grado de correlación de las diferentes escalas es alto.

Conclusiones: Tanto la edad como el sexo y la clase social influyen en el incremento del riesgo de presentar EHGNA y FH mientras el consumo de tabaco no afecta.

Palabras clave: Enfermedad del hígado graso no alcohólico (EHGNA), variables sociodemográficas, consumo de tabaco, clase social.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a clinical disease that encompasses different liver conditions in people who consume little or no alcohol[1]. The defining characteristic of this pathology is the excess fat stored in liver cells[2].

NASH is increasing in prevalence worldwide, but especially in more developed countries[3] and in the United States it is considered the most common form of chronic liver disease, affecting almost 25% of the population[4].

Some people with NASH may eventually develop non-alcoholic steatohepatitis, which is one of the most aggressive forms of the disease and is characterized by liver inflammation that can progress to severe scarring (cirrhosis) and liver failure. This pathologic picture is very similar to that caused by excessive alcohol consumption[5].

There are many known risk factors for NASH, including dyslipidemia[6], obesity[7], especially abdominal obesity[8], polycystic ovary syndrome[9], type 2 diabetes[10], hypothyroidism[11], hypopituitarism[12] and advanced age[13].

There are not too many studies that assess the effect of sociodemographic variables and tobacco consumption on the appearance of NASH, so the aim of this study is precisely to assess this association.

Material and methods

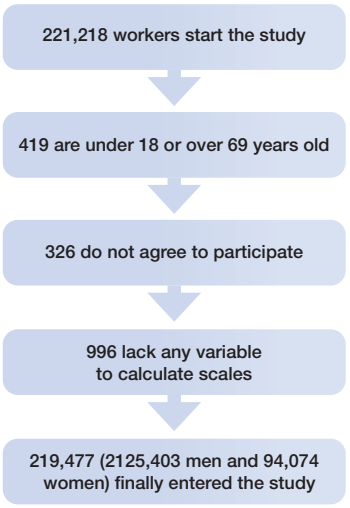
Descriptive and cross-sectional study in 219,477 Spanish workers from different Spanish regions (Balearic Islands, Canary Islands, Andalusia, Valencian Community, Madrid, Catalonia, Castile and Leon, Castile La Mancha, and Basque Country) and belonging mainly to labor sectors of public administration, health, construction, and commerce. Participants were selected from occupational medical examinations between the months of January 2017 and December 2019 from the different companies that participated in the study. Participants were recruited when they met the following inclusion criteria: age between 18 and 69 years, belonging to one of the companies included in the study, not being on temporary disability, giving written consent to participate in the study and to use their data for epidemiological purposes.

Figure 1 shows the flow diagram of the study participants.

Measurements and data collection

Anthropometric measurements and the determination of different analytical parameters were performed on all the workers who attended the occupational health check-ups.

Figure 1: flow chart of the participants in the study.



The anthropometric (height and weight), clinical and analytical measurements were taken by health professionals from the different occupational health units participating in the study, after standardization of the measurement techniques.

Weight (in kg) and height (in cm) were determined using a SECA 700 scale with an attached SECA 220 telescopic measuring rod. Waist circumference (WC) was measured with a SECA measuring tape with the person in a standing position, feet together, trunk straight and abdomen relaxed. The tape was placed parallel to the ground at the level of the last floating rib.

Blood pressure was determined with the person in a seated position and after 10 minutes of rest. A calibrated OMRON M3 automatic sphygmomanometer was used. Three determinations were made at one-minute intervals and the mean of the three was obtained. Blood was obtained after 12h of fasting. Samples were sent to reference laboratories and processed within 2-3 days. Automated enzymatic methods were used to determine glucose, total cholesterol and TG. HDL-c was determined by precipitation with dextran sulfate-MgCl2. LDL-c was calculated using the Friedewald formula (provided that TG was less than 400 mg/dL). The values of all these parameters are expressed in mg/dL.Friedewald formula:

LDL = colesterol – HDL – tryglicerides/5

The risk of NAFLD and liver fibrosis were determined by applying different scales:

- Fatty liver index (FLI)[14]

$$FLI = (e^{0.953*\log_e(\text{triglycerides}) + 0.139*BMI + 0.718*\log_e(GGT) + 0.053*\text{waist circumference} - 15.745}) / (1 + e^{0.953*\log_e(\text{triglycerides}) + 0.139*BMI + 0.718*\log_e(GGT) + 0.053*\text{waist circumference} - 15.745}) \times 100$$

FLI values above 60 are considered high risk.

• Hepatic steatosis index (HSI)[15]

HSI= 8 × AST/ALT + BMI + 2 if diabetes + 2 if female
Values above 36 are considered high risk.

• Zhejian University index (ZJU index)[16]

ZJU= BMI + glycaemia (mmol L) + tryglicerides (mmol L) + 3 AST/ALT + + 2 if female
Values above 38 are considered high risk.

• Fatty liver disease index (FLD)[17]

FLD = BMI + tryglicerides + 3 × (AST/ALT) + 2 × hyperglicaemia (present = 1; absent = 0).
Values above 37 are considered high risk.

• Framingham steatosis index (FSI)[18]

FSI = −7.981 + 0.011 × age (years) − 0.146 × sex (woman = 1; man = 0) + 0.173 × BMI (kg/m^2) + 0.007 × tryglicerides (mg/dL) + 0.593 × hypertension (yes = 1; no = 0) + 0.789 × diabetes (yes= 1; no = 0) + 1.1 × AST/ALT ratio ≥ 1.33 (yes= 1; no = 0)

• Lipid accumulation product (LAP)[19]

Men. (waist (cm) − 65) × (tryglicerides (mMol))
Women: (waist (cm) − 58) × (tryglicerides (mMol))
Values above 42,7 are considered high risk.

• BARD score. This is a scale that evaluates the risk of hepatic fibrosis in patients with NAFLD[20].

The presence of a BMI greater than 28 is scored with 1 point, an AST/ALT ratio greater than 0.8 is scored with 2 points and the presence of diabetes mellitus is also scored with 2 points. Values between 2 and 4 points indicate a high risk of liver fibrosis.

A person was considered a smoker if he/she had smoked at least one cigarette/day (or its equivalent in other types of consumption) in the last 30 days, or had quit smoking less than 12 months ago. A person who had not smoked in the last year or who had never smoked was considered a nonsmoker.

Social class was determined from the National Classification of Occupations 2011 (CNO-11) according to the proposal of the social determinants group of the Spanish Society of Epidemiology[21]. Three categories were established:

Class I: directors/managers, university professionals, sportsmen and artists; Class II: intermediate occupations and skilled self-employed workers; Class III: unskilled workers.

Statistical analysis

A descriptive analysis of the categorical variables was performed, calculating the frequency and distribution of the responses for each of them. For quantitative variables, the mean and standard deviation were calculated following a normal distribution.

Bivariate association analysis was performed using the chi2 test (with correction for Fisher's exact statistic when conditions required it) and Student's t test for independent samples (for comparison of means). Multivariate techniques were used to establish the variables associated with the most significant risk factors. Logistic regression was used for multivariate analysis, with calculation of the odds ratio and the Hosmer-Lemeshow goodness-of-fit test. The degree of correlation and concordance of the different variables studied was determined by applying Pearson's and Cohen's kappa tests, respectively. Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) version 28.0 (IBM Company, New York, NY, USA) for Windows, with an accepted level of statistical significance of 0.05.

Ethical considerations and/or aspects

The research team undertook at all times to follow the ethical principles of health sciences research established nationally and internationally (Declaration of Helsinki), paying special attention to the anonymity of the participants and the confidentiality of the data collected. Approval was requested from the Ethics and Research Committee of the Balearic Islands (CEI-IB), which was obtained with indicator IB 4383/20. Participation in the study was voluntary, so the participants gave their written and oral consent to participate in the study after receiving sufficient information about the nature of the study. To this end, they were given an informed consent form, as well as an information sheet explaining the objective of the study.

The data collected for the study were identified by a code and only the person responsible for the study can relate these data to the participants. The identity of the participants will not be disclosed in any report of this study. The investigators will not disseminate any information that could identify them. In any case, the research team undertakes to strictly comply with the Organic Law 3/2018, of December 5, on the protection of personal data and guarantee of digital rights, guaranteeing the participant in this study that he/she may exercise his/her rights of access, rectification, cancellation and opposition of the data collected

Table I: Characteristics of the population.

	Men n=125,403 Mean (SD)	Women n=94,074 Mean (SD)	p
Age	41.8 (10.5)	39.9 (10.5)	<0.0001
Height	175.2 (6.8)	162.3 (6.3)	<0.0001
Weight	82.6 (15.0)	68.0 (14.7)	<0.0001
SBP	126.1 (15.6)	115.4 (15.5)	<0.0001
DBP	77.3 (11.1)	72.3 (10.5)	<0.0001
Cholesterol	195.6 (37.9)	192.1 (35.5)	<0.001
HDL-c	52.1 (9.8)	57.2 (10.3)	<0.0001
LDL-c	118.4 (35.1)	116.3 (33.5)	<0.001
Tryglicerides	125.7 (76.0)	93.1 (45.6)	<0.0001
Glycaemia	93.4 (21.5)	88.3 (16.0)	<0.0001
AST	29.0 (17.5)	18.7 (11.6)	<0.0001
ALT	24.4 (13.3)	18.2 (7.9)	<0.0001
GGT	32.7 (31.8)	18.8 (16.3)	<0.0001
Creatinine	0.86 (0.17)	0.68 (0.14)	<0.0001
	%	**%**	**p**
18-29 years	14.4	19.4	<0.0001
30-39 years	26.6	28.9	
40-49 years	33.6	32.0	
50-59 years	21.5	16.8	
60-69 years	3.9	2.9	
Social class I	6.1	7.5	<0.0001
Social class II	14.5	20.5	
Social class III	79.4	72.0	
Non smokers	67.5	66.7	<0.001
Smokers	32.5	33.3	

SBP systolic blood pressure. DBP diastolic blood pressure. HDL High density lipoprotein. LDL Low density lipoprotein. AST aspartate transaminase. ALT alanine transaminase. GGT gamma-glutamyl transferase.

Table II: Mean values of different risk scales for nonalcoholic fatty liver disease and liver fibrosis according to sociodemographic variables and tobacco consumption.

		FLI	HSI	ZJU	FLD	FSI	LAP	BARD
Men	**n**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
18-29 years	18006	26.9 (24.2)	34.5 (6.7)	34.6 (5.3)	29.8 (5.2)	0.12 (0.13)	23.8 (21.2)	0.56 (0.79)
30-39 years	33411	36.4 (26.4)	36.4 (6.8)	36.5 (5.5)	31.6 (5.3)	0.17 (0.17)	32.0 (29.4)	0.79 (0.90)
40-49 years	42192	43.3 (26.7)	37.4 (6.8)	37.8 (5.6)	32.6 (5.3)	0.22 (0.19)	36.7 (31.0)	0.98 (0.95)
50-59 years	26955	45.5 (25.9)	37.6 (6.3)	38.3 (5.6)	32.9 (5.2)	0.26 (0.20)	37.1 (28.9)	2.02 (0.93)
60-69 years	4839	46.0 (25.2)	37.7 (6.1)	38.8 (5.3)	33.2 (4.9)	0.30 (0.20)	36.4 (26.2)	1.99 (0.89)
Social class I	7623	38.1 (25.5)	36.6 (6.6)	36.8 (5.2)	31.7 (4.9)	0.20 (0.17)	32.4 (28.0)	1.10 (1.06)
Social class II	18237	39.7 (25.5)	37.1 (6.4)	37.3 (5.3)	32.2 (5.0)	0.20 (0.18)	33.3 (27.2)	1.15 (1.05)
Social class III	99543	39.8 (27.1)	36.7 (6.8)	37.1 (5.8)	32.0 (5.5)	0.21 (0.19)	33.8 (29.4)	1.13 (1.05)
Non smokers*	84642	39.8 (26.8)	36.8 (6.7)	37.2 (5.7)	32.1 (5.4)	0.21 (0.19)	33.8 (28.9)	1.14 (1.05)
Smokers	40761	39.5 (26.7)	36.7 (6.9)	37.1 (5.7)	32.0 (5.3)	0.20 (0.18)	33.4 (29.3)	1.12 (1.06)
Women	**n**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
18-29 years	18270	14.3 (19.7)	34.4 (6.5)	35.1 (5.8)	28.4 (5.7)	0.10 (0.12)	15.9 (15.9)	0.29 (0.53)
30-39 years	27189	18.0 (22.5)	35.9 (7.1)	36.5 (6.3)	29.7 (6.2)	0.13 (0.15)	18.2 (17.8)	0.39 (0.61)
40-49 years	30123	20.1 (22.2)	36.7 (6.6)	37.2 (5.8)	30.4 (5.6)	0.15 (0.16)	19.7 (18.1)	0.45 (0.65)
50-59 years	15774	25.3 (24.1)	38.0 (6.8)	38.7 (6.1)	31.6 (5.7)	0.20 (0.18)	23.5 (20.6)	1.65 (0.78)
60-69 years	2718	26.9 (23.7)	38.6 (6.6)	39.4 (5.9)	32.1 (5.5)	0.23 (0.19)	24.2 (19.2)	1.69 (0.77)
Social class I	7044	13.0 (17.4)	34.2 (5.6)	34.9 (5.0)	28.2 (4.8)	0.11 (0.13)	14.5 (15.8)	0.43 (0.70)
Social class II	19284	17.0 (20.9)	35.7 (6.6)	36.2 (5.7)	29.4 (5.5)	0.13 (0.14)	17.2 (16.9)	0.55 (0.78)
Social class III	67746	20.8 (23.2)	36.7 (7.0)	37.3 (6.3)	30.4 (6.1)	0.15 (0.17)	20.4 (18.7)	0.68 (0.84)
Non smokers*	62706	19.6 (22.5)	36.4 (6.9)	37.0 (6.2)	30.1 (5.9)	0.15 (0.16)	19.4 (18.2)	0.64 (0.82)
Smokers	31368	19.2 (22.4)	36.2 (6.8)	36.8 (6.1)	29.9 (5.9)	0.14 (0.16)	19.1 (18.3)	0.63 (0.82)

FLI Fatty liver index. HSI Hepatic steatosis index. ZJU Zhejiang University index. FLD Fatty liver disease. FSI Framingham Steatosis index. LAP Lipid accumulation product. (*) No statistically significant differences between smokers and non-smokers on all scales. Age and social class show statistically significant differences in all scales.

Results

Table I shows the anthropometric and clinical characteristics of the workers included in the study. A total of 125,403 men (57.14%) and 94,074 women (42.86%) were included in the analyses. The mean age of the sample was 40.5 ± 10.5 years, and the majority group was between 30 and 49 years. Anthropometric, clinical and analytical values were higher among men. The highest percentage of workers (75.5%) belonged to social class III. A total of 33.3% of the women and 32.5% of the men were smokers. The percentage of patients with obesity I was 14.2%, 4.2% of the total sample had obesity II, and 1.5% of the population was classified in obesity category III.

Table II shows the mean values of different scales of nonalcoholic fatty liver disease and liver fibrosis according

to sociodemographic variables, such as age, sex, social class and tobacco consumption. The mean values of all the aforementioned risk scales increase with increasing age in both sexes. The lowest values in all the scales are observed in people belonging to the most favored social class (class I). Smokers present slightly lower values than non-smokers in both sexes, although the differences are not statistically significant. The mean values in all cases are lower in women.

Table III shows the prevalence of elevated values of different risk scales for nonalcoholic fatty liver disease and liver fibrosis according to sociodemographic variables such as age, sex and Social class, and tobacco consumption. A trend similar to that already discussed with the mean values is observed, i.e. an increase in prevalences as age increases and as one descends in the Social class. In general, prevalences are higher in non-smokers, although without statistical significance. Prevalences are higher in males.

Table III: Prevalence of high values of different risk scales for nonalcoholic fatty liver disease and liver fibrosis according to sociodemographic variables and tobacco consumption.

		FLI high	HSI high	ZJU high	FLD high	LAP high	BARD high
Men	**n**	**%**	**%**	**%**	**%**	**%**	**%**
18-29 years	18006	12.9	33.9	21.9	48.5	24.3	13.6
30-39 years	33411	21.5	45.8	32.3	59.9	37.5	21.0
40-49 years	42192	29.0	53.6	42.7	64.6	45.6	28.9
50-59 years	26955	31.6	56.3	47.2	65.1	49.2	65.1
60-69 years	4839	31.4	59.1	52.4	67.3	49.5	65.7
Social class I	7623	22.3	49.4	35.9	64.9	38.0	32.4
Social class II	18237	23.8	51.2	38.3	66.3	41.9	34.7
Social class III	99543	25.8	49.2	38.4	60.1	41.5	33.7
Non smokers	84642	25.4*	49.6*	38.2*	61.5*	41.6	33.8*
Smokers	40761	25.1	49.3	38.3	60.9	40.8	33.7
Women	**n**	**%**	**%**	**%**	**%**	**%**	**%**
18-29 years	18270	5.6	32.5	23.9	34.7	20.1	3.4
30-39 years	27189	8.3	40.6	31.6	39.9	25.6	5.7
40-49 years	30123	8.7	47.5	37.8	48.2	29.4	7.5
50-59 years	15774	11.8	57.4	48.0	54.0	37.9	48.6
60-69 years	2718	12.0	62.9	54.4	60.7	39.8	52.2
Social class I	7044	4.1	30.2	21.3	37.2	16.1	7.7
Social class II	19284	6.7	40.7	30.2	42.5	23.1	11.8
Social class III	67746	9.6	47.4	38.5	45.8	30.9	15.8
Non smokers	62706	8.6*	45.1	35.8	44.5*	28.4*	14.7
Smokers	31368	8.6	43.9	34.8	44.5	27.8	13.7

FLI Fatty liver index. HSI Hepatic steatosis index. ZJU Zhejiang University index. FLD Fatty liver disease. LAP Lipid accumulation product. (*) No statistically significant differences.

Table IV shows the results of the multivariate analysis using multinomial logistic regression. The risk of presenting elevated values for all the nonalcoholic fatty liver disease and liver fibrosis scales is higher in men, with odds ratios ranging from 1.03 (95% CI 1.02-1.05) for ZJU and 3.41 (95% CI 3.32-3.50) for FLI. The risk increases with age in all the scales, with the highest values for the BARD score. The level of risk increased as we descended in the Social class with similar odds ratios for all scales. Tobacco consumption in all scales does not show any influence in any case.

Table IV: Multinomial logistic regression.

	FLI high OR (95% CI)	HSI high OR (95% CI)	ZJU high OR (95% CI)	FLD high OR (95% CI)	LAP high OR (95% CI)	BARD high OR (95% CI)
Woman	1	1	1	1	1	1
Man	3.41 (3.32-3.50)	1.13 (1.11-1.15)	1.03 (1.02-1.05)	1.91 (1.87-1.94)	1.68 (1.65-1.71)	3.18 (3.11-3.26)
18-29 years	1	1	1	1	1	1
30-39 years	ns	1.17 (1.11-1.23)	1.26 (1.20-1.32)	1.18 (1.12-1.25)	ns	1.08 (1.02-1.13)
40-49 years	1.18 (1.11-1.25)	1.45 (1.38-1.52)	1.64 (1.56-1.72)	1.32 (1.25-1.38)	1.30 (1.24-1.36)	6.59 (6.26-6.94)
50-59 years	1.64 (1.55-1.74)	1.97 (1.88-2.07)	2.42 (2.30-2.54)	1.71 (1.62-1.80)	1.74 (1.66-1.83)	9.93 (9.41-10.48)
60-69 years	2.93 (2.75-3.13)	3.10 (2.95-3.27)	3.93 (3.74-4.14)	2.43 (2.31-2.56)	2.91 (2.77-3.07)	17.31 (16.28-18.40)
Social class I	1	1	1	1	1	1
Social class II	1.30 (1.26-1.35)	1.18 (1.15-1.21)	1.30 (1.27-1.33)	ns	1.27 (1.24-1.30)	1.21 (1.18-1.25)
Social class III	1.52 (1.44-1.59)	1.46 (1.41-1.52)	1.63 (1.57-1.69)	1.11 (1.07-1.14)	1.60 (1.54-1.67)	1.50 (1.43-1.58)
Non smokers	1	1	1	1	1	1
Smokers	ns	ns	ns	ns	ns	ns

FLI Fatty liver index. HSI Hepatic steatosis index. ZJU Zhejiang University index. FLD Fatty liver disease. LAP Lipid accumulation product.

Table V presents the results of the Pearson correlation coefficient between the different scales, showing a higher correlation between FLD with ZJU (0.978) and HSI (0.928) and between ZJU and HSI (0.923).

Table VI shows the results of Cohen's Kappa concordance index, whose highest value corresponds to ZJU and HSI (0.731).

Table V: Pearson correlation coefficient of the seven scales.

	FLI	HSI	ZJU	FLD	FSI	LAP	BARD score
FLI	1	0,712	0,813	0,864	0,809	0,809	0,731
HSI		1	0,923	0,928	0,590	0,513	0,587
ZJU			1	0,978	0,768	0,649	0,647
FLD				1	0,781	0,681	0,669
FSI					1	0,774	0,649
LAP						1	0,617
BARD score							1

FLI Fatty liver index. HSI Hepatic steatosis index. ZJU Zhejiang University index. FLD Fatty liver disease. FSI Framingham steatosis index. LAP Lipid accumulation product.

Table VI: Cohen's Kappa concordance index of the seven scales.

	FLI	HSI	ZJU	FLD	LAP	BARD score
FLI	1	0,350	0,504	0,130	0,532	0,524
HSI		1	0,731	0,273	0,458	0,401
ZJU			1	0,098	0,585	0,530
FLD				1	0,086	0,025
LAP					1	0,471
BARD score						1

FLI Fatty liver index. HSI Hepatic steatosis index. ZJU Zhejiang University index. FLD Fatty liver disease. LAP Lipid accumulation product.

Discussion

Both the mean values and the prevalence of high values of the nonalcoholic fatty liver disease and liver fibrosis risk scales are higher as age increases and as we descend in the Social class, and they are also lower in women.

In the multivariate analysis, it can be seen that the variable that most increases the risk of presenting highs of the different risk scales for nonalcoholic fatty liver disease and liver fibrosis is age, followed by sex and social class, without finding any influence of tobacco consumption.

The Pearson correlation index of the different scales is, in general, high, especially highlighting the relationship between FLD with ZJU and HSI and between ZJU and HSI. The degree of agreement using Cohen's kappa found in our study is moderate to insignificant among the scales evaluated, with the exception of ZJU and HSI in which there is good (substantial) agreement.

Different studies have assessed the prevalence of NASH according to age, with the conclusion that as age increases the prevalence of NASH also increases, a result that agrees with that obtained by us in this study. Data from the Third National Health and Nutrition Examination Survey (NHANES III) carried out in the United States in 3,270 persons showed very high rates of NASH, especially in older persons, even exceeding 40%[22] as in our study. Similar data are found in the studies by Alqahtani et al[23] and Bertolotti et al[24], the latter also showing a greater number of complications derived from NASH in older persons. A study carried out in a Spanish working population of more than 30,000 workers also found an increase in the prevalence of a risk scale, in this case FLI, with age[25]. The study by Abeysekera et al[26] conducted in more than 10,000 people in Bristol showed a higher prevalence of liver fibrosis determined by FibroScan in older people.

The work of Fresneda et al[25] found, as we did, a higher prevalence of elevated FLI values in males and in people from the most disadvantaged social classes. Data from 5,272 middle-aged adults who participated in the 2014-2018 Korean National Health and Nutrition Examination Surveys (KNHANES)[27] also showed a higher prevalence of elevated values of an EHGNA risk scale, in this case HSI, in people with lower socioeconomic status. A paper by Ramirez-Manent et al[28] in 15,057 Spanish workers showed that the risk of developing nonalcoholic fatty liver disease and liver fibrosis was much higher in men than in women.

The role of smoking in the development of NASH remains controversial, some authors such as Jung et al[29] found an increased prevalence in smokers. Other authors such as Zein et al[30] observed an increased likelihood of smoking-associated liver fibrosis. A cross-sectional study in 160,862 persons showed that smoking was associated with an increased risk

of NAFLD (adjusted odds ratio 1.10; 95% confidence interval, 1.06-1.14). Furthermore, among Smokers, the risk of NASH increased with the number of cigarettes (<10 and ≥10 pack-years vs. never Smokers; odds ratios 1.04 and 1.11; 95% CI, 1.01-1.08 and 1.05-1.16, respectively.

Strengths and limitations

As strengths of the study, we can highlight the large sample size (more than 200,000 people) and the large number of NASH and liver fibrosis risk scales used. The main limitation is that diagnostic techniques for NASH or liver fibrosis other than the risk scales were not performed.

Conclusions

Taking into account the results obtained in our study, we can conclude that in this Spanish working population there is a direct relationship between the values of the different NASH risk scales and liver fibrosis when considering different sociodemographic variables such as age, sex and social class, and we found no relationship with tobacco consumption. The degree of correlation of the different scales is good, especially between FLD with ZJU and HSI and between ZJU and HSI. The degree of concordance however is not as good except between ZJU and HSI.

Conflict of Interest

The authors declare that no competing interests exist.

References

1. Drożdż K, Nabrdalik K, Hajzler W, Kwiendacz H, Gumprecht J, Lip GYH. Metabolic-Associated Fatty Liver Disease (MAFLD), Diabetes, and Cardiovascular Disease: Associations with Fructose Metabolism and Gut Microbiota. Nutrients. 2021 Dec 27;14(1):103. doi: 10.3390/nu14010103.

2. Xian YX, Weng JP, Xu F. MAFLD vs. NAFLD: shared features and potential changes in epidemiology, pathophysiology, diagnosis, and pharmacotherapy. Chin Med J (Engl). 2020 Dec 14;134(1):8-19. doi: 10.1097/CM9.0000000000001263.

3. Huang DQ, El-Serag HB, Loomba R. Global epidemiology of NAFLD-related HCC: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol. 2021 Apr;18(4):223-38. doi: 10.1038/s41575-020-00381-6.

4. Estes C, Anstee QM, Arias-Loste MT, Bantel H, Bellentani S, Caballeria J, et al. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016-2030. J Hepatol. 2018 Oct;69(4):896-904. doi: 10.1016/j.jhep.2018.05.036.

5. Younossi Z, Tacke F, Arrese M, Chander Sharma B, Mostafa I, Bugianesi E, et al. Global Perspectives on Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis. Hepatology. 2019 Jun;69(6):2672-82. doi: 10.1002/hep.30251.

6. Kasper P, Martin A, Lang S, Kütting F, Goeser T, Demir M, et al. NAFLD and cardiovascular diseases: a clinical review. Clin Res Cardiol. 2021 Jul;110(7):921-37. doi: 10.1007/s00392-020-01709-7.

7. Liu Z, Zhang Y, Graham S, Wang X, Cai D, Huang M, et al. Causal relationships between NAFLD, T2D and obesity have implications for disease subphenotyping. J Hepatol. 2020 Aug;73(2):263-76. doi: 10.1016/j.jhep.2020.03.006.

8. Pouwels S, Sakran N, Graham Y, Leal A, Pintar T, Yang W, et al. Non-alcoholic fatty liver disease (NAFLD): a review of pathophysiology, clinical management and effects of weight loss. BMC Endocr Disord. 2022 Mar 14;22(1):63. doi: 10.1186/s12902-022-00980-1.

9. Javed Z, Papageorgiou M, Deshmukh H, Kilpatrick ES, Mann V, Corless L, et al. A Randomized, Controlled Trial of Vitamin D Supplementation on Cardiovascular Risk Factors, Hormones, and Liver Markers in Women with Polycystic Ovary Syndrome. Nutrients. 2019 Jan 17;11(1):188. doi: 10.3390/nu11010188.

10. Muzica CM, Sfarti C, Trifan A, Zenovia S, Cuciureanu T, Nastasa R, et al. Nonalcoholic Fatty Liver Disease and Type 2 Diabetes Mellitus: A Bidirectional Relationship. Can J Gastroenterol Hepatol. 2020 Dec 28;2020:6638306. doi: 10.1155/2020/6638306.

11. Martínez Escudé A, Pera G, Arteaga I, Expósito C, Rodríguez L, Torán P, et al. Relationship between hypothyroidism and non-alcoholic fatty liver disease in the Spanish population. Med Clin (Barc). 2020 Jan 10;154(1):1-6. English, Spanish. doi: 10.1016/j.medcli.2019.03.018.

12. Kang SJ, Kwon A, Jung MK, Chae HW, Kim S, Koh H, et al. High Prevalence of Nonalcoholic Fatty Liver Disease Among Adolescents and Young Adults With Hypopituitarism due to Growth Hormone Deficiency. Endocr Pract. 2021 Nov;27(11):1149-55. doi: 10.1016/j.eprac.2021.06.003.

13. Alqahtani SA, Schattenberg JM. NAFLD in the Elderly. Clin Interv Aging. 2021 Sep 13;16:1633-49. doi: 10.2147/CIA.S295524.

14. Zou B, Yeo YH, Cheung R, Ingelsson E, Nguyen MH. Fatty Liver Index and Development of Cardiovascular Disease: Findings from the UK Biobank. Dig Dis Sci. 2021 Jun;66(6):2092-100. doi: 10.1007/s10620-021-06954-y.

15. Chang JW, Lee HW, Kim BK, Park JY, Kim DY, Ahn SH, et al. Hepatic Steatosis Index in the Detection of Fatty Liver in Patients with Chronic Hepatitis B Receiving Antiviral Therapy. Gut Liver. 2021 Jan 15;15(1):117-27. doi: 10.5009/gnl19301.

16. Shi M, Liu P, Li J, Su Y, Zhou X, Wu C, et al. The performance of noninvasive indexes of adults in identification of nonalcoholic fatty liver disease in children. J Diabetes. 2021 Sep;13(9):744-53. doi: 10.1111/1753-0407.13169.

17. Lee I, Cho J, Park J, Kang H. Association of hand-grip strength and non-alcoholic fatty liver disease index in older adults. J Exerc Nutrition Biochem. 2018 Dec 31;22(4):62-8. doi: 10.20463/jenb.2018.0031.

18. Jung TY, Kim MS, Hong HP, Kang KA, Jun DW. Comparative Assessment and External Validation of Hepatic Steatosis Formulae in a Community-Based Setting. J Clin Med. 2020 Sep 3;9(9):2851. doi: 10.3390/jcm9092851

19. Anoop S S, Dasgupta R, Rebekah G, Jose A, Inbakumari MP, Finney G, et al. Lipid accumulation product (LAP) as a potential index to predict risk of insulin resistance in young, non-obese Asian Indian males from Southern India: observations from hyperinsulinemic-euglycemic clamp studies. BMJ Open Diabetes Res Care. 2021 Sep;9(1):e002414. doi: 10.1136/bmjdrc-2021-002414.

20. Soresi M, Cabibi D, Giglio RV, Martorana S, Guercio G, Porcasi R, et al. The Prevalence of NAFLD and Fibrosis in Bariatric Surgery Patients and the Reliability of Noninvasive Diagnostic Methods. Biomed Res Int. 2020 Apr 26;2020:5023157. doi: 10.1155/2020/5023157.

21. Domingo-Salvany A, Bacigalupe A, Carrasco JM, Espelt A, Ferrando J, Borrell C; del Grupo de Determinantes Sociales de Sociedad Española de Epidemiología. Propuestas de Social class neoweberiana y neomarxista a partir de la Clasificación Nacional de Ocupaciones 2011. Gac Sanit. 2013 May-Jun;27(3):263-72. doi: 10.1016/j.gaceta.2012.12.009.

22. Golabi P, Paik J, Reddy R, Bugianesi E, Trimble G, Younossi ZM. Prevalence and long-term outcomes of non-alcoholic fatty liver disease among elderly individuals from the United States. BMC Gastroenterol. 2019 Apr 16;19(1):56. doi: 10.1186/s12876-019-0972-6.

23. Alqahtani SA, Schattenberg JM. NAFLD in the Elderly. Clin Interv Aging. 2021 Sep 13;16:1633-1649. doi: 10.2147/CIA.S295524.

24. Bertolotti M, Lonardo A, Mussi C, Baldelli E, Pellegrini E, Ballestri S, et al. Nonalcoholic fatty liver disease and aging: epidemiology to management. World J Gastroenterol. 2014 Oct 21;20(39):14185-204. doi: 10.3748/wjg.v20.i39.14185. PMID: 25339806; PMCID: PMC4202348.

25. Fresneda S, Abbate M, Busquets-Cortés C, López-González A, Fuster-Parra P, Bennasar-Veny M, et al. Sex and age differences in the association of fatty liver index-defined non-alcoholic fatty liver disease with cardiometabolic risk factors: a cross-sectional study. Biol Sex Differ. 2022 Nov 4;13(1):64. doi: 10.1186/s13293-022-00475-7.

26.Abeysekera KWM, Fernandes GS, Hammerton G, Portal AJ, Gordon FH, Heron J, et al. Prevalence of steatosis and fibrosis in young adults in the UK: a population-based study. Lancet Gastroenterol Hepatol. 2020 Mar;5(3):295-305. doi: 10.1016/S2468-1253(19)30419-4.

27. Cho J, Lee I, Park DH, Kwak HB, Min K. Relationships between Socioeconomic Status, Handgrip Strength, and Non-Alcoholic Fatty Liver Disease in Middle-Aged Adults. Int J Environ Res Public Health. 2021 Feb 16;18(4):1892. doi: 10.3390/ijerph18041892. PMID: 33669288;

28. Ramírez-Manent JI, Altisench Jané B, Arroyo Bote S, López Roig C, González San Miguel H, López-González AA. Cardiometabolic profile of 15057 elderly Spanish workers: association of sociodemographic variables and tobacco consumption. BMC Geriatr. 2022 Nov 17;22(1):872. doi: 10.1186/s12877-022-03547-w.

29. Jung HS, Chang Y, Kwon MJ, Sung E, Yun KE, Cho YK, et al. Smoking and the Risk of Non-Alcoholic Fatty Liver Disease: A Cohort Study. Am J Gastroenterol. 2019 Mar;114(3):453-463. doi: 10.1038/s41395-018-0283-5.

30. Zein CO, Unalp A, Colvin R, Liu YC, McCullough AJ; Nonalcoholic Steatohepatitis Clinical Research Network. Smoking and severity of hepatic fibrosis in nonalcoholic fatty liver disease. J Hepatol. 2011 Apr;54(4):753-9. doi: 10.1016/j.jhep.2010.07.040.

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ORIGINAL

Knowledge, attitude and practice towards antibiotic use and resistance among non-medical university students: A cross sectional survey in the United Kingdom

Conocimiento, actitud y práctica hacia el uso de antibióticos y la resistencia entre los estudiantes universitarios no médicos: Una encuesta transversal en el Reino Unido

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Abstract

Objective: Student surveys conducted in Higher Educational Institutes globally have indicated a dearth of knowledge regarding antibiotics and their appropriate usage. The knowledge, attitude, and practices (KAP) of non-medical students towards antibiotics is under-researched in the United Kingdom so in this study, we aimed to assess the antibiotic KAP of non-medical students at the University of the West of England.

Methods: A cross-sectional survey was conducted among a diverse group of 602 university students using self-administered written questionnaires. Descriptive and inferential statistics were carried out using SPSS 24.

Results: The survey response rate was 99.7%. Knowledge of antibiotics was significantly higher among home (UK) students and those enrolled in Faculty of Health and Applied Sciences (P<0.001). Respondents displayed a good understanding of personal use of antibiotics affecting their own health however the relationship between individual consumption of antibiotics contributing to antibiotic resistance in the community was not clear. 71% of the respondents thought antibiotic resistance was a property of human body, rather than bacteria. Over half of the respondents failed to acknowledge it as a serious global and national problem.

Conclusions: This study highlighted the cultural differences in knowledge, attitudes and practices regarding antibiotics among students. Misconceptions about biological mechanisms of antibiotic resistance and lack of personal responsibility for the issue were clearly demonstrated among respondents. Identification of these misunderstandings could inform targeted interventions aimed at improving the understanding of causes and consequences of antibiotic resistance along with emphasis on potential social benefit made by rational personal use of antibiotics.

Keywords: antibiotic resistance, cross sectional survey, university, students, non-medical.

Resumen

Objetivo: Las encuestas realizadas a estudiantes de centros de enseñanza superior de todo el mundo han puesto de manifiesto la escasez de conocimientos sobre los antibióticos y su uso adecuado. El conocimiento, la actitud y las prácticas (CAP) de los estudiantes no médicos con respecto a los antibióticos está poco investigado en el Reino Unido, por lo que en este estudio nos propusimos evaluar el CAP sobre antibióticos de los estudiantes no médicos de la Universidad del Oeste de Inglaterra.

Métodos: Se realizó una encuesta transversal entre un grupo diverso de 602 estudiantes universitarios utilizando cuestionarios escritos autoadministrados. Se realizaron estadísticas descriptivas e inferenciales con el programa SPSS 24.

Resultados: La tasa de respuesta a la encuesta fue del 99,7%. El conocimiento de los antibióticos fue significativamente mayor entre los estudiantes de origen (Reino Unido) y los matriculados en la Facultad de Salud y Ciencias Aplicadas (P<0,001). Los encuestados mostraron una buena comprensión del uso personal de los antibióticos que afecta a su propia salud, sin embargo, la relación entre el consumo individual de antibióticos que contribuye a la resistencia a los antibióticos en la comunidad no estaba clara. El 71% de los encuestados pensaba que la resistencia a los antibióticos era una propiedad del cuerpo humano, más que de las bacterias. Más de la mitad de los encuestados no reconocen que se trata de un grave problema mundial y nacional.

Conclusiones: Este estudio puso de manifiesto las diferencias culturales en cuanto a conocimientos, actitudes y prácticas en relación con los antibióticos entre los estudiantes. Los encuestados demostraron claramente sus ideas erróneas sobre los mecanismos biológicos de la resistencia a los antibióticos y su falta de responsabilidad personal en el tema. La identificación de estos malentendidos podría servir de base para las intervenciones dirigidas a mejorar la comprensión de las causas y las consecuencias de la resistencia a los antibióticos, junto con el énfasis en el potencial beneficio social que supone el uso personal racional de los antibióticos.

Palabras clave: resistencia a los antibióticos, encuesta transversal, universidad, estudiantes, no médicos.

Introduction

Antimicrobial resistance (AMR) is a major public health issue presenting a significant threat globally in the 21st century. The World Health Organization has declared AMR as one of the top ten global public health threats facing humanity which requires urgent multisectoral action in order to achieve the Sustainable Development Goals[1].

The Global action plan on antimicrobial resistance identifies AMR as a complex problem calling for whole-of-society engagement[2]. University students, being an accessible antibiotic user group and influential advisors to friends and family, are a potential target to engage with for addressing the problem of AMR. Recent research, however, has been majorly confined to students with medical backgrounds since they will be future antibiotic providers and trained for appropriate anti-microbial prescribing and responsible antibiotic use[3-7].

In the United Kingdom, knowledge, attitude and practice (KAP) relating to antibiotic use and resistance amongst students in higher educational institutes has not received much research attention. A literature search revealed three studies exploring antibiotic KAP among health care students[8-10] with no published reports on university students affiliated to non-medical backgrounds in the country.

Furthermore, no study so far has attempted to assess these patterns across a wide spectrum of courses in an ethnically diverse population of students at the same time using the same survey instrument. The current study aimed to present a contemporary picture of the antibiotic KAP of a varied group of students from non-medical backgrounds in a large UK university. The information obtained may provide guidance for the improvement of health services on the university campus and in initiating targeted health promotion interventions for individuals identified at higher risk.

Methods

Study population

The study population consisted of students at the University of the West of England (UWE). UWE is the largest provider of higher education in the Southwest of England. The student community at UWE is quite diverse in terms of their age groups, ethnic backgrounds and study programmes[11].

Raosoft sample size calculator was used to determine the minimum required sample size[12]. Based on the calculation with a 5% margin of error, a 95% confidence level and a 50% response distribution, the effective sample size estimated was 380. However, a larger sample size of 600 students was eventually included in the study, yielding approximately 1.5 times the initial sample size projection.

Students were approached in public spaces including post rooms and cafeterias and questionnaires were distributed to all the participants along with the participant information sheet. Ethical approval was obtained from the University's Research Ethics Committee. Anonymised questionnaires were used to ensure confidentiality.

Survey instruments

Data were collected using a self-administered, pre-tested questionnaire containing 26 questions. The questionnaire was developed after undertaking a literature review of comparable studies and was tailored to suit the local population[13-16]. It consisted of three sections: the first section recorded the respondent's socio-demographic characteristics.

The second section investigated respondent's knowledge and attitudes relating to antibiotics and their use. It had 12 knowledge statements and 4 attitude statements. A five-point Likert scale was employed to evaluate the respondent's responses. Section three consisted of four questions providing information about the practice of antibiotic use.

The questionnaire was pre-tested for content, design, readability, and comprehension on twenty students. Necessary modifications were done to make the questionnaire easy to answer and improve the acceptability. The pre-test data were discarded in the final analysis. Cronbach's alpha was used to assess the reliability of the statements determining knowledge and attitude and were calculated to be 0.71 and 0.83, respectively, therefore confirming the adequacy of the internal consistencies of the statements.

Data collection and analysis

A total of 602 students were approached for the study, of which 600 agreed to participate. The study had students belonging to 74 different countries who were grouped into continents (except the home students) for ease of analysis. The responses for knowledge, attitudes, and practice sections were assessed by calculating the percentage of each response selected. Further, the questions relating to knowledge were scored using five-point Likert scales (1= Strongly disagree, 2= Disagree, 3= Don't Know, 4= Agree and 5= Strongly agree). The total knowledge score for each of the respondents was calculated by adding up scores for each of these 12 statements yielding a maximum obtainable score of 60.

Data were analysed using the Statistical Packages for Social Sciences (SPSS), version 24.0. Frequency tables were used to summarise the data on the socio-

demographic variables. To examine the relationship between knowledge of antibiotics and socio-demographic variables, Mann –Whitney U test and Kruskal– Wallis test were employed depending upon the levels of the demographic variables owing to the skewed distribution of data. Groups with number of cases <10, were amalgamated with the next category wherever appropriate (as in the case of age, level of education, and student's normal residence). In demographic variables for which a significant overall association with KAP was established, further post hoc analysis was performed to determine the differences between groups employing Mann-Whitney U tests. Bonferroni correction was applied to control for inflation in Type I error rates. Association between knowledge score and prudent antibiotic use was explored using Mann-Whitney U test. For all analyses, a p value of < 0.05 was considered to be statistically significant.

Table I: Demographic characteristics of the study participants.

Demographic characteristics	Number of respondents	Percentage
Gender		
Male	289	(48.3%)
Female	308	(51.2 %)
Prefer not to say	3	(0.5%)
Age		
Under 18	11	(1.8%)
18-22	504	(84.0%)
23-29	75	(12.5%)
30 or above	10	(1.7%)
Faculty		
Health and Applied Sciences	108	(18.0%)
Business and Law	275	(45.9%)
Environment and Technology	155	(25.8%)
Arts, Creative Industries and Education	62	(10.3%)
Level of education		
Foundation	86	(14.3%)
Undergraduate	426	(71.1%)
Postgraduate	86	(14.3%)
Doctoral	2	(0.3%)
Country of residence		
UK (Home)	315	(52.5%)
Europe	44	(7.3%)
Asia	186	(31.0%)
Africa	43	(7.2%)
North America	8	(1.3%)
South America	4	(0.7%)

Results

A total of 600 UWE students participated and completed the questionnaire survey, generating a response rate of 99.7%. The mean age of the participants was 20.4 years. The median antibiotic knowledge score for the respondents was 36 with 55.6% scoring ≤ median and remaining 44.4% scoring > median. **Table I** summarises the demographic characteristics of the study population.

Knowledge and perceptions about antibiotics and antibiotic resistance

Response distributions to knowledge-probing statements are shown in **table II**.

Table II: Overall responses to knowledge assessments statements.

	Statements	Strongly disagree N (%)	Disagree N (%)	Don't know N(%)	Agree N(%)	Strongly agree N (%)	Total N (%)
1	Antibiotics are effective against bacteria	01 (0.2%)	17 (2.8%)	71 (11.8%)	390 (65.0%)	121 (20.2%)	600 -100%
2	Antibiotics are effective against viruses	43 (7.2%)	116 (19.3%)	114 (19.0%)	294 (49.0%)	33 (5.5%)	600 -100%
3	Antibiotics work on most colds & coughs	13 (2.2%)	153 (25.5%)	126 (21.0%)	280 (46.7%)	28 (4.7%)	600 -100%
4	A course of antibiotics should be stopped when a person starts feeling better	92 (15.3%)	228 (38.0%)	73 (12.2%)	160 (26.7%)	47 (7.8%)	600 -100%
5	Humans can become resistant to antibiotics	7 (1.2%)	50 (8.3%)	116 (19.3%)	297 (49.5%)	130 (21.7%)	600 -100%
6	Viruses can become resistant to antibiotics	21 (3.5%)	50 (8.3%)	153 (25.5%)	307 (51.2%)	69 (11.5%)	600 -100%
7	Bacteria can become resistant to antibiotics	4 (0.7%)	20 (3.3%)	159 (26.5%)	299 (49.8%)	118 (19.7%)	600 -100%
8	Antibiotic resistance is an issue that could affect me and my family	6 (1.0%)	53 (8.8%)	181 (30.2%)	294 (49.0%)	66 (11.0%)	600 -100%
9	Resistance to antibiotics is a problem in my country	15 (2.5%)	104 (17.3%)	295 (49.2%)	160 (26.7%)	26 (4.3%)	600 -100%
10	Antibiotic resistance is a significant global problem	6 (1.0%)	30% (5.0%)	261 (43.5%)	255 (42.5%)	48 (8.0%)	600 -100%
11	Inappropriate personal use of antibiotics can contribute to the problem of antibiotic resistance for myself	9 (1.5%)	21 (3.5%)	128 (21.3%)	345 (57.5%)	97 (16.2%)	600 -100%
12	Inappropriate personal use of antibiotics can contribute to the problem of antibiotic resistance for the whole community	3 (0.5%)	64 (10.7%)	187 (30.2%)	288 (48.0%)	64 (10.7%)	600 -100%

Confusion regarding the understanding of the basic biological mechanism behind antibiotic resistance was demonstrated in the study. Almost seven in ten respondents incorrectly agreed that "*Humans can become resistant to antibiotics*". Faculty of Health and Applied Sciences (HAAS) had the highest proportion of respondents (81.5%) affirming to the statement. Also, 77% of the home students agreed with the statement. Antibiotic resistance was not perceived as an important national or global challenge by a sizeable proportion of students.

Almost two –thirds of the respondents (75%) recognised that inappropriate personal use of antibiotics can contribute to the problem of antibiotic resistance for themselves. Whereas the number of respondents agreeing to inapt personal antibiotic use contributing to the problem of antibiotic resistance for the whole community was relatively lower at 59%.

Knowledge of antibiotics was found to vary significantly with the faculty of enrolment ($p<0.001$) and country of residence ($p<0.001$). The respondents from Faculty of HAAS and home students had the highest mean ranks translating into higher antibiotic knowledge when compared to their counterparts (**Table III**). Further, the post hoc analysis performed for the variables of Faculty revealed statistically significant differences between the mean ranks of respondents from HAAS & FBL ($p<0.001$), HAAS & FET, ($p<0.001$), HAAS & ACE ($p<0.001$) respectively. For the country of normal residence, a significant difference was found between the mean ranks of respondents from UK and Asia ($p<0.001$).

Attitudes and beliefs towards antibiotic use

Almost one-third of the considered it appropriate to bring antibiotics from home to avoid hassles of booking an appointment and seeing a doctor at university, of which 60% were international students (**Table IV**).

Practices on antibiotics use among participants

Almost three quarters of the students had taken oral antibiotics in the past 12 months, with the majority (73%) having completed their last antibiotic course. Approximately 16% didn't finish the last antibiotic course, maximum rates reported among respondents from Africa and South America (27.7%) followed by Asia (20.0%). The majority of these attributed it to getting better (65%) and being forgetful (19%).

Table III: Association between knowledge of antibiotics & socio-demographic characteristics of respondents.

Demographic characteristics	N (%)	Median knowledge score	Interquartile range (P value)*	Z score (P value)**	χ^2
Gender					
Male	289 (48.3)	35.0	32.0 - 39.0	-1.52	
Female	308 (51.2)	36.0	33.0 - 40.0		
Age					
Under 18	11 (1.8)	34.0	33.0 - 38.0		0.30
18-22	504 (84.0)	36.0	33.0 - 40.0		(0.86)
23 and above	85 (12.5)	36.0	33.0 - 40.0		
Faculty					
Health and Applied Sciences (HAAS)	108 (18.0)	39.0	35.0 - 44.0		46.45
Business and Law (FBL)	275 (45.9)	35.0	32.0 - 38.0		(<0.001)
Environment and Technology (FET)	155 (25.8)	36.0	33.0 - 40.0		
Arts, Creative Industries and Education (ACE)	62 (10.3)	35.0	33.0 - 40.0		
Level of education					
Foundation	86 (14.3)	35.5	33.0 - 40.0		1.23
Undergraduate	426 (71.1)	36.0	33.0 - 40.0		(0.54)
Postgrad & Doctoral	88 (14.6)	35.0	32.5 - 38.5		
Student's normal residence					
UK (Home)	315 (52.5)	37.0	34.0 - 41.0		32.26
Europe+ North America	52 (8.6)	37.0	33.0 - 40.0		(<0.001)
Asia	186 (31.0)	34.0	32.0 - 37.0		
Africa + South America	47 (7.9)	37.0	32.0 - 41.5		

* Mann –Whitney U test ** Kruskal- Wallis test

Table IV: Overall responses to attitudes assessments statements.

	Statements	Strongly disagree N (%)	Disagree N (%)	Don't know N (%)	Agree N (%)	Strongly agree N (%)	Total N (%)
1	When I get a cold, I should take antibiotics to get better quickly	53 (8.8%)	289 (48.1%)	73 (12.2%)	169 (28.2%)	16 (2.7%)	600 -100%
2	When I have a cold, I should take antibiotics to prevent getting worse	26 (4.3%)	266 (44.3%)	101 (12.2%)	185 (30.8%)	21 (3.5%)	600 -100%
3	It is fine to bring antibiotics from home to avoid hassles of booking an appointment and seeing a doctor at university	37 (6.2%)	214 (35.7%)	144 (24.0%)	168 (28.0%)	37 (6.2%)	600 -100%
4	It is okay to keep unused antibiotics and use them later when needed without the advice of doctor	123 (20.5%)	293 (48.8%)	79 (13.2%)	95 (15.8%)	10 (1.7%)	600 -100%

Most of the respondents (87%) declared using prescribed antibiotics. Of those using unprescribed antibiotics, majority either (51%) purchased them from a pharmacy or obtained them from family and friends (25%). The rates of self-medication were highest among African and South American students (29.8%) followed by Asian respondents (21.5%). Home students reported lowest rates of self- medication at 4.4%. Respondents who had finished their last antibiotic course were found to be significantly more knowledgeable about antibiotics than those who failed to finish the prescription (p=0.01).

Discussion

To the best of our knowledge, this is the first study to survey antibiotic KAP of a diverse population of students from a range of courses in the UK, all affiliated to non-medical backgrounds.

Knowledge and perceptions

The findings indicate confusion among students regarding whether antibiotics are effective against bacteria or viruses and their role in treating coughs and colds as observed in previous student surveys[17-20].

Confusion persists regarding the biological mechanism underlying antibiotic resistance, it seems to be conceptualized as some change caused in the human body rendering antibiotics ineffective rather than interpreting it as an intrinsic property of the bacteria. This fits with findings published in public surveys[21-24].

Misconception about human body building resistance to antibiotics was significantly more prevalent among the home students and those enrolled in Faculty of Health and Applied Sciences, both of which were predictors of higher knowledge of antibiotics in the study. This is a unique finding, and no historical studies exist to make direct comparisons. It indicates that although the term antibiotic resistance and its severity is firmly instilled among students with higher antibiotic knowledge, the understanding of the biological mechanism and events behind the phenomenon remains largely obscure.

Students in our survey didn't perceive antibiotic resistance as a serious global and/or national challenge discordant with the findings reported in student surveys conducted on medical students[3,5,7,18].

When queried about perceptions of relationship between inappropriate use of antibiotics and the phenomenon of antibiotic resistance, respondents seemed to have demonstrated a good understanding of their personal use of antibiotics affecting their own health. However, understanding of the relationship between the individual consumption of antibiotics and development of antibiotic resistance in the community was limited. The findings are congruent with published reports[25-26] and clearly suggests a lack of understanding of the individual ownership of the cause and calls for development of interventions explaining how antibiotic resistance develops and spreads in the first place including a dimension that assigns individual responsibility.

Students from Faculty of Health and Applied Sciences seemed to be more knowledgeable about antibiotic use and resistance than their peers from other faculties. The study also revealed a significant relationship between knowledge of antibiotics and country of residence with the home students scoring notably better than their counterparts. This difference might be accounted for by the influence of the high-level efforts in the UK, including several antibiotic awareness campaigns undertaken since 2004, to educate the public about the appropriate use of antibiotics and increase awareness of the issue of antibiotic resistance[27-30].

Attitudes and beliefs

Misbeliefs regarding antibiotics speeding up recovery from colds and preventing more serious illness were found to be prevalent and were indicative of a lack of understanding of the efficacy of antibiotics and their role in treating viral infections.

Majority of the international students perceived it appropriate to bring antibiotics from home to avoid hassles of consulting a doctor at the university. This perception is likely to have been influenced by the apprehensiveness accompanying transition and acclimatization in a setting very different from their country of normal residence.

Practices

When enquired about the practices of antibiotic usage, low level of self-medication and high level of adherence to antibiotic prescription was observed. Self -medication rates and noncompliance with the course of antibiotics were found to be lowest among the home students which can in part be associated with the effectiveness of antibiotic stewardship programs in UK. Apart from the multiple antibiotic awareness campaigns targeting the general public, several regulatory measures including surveillance and legislative actions have been strictly in place to ensure the appropriate use of antibiotics[31-33]. High rates of self-medication and non-adherence were reported for respondents from Africa and South America along with their Asian peers, suggestive of a lack of regulation on antibiotic prescription and sales in these countries. Furthermore, differences in implementation of drug regulations affecting the availability of antibiotics over counter in different countries has been found to play an important role in promoting higher rates of self -medication and inappropriate use[34].

The more knowledgeable respondents were more likely to have completed their last course of prescribed

antibiotics and was found to be consistent with findings reported in previous surveys[35-37].

Strengths and Limitations

The strengths of the study include a high response rate of 99.7% and a large sample size. Our study has some limitations, it was not possible to carry out a random sampling procedure owing to the blanket policy of security measures in place which might have compromised the generalizability of the findings, though sincere efforts were made to maintain the representativeness of the sample.

Conclusions

Clear cultural differences in knowledge, attitudes and practices regarding antibiotic use were identified among respondents. Misconceptions about the biological mechanisms of antibiotic resistance and lack of personal responsibility for the issue was clearly demonstrated among the respondents. Antibiotic resistance was not perceived as a serious global or national problem among the study subjects. This highlights the need for developing targeted health promotion interventions within the university strategizing methods to engage with the less knowledgeable groups to improve topic-specific knowledge. Also, campaigns and educational efforts applying behavioral insights methodology and emphasising on potential social benefit made by rational personal use of antibiotics can help facilitate the desired behavioural change and foster responsible use of antibiotics.

Conflict of interest

The author has no conflict of interest to declare

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References

1. World Health Organization (2020) Antimicrobial Resistance Factsheet. Available: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance. Accessed 19 September 2021

2. World Health Organization (2015) Global action plan on antimicrobial resistance.Available:https://www.who.int/antimicrobial-resistance/publications/global-action-plan/en/. Accessed 19 August 2021

3. Abbo LM, Cosgrove SE, Pottinger PS, Pereyra M, Sinkowitz-Cochran R, Srinivasan A, et al. Medical students' perceptions and knowledge about antimicrobial stewardship: How are we educating our future prescribers? Clin Infect Dis. 2013;57(5):631-8

4. Minen MT, Duquaine D, Marx MA, Weiss D. A survey of knowledge, attitudes, and beliefs of medical students concerning antimicrobial use and resistance. Microb Drug Resist. 2010;16(4):285-9

5. Pulcini C, Williams F, Molinari N, Davey P, Nathwani D. Junior doctors' knowledge and perceptions of antibiotic resistance and prescribing: a survey in France and Scotland. Clin Microbiol Infect. 2011;17(1):80-7

6. Scaioli G, Gualano MR, Gili R, Masucci S, Bert F, Siliquini R. Antibiotic use: a cross-sectional survey assessing the knowledge, attitudes and practices amongst students of a school of medicine in Italy. PLoS One. 2015;10(4):e0122476

7. Yang K, Wu D, Tan F, Shi S, Guo X, Min Q, et al. Attitudes and perceptions regarding antimicrobial use and resistance among medical students in Central China. Springerplus. 2016;5(1):1779.

8. Dyar OJ, Hills H, Seitz LT, Perry A, Ashiru-Oredope D. Assessing the Knowledge, Attitudes and Behaviors of Human and Animal Health Students towards Antibiotic Use and Resistance: A Pilot Cross-Sectional Study in the UK. Antibiotics (Basel). 2018;7(1):10. Published 2018 Jan 30. doi:10.3390/antibiotics7010010

9. Inácio J, Barnes L-M, Jeffs S, Castanheira P, Wiseman M, Inácio S, et al. Master of Pharmacy students' knowledge and awareness of antibiotic use, resistance and stewardship. Curr Pharm Teach Learn. 2017;9(4):551-9.

10. Wright EP, Jain P. Survey of antibiotic knowledge amongst final year medical students. J Antimicrob Chemother. 2004;53(3):550-1

11. UWE Bristol (2021) Student and Staff numbers. Available: https://www.uwe.ac.uk/about/demographic-data/student-and-staff-numbers#a96fa7113-3b62-4ce7-af88-874fcd28c105 Accessed 10 November 2021

12. Raosoft Inc (2004) Raosoft Sample Size Calculator. Available: http://www.raosoft.com/samplesize. html. Accessed 10 July 2017

13. André M, Vernby A, Berg J, Lundborg CS. A survey of public knowledge and awareness related to antibiotic use and resistance in Sweden. J Antimicrob Chemother. 2010;65(6):1292-6.

14. Carter RR, Sun J, Jump RLP. A survey and analysis of the American public's perceptions and knowledge about antibiotic resistance. Open Forum Infect Dis. 2016;3(3):ofw112.

15. Eng JV, Marcus R, Hadler JL, Imhoff B, Vugia DJ, Cieslak PR, et al. Consumer attitudes and use of antibiotics. Emerging infectious diseases. 2003;9(9):1128-35

16. McNulty CA, Boyle P, Nichols T, Clappison P, Davey P. Don't wear me out—the public's knowledge of and attitudes to antibiotic use. Journal of Antimicrobial Chemotherapy. 2007;59(4):727-38

17. Huang Y, Gu J, Zhang M, Ren Z, Yang W, Chen Y, et al. Knowledge, attitude and practice of antibiotics: a questionnaire study among 2500 Chinese students. BMC Med Educ. 2013;13(1):163.

18. Khan AK, Banu G, Reshma KK. Antibiotic resistance and usage—a survey on the knowledge, attitude, perceptions and practices among the medical students of a Southern Indian teaching hospital. Journal of clinical and diagnostic research: JCDR. 2013;7(8):1613.

19. Lv B, Zhou Z, Xu G, Yang D, Wu L, Shen Q, et al. Knowledge, attitudes and practices concerning self-medication with antibiotics among university students in western China. Trop Med Int Health. 2014;19(7):769-79.

20. Shah SJ, Ahmad H, Rehan RB, Najeeb S, Mumtaz M, Jilani MH, et al. Self-medication with antibiotics among non-medical university students of Karachi: a cross-sectional study. BMC Pharmacol Toxicol. 2014;15(1):74

21. Abu Taha A, Abu-Zaydeh AH, Ardah RA, Al-Jabi SW, Sweileh WM, Awang R, et al. Public knowledge and attitudes regarding the use of antibiotics and resistance: Findings from a cross-sectional study among Palestinian adults. Zoonoses Public Health. 2016;63(6):449–57.

22. Awad AI, Aboud EA. Knowledge, attitude and practice towards antibiotic use among the public in Kuwait. PLoS One. 2015;10(2):e0117910.

23. Lim KK, Teh CC. A cross sectional study of public knowledge and attitude towards antibiotics in Putrajaya, Malaysia. South Med Rev. 2012;5(2):26-33.

24. Oh AL, Hassali MA, Al-Haddad MS, Sulaiman SAS, Shafie AA, Awaisu A. Public knowledge and attitudes towards antibiotic usage: a cross-sectional study among the general public in the state of Penang, Malaysia. The Journal of Infection in Developing Countries. 2010;5(05):338-47.

25. Brooks L, Shaw A, Sharp D, Hay AD. Towards a better understanding of patients' perspectives of antibiotic resistance and MRSA: a qualitative study. Fam Pract. 2008;25(5):341- 8.

26. Hawkings NJ, Wood F, Butler CC. Public attitudes towards bacterial resistance: a qualitative study. J Antimicrob Chemother. 2007;59(6):1155-60.

27. Bhattacharya A, Hopkins S, Sallis A, Budd EL, Ashiru-Oredope D. A process evaluation of the UK-wide Antibiotic Guardian campaign: developing engagement on antimicrobial resistance. J Public Health (Oxf) [Internet]. 2016; Available from: http://dx.doi.org/10.1093/pubmed/fdw059

28. Chaintarli K, Ingle SM, Bhattacharya A, Ashiru-Oredope D, Oliver I, Gobin M. Impact of a United Kingdom-wide campaign to tackle antimicrobial resistance on self-reported knowledge and behaviour change. BMC Public Health [Internet]. 2016;16(1). Available from: http://dx.doi.org/10.1186/s12889-016-3057-2

29. Lambert MF, Masters GA, Brent SL. Can mass media campaigns change antimicrobial prescribing? A regional evaluation study. J Antimicrob Chemother. 2007;59(3):537-43.

30. McNulty CAM, Nichols T, Boyle PJ, Woodhead M, Davey P. The English antibiotic awareness campaigns: did they change the public's knowledge of and attitudes to antibiotic use? J Antimicrob Chemother. 2010;65(7):1526-33

31. Ashiru-Oredope D, Sharland M, Charani E, McNulty C, Cooke J. Improving the quality of antibiotic prescribing in the NHS by developing a new Antimicrobial Stewardship Programme: Start Smart—Then Focus. Journal of antimicrobial chemotherapy. 2012;67(suppl_1):51-63.

32. McNulty CAM, Nichols T, French DP, Joshi P, Butler CC. Expectations for consultations and antibiotics for respiratory tract infection in primary care: the RTI clinical iceberg. Br J Gen Pract. 2013;63(612):e429-36.

33. World Health Organization (2017) Evaluation of antibiotic awareness campaigns. Available: http://www.who.int/selection_medicines/committees/expert/21/applications/antibacterials-ccps_rev/en/. Accessed 10November 2019

34. Grigoryan L, Burgerhof JGM, Degener JE, Deschepper R, Lundborg CS, Monnet DL, et al. Attitudes, beliefs and knowledge concerning antibiotic use and self-medication: a comparative European study. Pharmacoepidemiol Drug Saf. 2007;16(11):1234-43.

35. Donkor ES, Tetteh-Quarcoo PB, Nartey P, Agyeman IO. Self-medication practices with antibiotics among tertiary level students in Accra, Ghana: a cross-sectional study. Int J Environ Res Public Health. 2012;9(10):3519-

36. Fatokun O. Exploring antibiotic use and practices in a Malaysian community. Int J Clin Pharm. 2014;36(3):564-9.

37. Sarahroodi S, Arzi A, Sawalha AF, Ashtarinez A. Antibiotics self-medication among southern Iranian university students. Int J Pharmacol. 2009;6(1):48-52.

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ORIGINAL

Desarrollo de competencias profesionales para prevenir las agresiones a través de la simulación virtual en estudiantes de enfermería: estudio experimental

Development of professional skills to prevent aggression through virtual simulation in nursing students: experimental study

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Resumen

Objetivos: Este estudio tiene como objetivo evaluar los efectos de la simulación virtual sobre el aprendizaje práctico y la adquisición de competencias de comunicación, relación interpersonal, actitudes y trasferencia, para la gestión de conflictos, en estudiantes de enfermería de último curso, frente al método tradicional de trabajo con casos clínicos escritos.
Métodos: Estudio experimental con dos grupos paralelos aleatorizados con 90 estudiantes de enfermería. El grupo control recibió una intervención basada en simulación tradicional (n = 45) y el grupo experimental recibió una intervención basada en simulación virtual (n = 45), ambas orientadas a la adquisición de competencias de comunicación, relación interpersonal, actitudes y trasferencia, para la gestión de conflictos. La adquisición de estas competencias se evaluó mediante la escala ECOEnf con las unidades competenciales 6 (UC6) y 7 (UC7).
Resultados: Se compararon las puntuaciones antes y después de la intervención, sin observarse diferencias estadísticamente significativas en el grupo control, en la UC6 (p=0,54) y en la UC7 (p=0,83), así como en el grupo intervención en la UC6 (p=0,21) y en la UC7 (p=0,32). Al ajustar por las variables sociodemográficas tampoco se encontraron diferencias en cada grupo después de la intervención. Al comparar las diferencias entre grupos en el momento después de la intervención, no se hallaron diferencias estadísticamente significativas ni en la UC6 (p=0,57) ni en la UC7 (p=0,89).
Conclusiones: Con los datos del presente estudio no se puede demostrar que la simulación mediante realidad virtual sea un método de aprendizaje estratégico.

Palabras clave: Enfermería, habilidades de comunicación y actitud, agresiones hacia profesiones de la salud, simulación

Abstract

Objectives: This study aims to evaluate the effects of virtual simulation on practical learning and the acquisition of communication skills, interpersonal relationships, attitudes and transference, for conflict management, in final year nursing students, compared to the method traditional way of working with written clinical cases.
Methods: Experimental study with two parallel randomized groups with 90 nursing students. The control group received an intervention based on traditional simulation (n = 45) and the experimental group received an intervention based on virtual simulation (n = 45), both aimed at the acquisition of communication skills, interpersonal relationships, attitudes and transference, to conflict management. The acquisition of these skills was evaluated using the ECOEnf scale with skill units 6 (UC6) and 7 (UC7).
Results: The scores were compared before and after the intervention, without observing statistically significant differences in the control group, in the UC6 (p=0.54) and in the UC7 (p=0.83), as well as in the group intervention in UC6 (p=0.21) and in UC7 (p=0.32). When adjusting for sociodemographic variables, no differences were found in each group after the intervention. When comparing the differences between groups at the time after the intervention, no statistically significant differences were found in either the UC6 (p=0.57) or the UC7 (p=0.89).
Conclusions: With the data of this study, it cannot be demonstrated that virtual reality simulation is a strategic learning method.

Keywords: Nursing, communication skills and attitude, aggression towards health professions, simulation.

Introducción

La profesión sanitaria es una población expuesta a un alto riesgo de violencia, al trabajar en contacto con el público y con personas que se encuentran en dificultades. La violencia afecta a la salud de los trabajadores sanitarios y tiene consecuencias sociales y psicológicas que permanecen frecuentemente escondidas. Además, los profesionales sanitarios reciben formas de violencia física y verbal, esta última tan dañina y destructiva como el uso de la fuerza física[1,2]. Sin embargo, se puede decir que este tipo de violencia ocupacional es predecible y, por tanto, evitable. Números estudios ponen de manifiesto que la percepción de una provocación es un predictor significativo de la violencia ocupacional[3,4]. Aun sabiendo esto las agresiones a profesionales sanitarios han ido aumentando en los últimos años[5]. Por ello, los futuros profesionales necesitan aprender a actuar ante estas situaciones. El desarrollo de las habilidades de gestión de conflictos debe empezar en el periodo de formación universitaria, donde empiezan a darse las primeras situaciones de violencia[6,7].

Una de las posibles metodologías para la adquisición de estas habilidades es la simulación a través de realidad virtual (o simulación virtual), gracias a la recreación de múltiples situaciones ficticias[8,9]. Hay múltiples estudios que demuestran sus beneficios en el desarrollo de competencias instrumentales[10], pero pocos estudios aleatorizados que demuestren su eficacia en el desarrollo de las competencias de comunicación, relación interpersonal, actitudes y trasferencia[11,12]. En este sentido, podría ser útil el uso de la simulación virtual como metodología para el aprendizaje de competencias orientadas hacia la reducción y prevención de las agresiones a enfermeras, frente a las simulaciones convencionales basadas en las lecturas y reflexiones sobre casos de situaciones de violencia a profesionales, escritos[13].

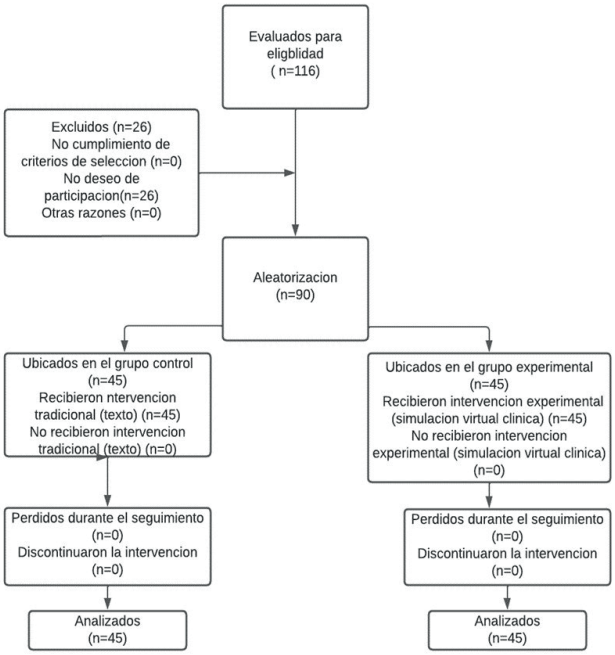
Por ello, este estudio tiene como objetivo evaluar los efectos de la simulación virtual sobre el aprendizaje práctico y la adquisición de competencias de comunicación, relación interpersonal, actitudes y trasferencia, para la gestión de conflictos, en estudiantes de enfermería de último curso, frente al método tradicional de trabajo con casos clínicos escritos.

Material y métodos

Diseño. Se realizó un estudio experimental con dos grupos paralelos aleatorizados, grupo control, que recibió una intervención educativa basada en simulación tradicional y grupo experimental, que recibió una intervención educativa basada en simulación virtual, ambas orientadas a la adquisición de competencias de comunicación, relación interpersonal, actitudes y trasferencia, para la gestión de conflictos[14,15].

Población. Como población del estudio, se consideró la totalidad de estudiantes de Enfermería de cuarto curso (n=116) de la Facultad de Enfermería de Castilla la Mancha, España. Los criterios de inclusión fueron: ser estudiante de Enfermería de cuarto curso de dicha facultad y los criterios de exclusión: no desear participar voluntariamente en el estudio y no cumplimentar el consentimiento informado escrito. De los 116 estudiantes de cuarto año del grado de Enfermería finalmente participaron en el estudio 90 (45 en el grupo control y 45 en el grupo experimental) (**Figura 1**).

Figura 1: Diagrama de flujo para el screening y aleatorización de participantes.



Variables del estudio.

- Adquisición de competencias: como instrumento autoadministrado para evaluar la adquisición de competencias se utilizó un cuestionario autoadministrado, la Escala de Evaluación de Competencias Enfermeras (ECOEnf)[16] que fue diseñada y validada en español para dar respuesta a la evaluación de las competencias recogidas en la Orden Ministerial CIN 2134/2008[17]. En la escala "ECOEnf" se determinan 5 Unidades Competenciales (UC), que tienen que ver directamente con las funciones enfermeras y el proceso de atención de Enfermería: UC1.- Valoración y Diagnóstico; UC2: Planificación de cuidados; UC3: Intervención de Enfermería; UC4: Evaluación y Calidad; UC5: Gestión Clínica. Además de estas unidades competenciales, que hacen referencia específicamente a las funciones del profesional de enfermería, se incluyen competencias transversales de UC6: Comunicación y Relación Interpersonal; UC7: Actitudes, Valores y Transferencia. Cada ítem

se valora con una escala tipo Likert con valores que van del 1 al 3 en función de la autopercepción del nivel de logro de adquisición y desempeño de las competencias (1 = Avanzado, 2 = Intermedio y 3 = Básico). Para el estudio solo se emplearon la UC6, que consta de 13 ítems, y la UC7, de 14 ítems para la UC7. En función de las puntuaciones en cada unidad competencial los sujetos pueden categorizarse en función de su nivel de competencia o logro (avanzado, intermedio y básico), dividiendo la puntuación obtenida en cada competencia por la puntuación máxima posible: nivel avanzado (13,0-42,0%), nivel intermedio (42,1-71,0%) y nivel básico (71,1-100,0%) para la UC6, y nivel avanzado (14,0-42,7%), nivel intermedio (42,8-71,5%) y nivel básico (71,6-100,0%) para la UC7. Esta herramienta es válida y fiable, cuenta con un Índice de validación de contenido (CVI) superior a 0,85 y un Índice Kappa total de 0,83[18].

- Covariables: se recogieron las siguientes variables para evaluar su influencia en la intervención del estudio (adquisición de competencias): edad y sexo de todos los participantes, medio de acceso a la universidad (titulación de acceso al grado, examen de acceso a la titulación o similar), posesión de otro título universitario, situación laboral actual (en el ámbito sanitario) y experiencia profesional previa en el ámbito sanitario.

Intervención. Los alumnos de enfermería fueron reclutados y aleatorizados, tras su aceptación en la participación del estudio, entre noviembre y enero del 2021. Los estudiantes fueron asignados aleatoriamente a un grupo control (simulación tradicional) y otro grupo de intervención (simulación virtual) mediante una asignación aleatoria simple utilizando el programa SPSS versión 24 para Windows. Las covariables del estudio se recogieron antes de la intervención y tras la inclusión de los participantes en el estudio. Antes y después de la intervención se evaluaron las autopercepciones de competencias específicas de comunicación y relación interpersonal (UC6), y las de actitudes y trasferencia (UC7) mediante la escala ECOEnf. La intervención (método de la realidad virtual) consistió en la visualización de 3 vídeos de casos de situaciones de posible violencia (separados por intervalos de 5 minutos), a través de gafas de realidad virtual. Al final del visionado de los vídeos los alumnos debían reflexionar y responder a una pregunta por video, con 3 opciones de respuesta (presentadas por los investigadores del estudio), debiendo seleccionar la respuesta más correcta de acuerdo con las competencias del profesional ante cada una de las 3 situaciones. Para la edición y proyección de los vídeos se utilizó el programa Lumion. Los estudiantes que fueron aleatorizados al grupo control recibieron los mismos casos de los videos, pero a través de un documento escritos para la lectura. Ambas intervenciones abordaban las habilidades de comunicación, relación personal y actitudes, que debían adquirir los estudiantes de enfermería de cuarto curso.

Análisis estadístico

Los resultados de las variables categóricas se presentaron en forma de frecuencias absolutas (n) y porcentajes (%). Las variables cuantitativas se presentaron como medias y desviaciones típicas, o solo medias. Para evaluar la validez del cuestionario se calculó el índice de validez de contenido (IVC) con las respuestas de los alumnos y el índice Kappa. Las características de los participantes se compararon mediante la prueba de chi-cuadrado para las variables categóricas y las pruebas T-Student (pareados e independientes) y ANOVA univariados para las variables cuantitativas continuas. Se compararon los resultados pre y postest por grupo de estudiantes, y entre grupos. Se tomaron las variables sociodemográficas como variables control para evaluar su efecto sobre las puntuaciones de la escala ECOEnf después de la intervención, en cada uno de los grupos. Los resultados se consideraron estadísticamente significativos con un nivel de significación $p < 0,05$. Todos los análisis de los datos fueron efectuados mediante el programa SPSS versión 24 para Windows.

Consideraciones éticas. Este estudio fue aprobado por el Comité de Ética de la Universidad de Castilla la Macha. Los estudiantes que fueron voluntarios se convocaron a una reunión de información en la que se facilitó a cada participante un documento describiendo el proyecto. Si los estudiantes deseaban participar, una vez que habían comprendido la información, se les pidió que firmaran un consentimiento por escrito. Este estudio se llevó a cabo respetando los principios de investigación biomédica de la declaración de Helsinky. Se respetó la confidencialidad y privacidad de su información en cumplimiento de la normativa vigente en materia de protección de datos personales. Los datos se ingresaron en bases de datos seguras y el acceso a los datos se restringió a los investigadores. El análisis de datos fue limitado para los propósitos de este estudio.

Resultados

Datos sociodemográficos

Respecto a los datos sociodemográficos, dentro del grupo control la mayoría de los participantes tenía una edad inferior a 21 años (53%), eran mujeres (76%), habían accedido a la universidad mediante prueba de acceso (76%), un 20% tenía otra titulación de grado y la mayoría no compatibilizaban sus estudios con trabajo (79%). En el grupo experimental la mayoría de los estudiantes tenían menos de 21 años (51%), eran mujeres (82%), habían accedido al grado a través de una prueba de acceso (80%), no tenían otra titulación (72%) y no se encontraban trabajando (93%). No se hallaron diferencias estadísticamente significativas entre ambos grupos en los datos sociodemográficos (**Tabla I**).

Diferencias intragrupos en las UC6 y UC7 de la escala ECOEnf

El presente estudio, realizado con las UC6 y UC7, se obtuvieron datos específicos de validez de IVC de 0,92 y 0,84, y de índice Kappa de 0,92 y 0,83, respectivamente.

Los grupos fueron homogéneos en las puntuaciones basales tanto en la UC6 (GC: 19,91±4,93 vs GE: 20,93±5,67, p=0,36) como en la UC7 (GC: 19,76±5,15 vs GE: 20,49±5,15, p=0,50).

Se compararon las puntuaciones antes y después de la intervención, sin observarse diferencias estadísticamente significativas en el grupo control, tanto en la UC6 (pre: 19,91±4,93 vs post: 19,60±4,91, p=0,54), como en la UC7 (pre: 19,76±5,15 vs post: 19,84±5,58, p=0,83). Respecto al grupo intervención, tampoco se observaron diferencias antes-después en la UC6 (pre: 20,93±5,67 vs post: 20,22±5,41, p=0,21) y en la UC7 (pre: 20,49±5,15 vs post: 20,00±5,18, p=0,32). Como se puede ver en la **tabla II**, al comparar las diferencias antes y después de la intervención intragrupo por nivel de logro (avanzado, intermedio y básico), solo se observaron diferencias estadísticamente significativas en el grupo control en el nivel avanzado (p=0,02).

Finalmente, se analizaron las diferencias en las puntuaciones en cada una de las unidades competenciales después de la intervención ajustando por las variables sociodemográficas, sin encontrase diferencias estadísticamente significativas en ninguno de los dos grupos (**Tabla III**).

Diferencias entregrupos en las UC6 y UC7 de la escala ECOEnf

Al comparar las diferencias entre grupos en el momento después de la intervención, no se hallaron diferencias estadísticamente significativas ni en la UC6 (GC: 19,60±4,91 vs GI: 20,22±5,41, p=0,57) ni en la UC7 (GC: 19,84±5,58 vs GI: 20,00±5,18, p=0,89).

Diferencias entre grupos a las preguntas de los 3 casos clínicos

Respecto a las diferencias entre grupos en las respuestas correctas de los alumnos a las preguntas planteadas para cada uno de los casos, se hallaron diferencias entre grupos en el caso 1 (p=0,02), pero no en el caso 2 (p=0,86) y en el caso 3 (p=0,16). Sin embargo, las diferencias no se correspondieron a un mayor porcentaje de respuestas correctas (opción B, **Figura 2**)

Tabla I: Diferencias sociodemográficas entre grupos control y experimental.

Subgrupo	Grupo control (n = 45)	Grupo experimental (n = 45)	p-valor
Edad			
<21	24 (53%)	23 (51%)	p=0,833
21-25	15 (32%)	21 (47%)	
26-30	1 (4%)	0 (0%)	
31-35	1 (4%)	0 (0%)	
>40		4 (9%)	1 (2%)
Sexo			
Mujer	34 (76%)	37 (82%)	p=0,438
Hombre	11 (24%)	8 (18%)	
Titulación de acceso			
PAU	34 (76%)	36 (80%)	p=0,612
FP	8 (18%)	7 (16%)	
>25 años	2 (4%)	1 (2%)	
>45 años	1 (2%)	1 (2%)	
Posesión de otro título	**n = 42**	**n = 44**	
No			
Grado	32 (78%)	32 (72%)	p=0,529
Diplomado	8 (20%)	10 (23%)	
	1 (2%)	2 (5%)	
Trabajo actual			
No	37 (82%)	42 (93%)	p=0,108
Atención hospitalaria	4 (10%)	0	
Geriátricos	2 (4%)	0	
Prácticas enfermeria	2 (4%)	3 (7%)	
Experiencia profesional previa			
No	32 (71%)	40 (89%)	p=0,245
<1 año	4 (9%)	4 (9%)	
1-2 años	0 (0%)	1 (2%)	
2-3 años	2 (4%)	0	
3-4 años	2 (4%)	0	
5-10 años	2 (4%)	0	
>10 años	3 (8%)	0	

Tabla II: Diferencias (medias) antes después en cada grupo (control y experimental) por nivel de logro.

Subgrupo	Grupo control						Grupo experimental					
	UC6			UC7			UC6			UC7		
	pre	post	p-valor	pre	post	p-valor	pre	post	p-valor	pre	post	p-valor
Avanzado	14,14	15,00	p=0,24	14,40	14,73	p=0,02	14,00	14,25	p= 0,59	15,25	15,31	p=0,79
Intermedio	22,33	21,37	p=0,16	21,97	22,03	p=0,91	22,21	21,86	p=0,61	23,04	22,75	p=0,62
Básico	28*	31*	-	36*	33*	-	30,40	25,40	p=0,13	33*	18*	-

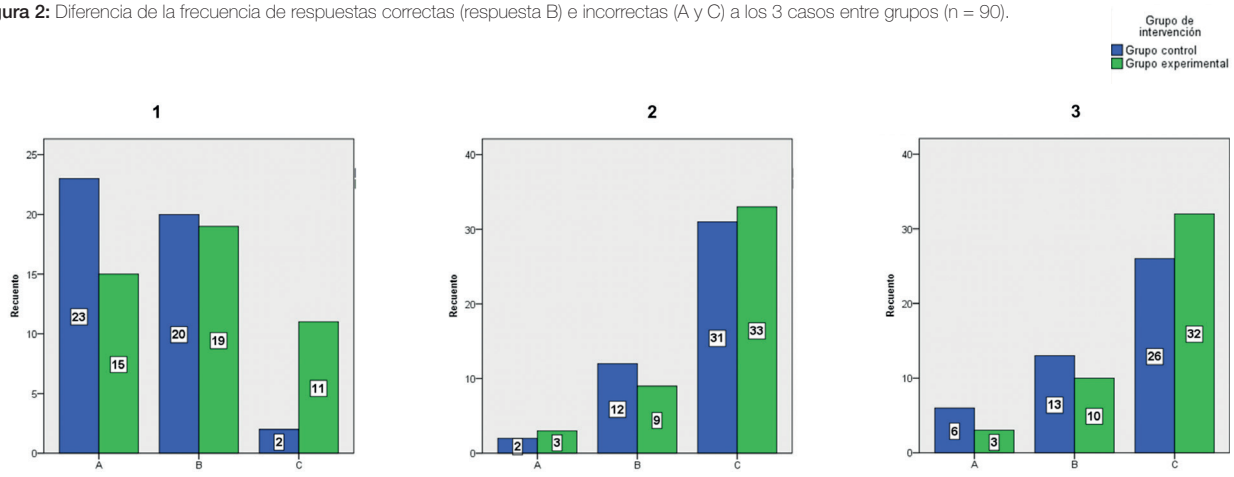
* Estos valores son resultado de una sola observación y por tanto no se analizaron diferencias

Tabla III: Efectos de factores sociodemográficos sobre las mediciones de UC6 y UC7 postest en el grupo experimental y control (n = 90).

Grupo	Grupo control				Grupo experimental			
Factor	UC6		UC7		UC6		UC7	
	Media±DT	**p-valor**	**Media±DT**	**p-valor**	**Media±DT**	**p-valor**	**Media±DT**	**ANOVA**
Edad (años)								
< 21	20,38±4,85	p=0,19	19,96±5,13	p=0,37	20,87±5,23	p=0,34	20,35±4,85	p=0,50
21-25	20,13±5,06		21,20±6,65		19,86±5,57		19,90±5,59	
26-30	-		-		-		-	
31-35	-		-		-		-	
> 40	14,25±1,89		15,25±1,89		-		-	
Sexo								
Femenino	20,03±4,73	p=0,31	20,03±5,67	p=0,70	20,49±5,21	p=0,487	20,30±5,21	p=0,41
Masculino	18,27±5,44		19,27±5,58		19,00±6,50		18,63±5,18	
Titulación de acceso al grado								
Selectividad/ PAU o similar	20,09±4,72	p=0,43	19,79±5,37	p=0,52	21,25±5,39	p=0,06	20,78±5,30	p=0,09
Formación profesional	19,13±5,99		21,50±7,03		16,00±3,01		16,29±2,14	
Acceso mayor de 25 años	14,50±2,12		-		-		-	
Acceso mayor de 45 años	-		-		-		-	
Otro título universitario								
Diplomatura	-	p=0,25	-	p=0,50	19,00±7,07	p=0,515	19,00±7,07	p=0,49
Grado	17,29±5,16		19,14±7,58		21,80±5,25		22,10±5,47	
No	20,09±5,01		19,91±5,40		19,68±5,52		19,35±5,14	
Bachillerato	23,50±3,54		24,50±4,95		-		-	
Trabajo actual en el ámbito sanitario								
No	19,86±4,91	p=0,08	19,86±5,42	p=0,12	20,40±5,53	p=0,62	20,12±5,29	p=0,59
Sí, en atención hospitalaria	16,75±3,10		18,50±6,61		-		-	
Sí, en geriátricos	14,50±2,12		14,50±0,71		-		-	
Prácticas de Enfermería	25,50±0,71		27,50±0,71		16,50±2,12		16,50±2,12	
Experiencia profesional previa en el ámbito sanitario (años)								
No tengo experiencia	19,67±4,83	p=0,21	19,69±5,43	p=0,14	20,50±5,53	p=0,62	20,18±5,10	p=0,61
< 1	23,25±5,56		23,75±6,19		18,25±4,65		19,50±6,81	
1-2	-		-		-		-	
3-4	-		-		-		-	
5-10	-		-		-		-	
> 10	14,67±2,08		15,33±2,31		-		-	

*Nota: se han eliminado los datos de 1 sola observación

Figura 2: Diferencia de la frecuencia de respuestas correctas (respuesta B) e incorrectas (A y C) a los 3 casos entre grupos (n = 90).



Discusión

Los resultados obtenidos a través del trabajo de campo no permiten demostrar que la simulación virtual utilizada en el grupo experimental con respecto al método tradicional de simulación mejore la adquisición de las UC6 y UC7. Aunque se observaron mejoras en los resultados después de la intervención en el grupo experimental, relacionados con un nivel de logro avanzado, para las dos UC, estas diferencias no fueron estadísticamente significativas. Por otro lado, no se observaron mejoras cuando se agruparon los datos por niveles, avanzado, intermedio y básico. Aunque se encontraron diferencias en la frecuencia de respuestas entre grupos en el caso 1, pero no en el resto, estas diferencias no se debieron a un mayor porcentaje de respuestas correctas, sino a diferencias entre grupos en las respuestas incorrectas. Por tanto, con los datos obtenidos en nuestro estudio, no podemos decir que haya diferencias entre grupos en la variable independiente y, por tanto, nuestro estudio no permite apoyar la hipótesis de que la simulación virtual sea superior a una simulación basada en el uso de casos clínicos escritos. En nuestra muestra, el hallazgo de equivalencias estadísticas entre los grupos de intervención, sobre todo en el momento postest, puede corresponderse con las características de los participantes, siendo alumnos de cuarto año de Enfermería, mayormente solo estudiantes y sin experiencia laboral en el ámbito sanitario. Ello podría haber obrado como condicionante de las autopercepciones acerca de la utilidad de ambos métodos de intervención sobre la formación de competencias comunicacionales y actitudinales.

A diferencia de nuestros resultados, los resultados obtenidos hasta el momento, de las evaluaciones aplicadas, concluyen que existen diferencias significativas en el aprendizaje de los que usan algún tipo de modelo simulado con relación a quienes se les aplica únicamente el método tradicional[19]. Estudios como los de Cuesta Cambra y Mañas Viniegra[20] y Levett-Jones et al.[21], la simulación virtual favorece el desarrollo de las competencias profesionales, en especial del personal de Enfermería.

A pesar de ello, la investigación en simulación con realidad virtual puede permitir trabajar aspectos que antes solo se podían trabajar desde la práctica con el paciente como son la humanización de los cuidados, la empatía, los aspectos emocionales etc. que podrían abrir un nuevo paradigma de aprendizaje en un entorno tan cambiante como el actual. Las técnicas de aprendizaje a través de realidad virtual pueden resultar un método de aprendizaje interesante, ya que la realidad virtual permite la recreación avanzada de un mundo en el que los estudiantes pueden controlar e interactuar. Bajo este paradigma, el docente deja de ser la única fuente de información en el aula, permitiendo un aprendizaje más activo por parte del alumno. Es muy importante señalar que el uso de recursos tecnológicos podría ayudar en la motivación de los aprendizajes significativos en colegios y universidades. Además, es importante unificar métodos tradicionales con métodos novedosos para avanzar metodológicamente en las técnicas de los profesores y en el aprendizaje de los estudiantes.

Limitaciones

Respecto a las limitaciones del estudio, la muestra estuvo constituida solo por 90 estudiantes de cuarto grado de enfermería que, si bien se aproxima al tamaño de la población de estudiantes de enfermería, no tiene en cuenta el grueso de estudiantes de enfermería de otros cursos, puede ser poco representativo de la población general de estudiantes de enfermería, y podría estar ocultando resultados estadísticamente significativos. Por otro lado, el tiempo de seguimiento fue demasiado corto para evaluar completamente la adquisición de competencias en comunicación. Por tanto, sería interesante la implementación de estudios con un mayor tamaño muestral y mayor representación de otros cursos del grado, con un tiempo de seguimiento de varios meses post-intervención para ver si aparecen diferencias a largo plazo.

Conclusiones

Con los datos del presente estudio no se puede demostrar que la simulación mediante realidad virtual sea un método de aprendizaje estratégico. En este sentido, se debe apostar por más estudios con muestras de estudiantes de enfermería de mayor tamaño y un tiempo de seguimiento mayor.

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Conflictos de interés

Ninguno.

Contribuciones de los autores

LIMS y JVB han contribuido a la conceptualización del trabajo y metodología; GM y RC han contribuido a la escritura inicial del manuscrito; MGP y EC han contribuido a la revisión y edición del manuscrito. Todos los autores han hecho contribuciones sustanciales en el trabajo, incluyendo la conceptualización y diseño del estudio, adquisición de datos, o análisis e interpretación de los datos; escritura del manuscrito y revisión crítica de su contenido y aprobación final de la versión enviada. Financiación: Este trabajo de investigación no ha recibido ningún tipo de apoyo financiero específico de instituciones públicas, privadas o sin ánimo de lucro.

Referencias

1. Andrés MC, Susana S, Andrea S, Luisa P, Raul M, Alberto CJ, et al. Maltrato a los profesionales de la salud. Rev Médica Univ. 2016;12(2):1-11.

2. Ministerio de Sanidad C y BS. Informe de agresiones a profesionales del Sistema Nacional de Salud. 2019.

3. Gabriel E, Acevedo M, López De Neira J, Nassif LN. Violencia ocupacional hacia los trabajadores de salud de la ciudad de Córdoba [Internet]. 2010. Available from: http://lildbi.fcm.unc.edu.ar/lildbi/tesis/faria_maria_alejandra.pdf

4. Serrano M, Ibáñez M. La prevención de las situaciones de impacto emocional en el ambiente laboral. Estudio teórico y análisis de su incidencia en el personal sanitario de la comunidad autónoma de Euskadi-España. Trab y Soc. 2015;25:463-92.

5. Cai J, Qin Z, Wang H, Zhao X, Yu W, Wu S, et al. Trajectories of the current situation and characteristics of workplace violence among nurses: a nine-year follow-up study. BMC Health Serv Res. 2021 Nov;21(1):1220.

6. (SAP) SA de P. Violencia hacia el Equipo de Salud en el ámbito laboral. Manual de Prevención y Procedimientos. 2014.

7. Arimany-Manso J, Clos-Masó D, Gómez-Durán EL. [Attacks on health professionals]. Vol. 48, Atencion primaria. 2016. p. 147-8.

8. Mart C. Agresiones a profesionales sanitarios. procedimiento de prevención y actuación. :308-48.

9. Gimenez C, Marcela V, Martigani I, Dolores M, Marta J, Guillermo LM, et al. Uso de simuladores en la enseñanza de las Ciencias de la Salud Programa. 2014.

10. López JG, Spirko L V. Simulation, a teaching aid for medical education . Simulación, Herram para la Educ médica [Internet]. 2007;23(1):79-95. Available from: http://www.scopus.com/inward/record.url?eid=2-s2.0-78349288450&partnerID=40&md5=e4ff679e6595a67a5f92f70e0a4b3e4a

11. Komprood SR. Nursing student attitudes toward oncology nursing: an evidence-based literature review. Clin J Oncol Nurs. 2013 Feb;17(1):E21-8.

12. Padilha JM, Machado PP, Ribeiro A, Ramos J, Costa P. Clinical Virtual Simulation in Nursing Education: Randomized Controlled Trial. J Med Internet Res. 2019 Mar;21(3):e11529.

13. Liaw SY, Ooi SW, Rusli KD Bin, Lau TC, Tam WWS, Chua WL. Nurse-Physician Communication Team Training in Virtual Reality Versus Live Simulations: Randomized Controlled Trial on Team Communication and Teamwork Attitudes. J Med Internet Res. 2020 Apr;22(4):e17279.

14. Pértegas S, Pita Fernández S. La fiabilidad de las mediciones clínicas: el análisis de concordancia para variables numéricas Pita. Aten Primaria en la Red. 2004;(1995):1-11.

15. Mukunda S, Shustak RJ, Szyld D, Moral I del, Maestre JM. Reflexiones sobre una rotación educativa en simulación médica. FEM Rev la Fund Educ Médica. 2015;18(3):169-71.

16. Gómez del Pulgar García-Madrid M, Pacheco del Cerro E, González Jurado MA, Fernández Fernández MP, Beneit Montesinos JV. Diseño y validación de contenido de la escala "ECOEnf" para la evaluación de competencias enfermeras. Vol. 26, Index de Enfermería . scieloes ; 2017. p. 265-9.

17. Boletin Oficial del Estado. Orden CIN/2134. Orden CIN/2134/2008, 3 julio por la que se Establ los requisitos para la Verif los títulos Univ Of que habiliten para el Ejerc la profesión Enfermero [Internet]. 2008;174:31680–3. Available from: https://www.boe.es/boe/dias/2008/07/19/pdfs/A31680-31683.pdf

18. Gómez del Pulgar García Madrid M, Hernández-Iglesias S, Crespo Cañizares A, Pérez Martín AM, González Jurado MA, Beneit Montesinos JV. Fiabilidad de una escala para la evaluación de competencias enfermeras: estudio de concordancia. Educ Médica [Internet]. 2019;20(4):221-30. Available from: https://www.elsevier.es/es-revista-educacion-medica-71-articulo-fiabilidad-una-escala-evaluacion-competencias-S1575181318303450

19. Quail M, Brundage SB, Spitalnick J, Allen PJ, Beilby J. Student self-reported communication skills, knowledge and confidence across standardised patient, virtual and traditional clinical learning environments. BMC Med Educ. 2016 Feb;16:73.

20. Cuesta Cambra DU, Mañas Viniegra L. Integración de la realidad virtual inmersiva en los Grados de Comunicación. Rev ICONO14 Rev científica Comun y Tecnol emergentes. 2016;14(2):1.

21. Levett-Jones T, Bowen L, Morris A. Enhancing nursing students' understanding of threshold concepts through the use of digital stories and a virtual community called "Wiimali". Nurse Educ Pract. 2015 Mar;15(2):91-6.

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ORIGINAL

Challenges of Adhering to Hand Washing Protocols as a COVID-19 Prevention Measure Among Slum Dwellers in Nairobi, Kenya

Desafíos de la adhesión a los protocolos de lavado de manos como medida de prevención del COVID-19 entre los habitantes de los barrios marginales de Nairobi, Kenia

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Abstract

In an effort to mitigate the outbreak of COVID-19, many countries have imposed drastic lockdown, movement control or shelter in place orders on their residents. The effectiveness of these mitigation measures is highly dependent on cooperation and compliance of all members of society. The knowledge, attitudes and practices people hold toward the disease play an integral role in determining a society's readiness to accept behavioral change measures from health authorities. Urban informal settlements are characterized by large populations occupying a small land area. Housing in informal settlements is close to each other with most households making do with poor quality and erratic water supply. How challenges of sanitation in slum dwellings in Kenya affect spread of COVID 19 is not known. Social distancing, wearing masks and hand washing among other measures are known to reduce the spread of COVID 19. Although access to hand-washing facilities with soap and water is near universal in High Income Countries, the same is not true for Low Income Countries. The purpose of this survey was to assess the challenges of hand washing as a covid-19 prevention measure among urban slum populations in Kenya. Key information of practices on hand-washing practices among this sub-population will inform the ministry of health, its collaborators and interested health sectors, on areas of improvement. A descriptive cross-sectional survey for quantitative data was be used. Solvins formula for calculation of a sample size was used. Properly designed data collection tool was used in collecting the primary data on hand washing to prevent transmission of COVID-19 with a combination of face-to-face interviews. A pre-test of the data collection tool prior to pilot data collection was performed to ascertain validity and reliability. Data was analyzed using descriptive statistics such as frequencies, mean and standard deviation and displayed using tables and figures. Inferential statistics for predictive associations between variables was performed. In the analysis, data was combined to allow reporting on an array of issues. The results indicate salient challenges on hand-washing and show an acceptable level of knowledge in mitigating COVID-19 through hand-washing and hygiene and, highlight the importance of consistent messaging from local health authorities and the government as well as the need for tailored community health education and sensitization programs to improve levels of knowledge, attitudes and practices mostly on handwashing as this pandemic may be there for some time or there could be possible upsurge in future.

Keywords: Covid-19, Hand washing, Slum dwellers, Challenges.

Resumen

En un esfuerzo por mitigar el brote de COVID-19, muchos países han impuesto a sus residentes órdenes drásticas de bloqueo, control de movimientos o confinamiento. La eficacia de estas medidas de mitigación depende en gran medida de la cooperación y el cumplimiento de todos los miembros de la sociedad. Los conocimientos, las actitudes y las prácticas que la gente tiene hacia la enfermedad desempeñan un papel integral en la determinación de la disposición de una sociedad a aceptar las medidas de cambio de comportamiento de las autoridades sanitarias. Los asentamientos urbanos informales se caracterizan por tener grandes poblaciones que ocupan una pequeña superficie de terreno. Las viviendas de los asentamientos informales están muy cerca unas de otras y la mayoría de los hogares se conforman con un suministro de agua de mala calidad y errático. No se sabe cómo afectan los problemas de saneamiento en las viviendas de los barrios marginales de Kenia a la propagación de COVID 19. Se sabe que el distanciamiento social, el uso de mascarillas y el lavado de manos, entre otras medidas, reducen la propagación del COVID 19. Aunque el acceso a las instalaciones para lavarse las manos con agua y jabón es casi universal en los países de renta alta, no ocurre lo mismo en los países de renta baja. El objetivo de esta encuesta era evaluar los retos del lavado de manos como medida de prevención del COVID 19 entre las poblaciones de los barrios marginales urbanos de Kenia. La información clave sobre las prácticas de lavado de manos entre esta subpoblación informará al ministerio de salud, a sus colaboradores y a los sectores sanitarios interesados, sobre las áreas de mejora. Se utilizó una encuesta transversal descriptiva para obtener datos cuantitativos. Se utilizó la fórmula de Solvins para calcular el tamaño de la muestra. Se utilizó una herramienta de recopilación de datos adecuadamente diseñada para recoger los datos primarios sobre el lavado de manos para prevenir la transmisión del COVID-19 con una combinación de entrevistas cara a cara. Se realizó una prueba previa de la herramienta de recopilación de datos antes de la recopilación de datos piloto para determinar la validez y la fiabilidad. Los datos se analizaron mediante estadísticas descriptivas como las frecuencias, la media y la desviación estándar, y se presentaron mediante tablas y figuras. Se realizó una estadística inferencial para la predicción de asociaciones entre variables. En el análisis se combinaron los datos para poder informar sobre una serie de cuestiones. Los resultados indican los desafíos más destacados en materia de lavado de manos y muestran un nivel aceptable de conocimientos para mitigar la COVID-19 mediante el lavado de manos y la higiene, y destacan la importancia de que las autoridades sanitarias locales y el gobierno envíen mensajes coherentes, así como la necesidad de programas de educación sanitaria y sensibilización de la comunidad adaptados para mejorar los niveles de conocimientos, actitudes y prácticas, sobre todo en materia de lavado de manos, ya que esta pandemia puede durar algún tiempo o podría recrudecerse en el futuro.

Palabras clave: Covid-19, lavado de manos, habitantes de barrios marginales, desafíos.

Introduction

The coronavirus disease 2019 (COVID-19) emerged in Wuhan, China at the end of 2019. Since then, it has spread in many countries and has been declared a global pandemic by the World Health Organization (WHO). To date, there are more than 3,343,500 people have died from coronavirus[1,2]. Lockdown measures were perceived as necessary to curb the spread of the virus as rapid human-to-human transmission occurred and much about the virus remained unknown[3]. Due to the obscurity of this novel virus, there has been a lot of confusion and misunderstanding about the virus itself, how it can spread and the necessary precautions that should be taken to prevent infection. This becomes increasingly challenging with the vast amount of misinformation and disinformation shared on social media that is clouding people's understanding of COVID-19[4].

In Kenyan context, as pertains the Corona Virus pandemic, from 3 January 2020 to 5:33pm CEST, 7 July 2021, there have been 186,453 confirmed cases of COVID-19 with 3,697 deaths, reported to WHO. As of 5 July 2021, a total of 1,417,100 vaccine doses have been administered (WHO, 2021). Generally, the WASH situation in the urban slums is below the minimum standard recommended by the World Health Organization (WHO)[5]. In Kenyan Nairobi slums, only 22 percent of households in Nairobi has water connections, while 75 percent accesses water through water vendors who overcharge, making slum dwellers pay more for their water than people living in middle- or high-income areas. The provision of sanitary services is also inadequate (UN-Habitat & Slum Upgrading Program).

In the context of waste management and practices, slums and squatter settlements areas are increasingly experiencing difficulties due to ever-increasing gap between generation, accumulation and removal. The solutions for waste management problems thus continues to compromise general standards of required hygiene. This perceived typical phenomenon in slums only does it not affect health of the dwellers but also, other arms of hygiene especially, water and sanitation.

The knowledge, attitudes and practices (KAP) toward COVID-19 play an integral role in determining a society's readiness to accept behavioral change measures from health authorities. KAP studies provide baseline information to determine the type of intervention that may be required to change misconceptions about the virus. Assessing the KAP related to hand washing in an effort to curb the spread of COVID-19 among the perceived vulnerable groups defined by the social

economic status, the slum dwellers, this would be helpful to provide better insight to address poor knowledge about the disease and the development of further or harnessing the current preventive strategies and health promotion programs. Among the lessons learned from the SARS outbreak is that knowledge and attitudes are associated with levels of panic and emotion which could further complicate measures to contain the spread of the disease[6]. The survey also gives a general picture of informal settlement population's COVID-19 prevention practices and this can better prepare the government to address future health crises involving infectious diseases using similar approach for COVID-19 prevention. The results of this pilot study are important to inform future efforts focusing on a broad scope approach with an aim of societal readiness to comply with pandemic control measures.

Survey Methodology

The data tool and collection

A new data entry form was developed and validated after the first was found to have some missing variables to inform the survey objectives. A mixed method of both qualitative and quantitative approach was utilized to achieve the preliminary objectives of this pilot study. A survey was most appropriate as it allowed large populations to be assessed with relative ease[7]. In this study, a cross-sectional survey was deemed most appropriate to gather information on COVID-19 for the informal settlement context. Data collection was performed face to face for this pilot study using a KAP model to collect data among slum dwellers in selected slums in Nairobi namely; *Kibra* and *Mukuru kwa Njenga*.

Ethically, as it should be in a research quest dealing with human subjects, utmost consent to interview the participants was sought and, considering the fact that it was still in COVID-19 era, measures are put in place to ensure that there was no risk of compromising the participants' health more so, contracting the virus. Masks were provided to all research assistants and the chief investigators as well as hand sanitizers. It was also paramount that, time spent with a specific participant was as minimal as possible.

The pilot sample size and the Sampling Procedure

A cluster stratified sampling technique was used to determine the sample size convenient for the pilot study in the context of the of the chosen study sites' population size as below, and with a 50% of the proportionate allocated population as shown below. Simple random sampling was then used to select individual participants

*i. Sample size in Mukurukwa Njenga slum which has 300,000 slum dwellers: Proportionate Allocation= Number of elements selected = 300,000/ 1,250,000*400 =* ***96***

*ii. Sample size in Kibera slum which has 250,000 slum dwellers: Proportionate Allocation= Number of elements selected = 250,000/ 1,250,000*400 =* ***80***

Therefore, we used 162 participants for this pilot study after some 14 questionnaires were found to be improperly filled during data collection. The forms / data collection tools were distributed to selected participants for filling via self-administered questionnaire approach with close supervision by research team members to ensure valid information was completed. Where applicable, face to face interviews were also conducted Primary data on hand washing was collected using a knowledge, attitude, and practices questionnaire tool on their influence on hand washing. This tool was convenient, timely and financially.

The thematic areas of pilot data collection

With a view of achieving the objectives of this study, data from primary sources was used. The primary data consisted of knowledge, attitude and practices on hand washing, water station services and utilization of the existing hand-washing equipment for COVID 19 prevention. Major issues to be examined on the set hand washing stations improvised by several organizations including KMTC included; accessibility, reliability, quality and quantity and sustainability of the water and sanitation services.

The data collection tool

The questionnaire consisted of four main themes: 1) demographics, which surveyed participants' socio-demographic information, including gender, age, slum of residence, religion, marital status, occupation, and household size; 2) challenges of hand washing as a COVID-19 prevention measure 3) knowledge about COVID-19; 3) knowledge, attitude and practice of hand washing as a COVID-19 prevention measure. The survey was offered in the English and translation to Kiswahili by the data collection team. This approach was used to ensure linguistic and conceptual equivalence.

The Pilot Data entry and Analysis

Data entry into the SPSS started on 5th April 2021 for one week and this was followed by data analysis and report generation for the pilot survey.

Throughout the period of the pilot testing, the approach very little amendments mostly on the timing of data collection and the best way to harmoniously retrieve information from the study population. The information gathered was optimum utilized to address the pertinent objective of the pilot study as well as the preliminary results to inform the broad scope approach for the main study was successfully backed up.

Data was analyzed using descriptive statistics such as frequencies, mean and standard deviation and displayed using tables and figures. Inferential statistics for predictive associations between variables was conducted. In the

analysis, data from survey was combined to allow reporting on the objectives of the study. Because questionnaires are typically short, analysis was completed quickly after data gathering, and the report was prepared prior to dissemination to KMTC and UN-Habitat.

Results

Pre-testing data collection tool

Pre-testing measured the reaction of the selected group of individuals and helped in establishing whether the priority audience would easily provide information using the then current components of the data collection tool - usually whether the draft materials understandable, believable and appealing. On the same approach, we ascertained the feasibility of using the same tool in it's the then format. We were able to eliminate some few components which were overlapping especially in collecting a string type qualitative data as would be in SPSS analysis. This was done at section 2 and 3 of data collection.

The Pilot study basic report

Demographic Characteristics

A total of 162 participants participated in the study. Out of the total, the most of participants were between the ages of 25 - 34 years 65 (40.1%), with only 5 (3.1%) being over the age of 45 years. The gender of the participants was closely the same at Male, 80 (49.4%) and Female 82 (50.6%), while most were Christians 123 (75.9%) the household size with majority was at 1-5, 93 (57.4%) as per the number of family members (**Table I**).

Assessment of Challenges of hand washing as a COVID-19 prevention measure with selected demographic characteristics using a contingency coefficient

With six questions requiring a yes or a no answer, together with five statements on a Likert scale of 1 to 5 ascertaining the possible challenges with respect to specific demographic and related population characteristic, the pilot study established that, the symmetric measures contingency coefficients generated were far from zero indicating a level of dependence. The frequency table below (**Table II**) demonstrate the cumulative responses to explain the proportions of specific challenges among the participants. On this note, over 50% of respondents indicated that challenges where a norm in the slums with greater percentage reporting 'no' on; lack of access to alcohol-based hand rub, 112 (69.6%), lack of sufficient wash-stations 10 (64.0%) and, lack of adequate water and soap supply 116 (71.6%) and 110 (67.9%) respectively.

The Likert scale of 1-5 defining; 1=very low extent, 2=Low extent, 3=moderate extent, 4=high extent and 5=very high extent demonstrated that, challenges' extent was above 60%, as depicted in **table III** below with each sited challenge demonstrating a mean score of above 3, equivalent to 60%, this being similar to the responses given in terms of 'yes' or 'no' above.

Knowledge, attitude and practices of hand washing as a COVID-19 Prevention measure

Knowledge on Handwashing as a COVID-19 Control Measure

Four broad questions were used to measure knowledge on the hand washing as a COVID-19 control measure. Most participants acknowledged having known of the COVI-19 control measures from government directed TV adverts and the normal TV programs 54(33.3%) and 61(37.7%) respectively with other sources of information

Table I: Key participants' demographic characteristics.

		Frequency	Percent	Valid Percent	Cumulative Percent
Education level					
Valid	Primary level	26	16.0	16.0	16.0
	Secondary level	78	48.1	48.1	64.2
	Tertiary level	58	35.8	35.8	100.0
	Total	162	100.0	100.0	
Sex of the participant					
Valid	Male	80	49.4	49.4	49.4
	Female	82	50.6	50.6	100.0
	Total	162	100.0	100.0	
Size of household					
Valid	1-5	93	57.4	57.4	57.4
	6- 10	62	38.3	38.3	95.7
	11 and above	7	4.3	4.3	100.0
	Total	162	100.0	100.0	
Age of participant					
Valid	18 – 24 years	57	35.2	35.2	35.2
	25 – 34 years	65	40.1	40.1	75.3
	35 – 44 years	35	21.6	21.6	96.9
	45 + years	5	3.1	3.1	100.0
	Total	162	100.0	100.0	

recording lower percentages (**Table IV**). The average knowledge score for participants was above average between 1.0556 and 4.1728 on several knowledge scores (**Table V**), with majority being aware that, poor hand washing practices can further enhance the spread of corona virus in your community 154 (95.1%) (**Table VI**). The overall correct answer rate of the knowledge questions was above 60% while the range of correct answer rates for all participants were between 50 to 100%. Most participants know that hand washing prevents corona spread 134 (82.7%) (**Table VII**) representing an acceptable level of knowledge on COVID-19.

Table II: Challenges associated with hand-washing and hygiene in COVI-19 Prevention.

		Frequency	Percent	Valid Percent	Cumulative Percent
Have you received any training in hand hygiene during this COVID period?					
Valid	yes	83	51.2	51.2	51.2
	no	78	48.1	48.1	99.4
	3.00	1	.6	.6	100.0
	Total	162	100.0	100.0	
Do you easily access alcohol-based hand rub for hand hygiene?					
Valid	yes	49	30.2	30.4	30.4
	no	112	69.1	69.6	100.0
	Total	161	99.4	100.0	
Is there sufficient hand washing points where you live?					
Valid	yes	57	35.2	35.4	35.4
	no	103	63.6	**64.0**	99.4
	3.00	1	.6	.6	100.0
	Total	161	99.4	100.0	
Missing	System	1	.6		
Total		162	100.0		
The hand washing points and are accessible within à 100 Meters					
Valid	yes	82	50.6	50.6	50.6
	no	80	49.4	49.4	100.0
	Total	162	100.0	100.0	
Hand Washing stations have adequate water supply					
Valid	yes	46	28.4	28.4	28.4
	no	116	71.6	**71.6**	100.0
	Total	162	100.0	100.0	
Hand washing points have adequate supply of soap					
Valid	yes	51	31.5	31.5	31.5
	no	110	67.9	67.9	99.4
	3.00	1	.6	.6	100.0
	Total	162	100.0	100.0	

Table III: Extent of challenges measured on the mean of a Likert scale of 1 to 5.

		Statistics					
		Distance to hand washing station from the house affects my frequency of hand washing	Consistency of Water supply	Crowding at hand washing station	Lack of soap at hand washing station	High cost of water and soap	Poor accessibility to the water points/ stations
N	Valid	162	161	162	161	159	161
	Missing	0	1	0	1	3	1
Mean		**3.1481**	**2.9255**	**3.4074**	**3.3292**	**3.5723**	**3.4783**
Sum		510.00	471.00	552.00	536.00	568.00	560.00

Table IV: Source of information on COVID-19 Control protocol.

		Statistics				
		What do you think can happen/happens due to improper hand washing in terms of health?	Do you think poor hand washing practices can further enhance the spread of corona virus in your community?	What do you think can happen in future as regards corona spread with improper hand washing?	I basically know about principles of hand washing to prevent corona spread	I know that hand washing prevents corona spread
N	Valid	160	162	160	162	162
	Missing	2	0	2	0	0
Mean		**1.6125**	**1.0556**	**1.9938**	**3.9321**	**4.1728**
Std. Error of Mean		.06515	.02006	.10877	.08718	.08006
Std. Deviation		.82407	.25538	1.37588	1.10968	1.01895

Attitude on Handwashing and hygiene as a covid-19 Control Measure

Participants were asked a question guided by three attitude rating in assessment of attitudes. The question asked whether or not it concerns them how hand washing is practiced to prevent corona spread in your community and the rating of attitude was on; To what extent they were satisfied about hand washing behavior, how interested would they try to mitigate poor hand washing behavior and how important they regard hand washing.

For the first question, a majority of participants 138 (85.2%) were concerned with how hand washing was being practiced. Even so, 66 % of participants were unsatisfied with the handwashing practices, while 81.5 agreed that they would mitigate poor handwashing practices and 74.8% regarded hand-washing as important (**Table VII**).

Table V: Knowledge assessment by use of Likert scale mean and Proportions on a 'yes' or no and by Likert scale on knowledge score.

		Frequency	Percent	Valid Percent	Cumulative Percent
Do you think poor hand washing practices can further enhance the spread of corona virus in your community?					
Valid	yes	154	95.1	95.1	95.1
	no	7	4.3	4.3	99.4
	3.00	1	.6	.6	100.0
	Total	162	100.0	100.0	
I know that hand washing prevents corona spread					
Valid	Strongly Disagree	8	4.9	4.9	4.9
	Disagree	2	1.2	1.2	6.2
	Neutral	18	11.1	11.1	17.3
	Agree	60	37.0	37.0	54.3
	Strongly Agree	74	45.7	45.7	100.0
	Total	162	100.0	100.0	

Table VI: .

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Government TV Ads	54	33.3	33.3	33.3
	Government sms	16	9.9	9.9	43.2
	TV programs	61	37.7	37.7	80.9
	Friends	8	4.9	4.9	85.8
	Acquaintances/Neighbors	5	3.1	3.1	88.9
	Other family members	5	3.1	3.1	92.0
	Social media (twitter, text, Facebook etc.)	5	3.1	3.1	95.1
	Internet	1	.6	.6	95.7
	Work colleagues	2	1.2	1.2	96.9
	Church/ Worship Centre	5	3.1	3.1	100.0
	Total	162	100.0	100.0	

Table VII: Attitude on Handwashing and hygiene as a covid-19 Control Measure.

		Frequency	Percent	Valid Percent	Cumulative Percent
To what extent are you satisfied about hand washing behavior in your community?					
Valid	Very dissatisfied	29	17.9	17.9	17.9
	Dissatisfied	78	48.1	48.1	66.0
	Satisfied	37	22.8	22.8	88.9
	Very satisfied	17	10.5	10.5	99.4
	5.00	1	.6	.6	100.0
	Total	162	100.0	100.0	
Does it concern you how hand washing is practiced to prevent corona spread in your community?					
Valid	yes	138	85.2	85.2	85.2
	no	22	13.6	13.6	98.8
	5.00	2	1.2	1.2	100.0
	Total	162	100.0	100.0	
How interested would you try to mitigate poor hand washing behavior in your community?					
Valid	Very un-interested	12	7.4	7.4	7.4
	Un-interested	18	11.1	11.1	18.5
	Interested	92	56.8	56.8	75.3
	Very interested	40	24.7	24.7	100.0
	Total	162	100.0	100.0	
How important do you regard hand washing?					
Valid	Not important	8	4.9	4.9	4.9
	Partially Important	20	12.3	12.3	17.3
	Important	127	78.4	78.4	95.7
	Not important	7	4.3	4.3	100.0
Do you follow the guidelines indicating that you should wash your hand regularly					
Valid	yes	141	87.0	87.0	87.0
	no	21	13.0	13.0	100.0
	Total	162	100.0	100.0	

Assessment of Practices of Hand-washing as a covid-19 Control Measure

Practices toward COVID-19 were measured using three questions enquiring on: 1) following the guidelines indicating that they should wash their hand regularly 141 (87.0%), 2) reminding other people to properly wash their hands when not doing it properly or not at all 127 (78.4%) and 3) whether there are better practices that could be adopted in ensuring hand hygiene in community by the government based on the nature settlement, the slum. 121(74.7%) (**Table VIII**).

Table VIII: Assessment of Practices of Hand-washing as a covid-19 Control Measure.

		Frequency	Percent	Valid Percent	Cumulative Percent
Do you remind other people to properly wash their hands when you see them not doing it properly or not at all?					
Valid	yes	127	78.4	78.4	78.4
	no	35	21.6	21.6	100.0
	Total	162	100.0	100.0	
Do you think that there are better practices that could be adopted in ensuring hand sanitation in your community by the government based on the nature of your settlement, the slum?					
Valid	yes	121	74.7	74.7	74.7
	no	41	25.3	25.3	100.0
	Total	162	100.0	100.0	

Table IX: Knowledge as measured by Education level (ANOVA).

		ANOVA				
		Sum of Squares	df	Mean Square	F	Sig.
Do you think poor hand washing practices can further enhance the spread of corona virus in your community?	Between Groups	.014	2	.007	.107	.898
	Within Groups	10.486	159	.066		
	Total	10.500	161			
I basically know about principles of hand washing to prevent corona spread	Between Groups	**7.544**	**2**	**3.772**	**3.145**	**.046**
	Within Groups	190.709	159	1.199		
	Total	198.253	161			
I know that hand washing prevents corona spread	Between Groups	2.705	2	1.353	1.308	.273
	Within Groups	164.455	159	1.034		
	Total	167.160	161			

Table X: Correlation between Education level and the proper hand-washing practices among the participants.

Correlations					
		Education level	Do you think that there are better practices that could be adopted in ensuring hand sanitation in your community by the government based on the nature of your settlement, the slum?	Do you remind other people to properly wash their hands when you see them not doing it properly or not at all??	Do you follow the guidelines indicating that you should wash your hand regularly
Education level	Pearson Correlation	1	-.105	-.041	-.110
	Sig. (2-tailed)		.186	.600	.163
	N	162	162	162	162
Do you think that there are better practices that could be adopted in ensuring hand sanitation in your community by the government based on the nature of your settlement, the slum?	Pearson Correlation	-.105	1	.108	.325**
	Sig. (2-tailed)	.186		.170	.000
	N	162	162	162	162
Do you remind other people to properly wash their hands when you see them not doing it properly or not at all?	Pearson Correlation	-.041	.108	1	.557**
	Sig. (2-tailed)	.600	.170		.000
	N	162	162	162	162
Do you follow the guidelines indicating that you should wash your hand regularly	Pearson Correlation	-.110	.325**	.557**	1
	Sig. (2-tailed)	.163	.000	.000	
	N	162	162	162	162

**. Correlation is significant at the 0.01 level (2-tailed).

Specific demographic characteristics and selected key Knowledge, Attitude and Practice measures

Knowledge as measured by Education level (ANOVA)

The analysis of variance on specific demographic characteristics and a key selected knowledge measures demonstrated that, basically most of the participants with secondary education and above knew about principles of hand washing to prevent corona spread (significance level of .046) (**Table IX**).

The association between Education level and the proper hand-washing practices among the participants

The analysis revealed that, education level positively predicted the hand-washing practices among the residents of the slums for this pilot study indicating that the government can benchmark better practices guideline, that they remind others of proper practices and that they follow the stipulated guidelines as directed by the government with significance levels of $p<0.05$ (**Table X**).

Discussion

COVID-19 is a relatively new virus that has had devastating effects within the short time since it was first detected in December 2019. To date, there has been limited published data on population knowledge, attitudes and practices toward COVID-19, specifically in informal urban settlements. The novelty of this disease, along with its uncertainties, make it critical for health authorities to plan appropriate strategies to prepare and manage the public health in a blanket approach and by focus on most vulnerable sub-populations in the community. It is therefore of utmost importance that the challenges and knowledge, attitudes and practices of the informal settlement population be studied to guide these efforts.

The key challenges associated with adhering to handwashing protocols mapped out from this study indicated that, over 50% of the population experienced challenges especially, lack of access to alcohol-based hand rub, lack of sufficient wash-stations and, lack of adequate water and soap supply. Most of these challenges as depicted from Likert scale showed that they were associated with poor demographic characteristics ranging from education to nature of settlements as indicated by other studies[8], similar to an Indian survey[9].

Most participants acknowledged having known of the COVI-19 control measures from government directed TV adverts and the normal TV programs with other sources of information recording lower percentages, these populations can only get such information in substantial manner as hand technology (advanced cellphones for instance) are consider luxury to them and can't afford as sited by past studies[10]. The average knowledge score for participants as measured across the Likert scale on the indicators of the same was above average between 1.0556 and 4.1728 on several knowledge scores. This was seemingly the same in findings from a study which established the fact that, despite the challenges, the general knowledge of hand-hygiene was universal as this is taught even at basic education level[11], with majority being aware that, poor hand washing practices can further enhance the spread of corona virus in your community (95.1%), this result replicating similar findings[12]. The overall rate of the knowledge questions was above 60% while the range of correct answer rates for all participants were between 50 to 100% with majority knowing that hand washing prevents corona spread (82.7%)[13]. Also, several studies conducted among Syrians have indicated high levels of COVID-19 knowledge among the general population[14].

The present study found that a large majority of participants held positive attitudes toward overcoming COVID-19 through hand-washing as the most feasible way, citing other measures as a little bit expensive and difficult to comply with. The attitude of the participants demonstrated that, majority of participants (85.2%) were concerned with how hand washing was being practiced. Even so, 66 % of participants were unsatisfied with the handwashing practices, a greater percentage at 81.5% agreed that they would mitigate poor handwashing practices and 74.8% regarding the practice of hand washing in preventing covi-19 spread as important. These current collective results are similar to others[15]. Generally, high levels of positive attitudes were also detected in the KAP study conducted in China[16], which replicates this current pilot study.

Practices of hand washing and hygiene towards COVID-19 prevention showed that a greater percentage over 80% were following the guidelines indicating that they should wash their hand regularly and would remind other people to properly wash their hands[17,18]. They also felt that, based on their presumed "isolated lifestyle", better practices could be adopted in ensuring hand hygiene in community by the government as perceived before in other studies[19].

From the general perspective view of the entire KAP analysis, we attributed the positive attitudes and seemingly good practices on hand-washing to the drastic measures taken by the Kenyan government in mitigating the spread of the virus, but bearing in mind that challenges are bound to compromise these efforts in the context of informal urban settlements.

Specific demographic characteristics and a key selected knowledge measures with ANOVA test demonstrated that, basically participants with secondary education and

above knew about principles of hand washing to prevent corona spread with a significance association as well as practices on handwashing demonstrating depicting a positive correlation at a significant p-value with Pearson correlation test for association. This is commensurate with past studies implicating that education positive predicts the proper handwashing knowledge and practices[20].

COVID-19 has been a teething public health problem around the world. Vaccination programs for the same has been benchmarked across several countries in the world. Social scientists, especially those in public health and health communication, are working to identify the levels of knowledge, attitudes and practices on COVID-19 among the public in different settings as to design cost-effective public health campaigns and education programs. The current survey, in fact, exposes the need for more comprehensive sensitization, support and improving the infrastructure needed in offering services to mitigate the COVID-19 and focus on consistency of information from the government and related authorities on handwashing as a measure to control COVID-19. Due to the levels of media use with TV messages by the government and messages from TV and evidence from prior research[21], authorities would benefit from utilizing both such to reach the presumed marginal areas, the informal settlements in disseminating these messages.

Conclusions

In summary, the present study was able to provide a comprehensive examination of the challenges and knowledge, attitudes and practices among informal settlements population towards hand washing and hygiene as a protocol to mitigate the spread of COVID-19. The findings suggest that they possess an acceptable level of knowledge on COVID-19 and are generally positive in their outlook on overcoming the pandemic. Even so, consistent messaging from the government and/ or health authorities are key to aid public knowledge and understanding of COVID-19 and the feasibility of hand washing, especially in their settings. Specific health education programs to raise COVID-19 knowledge and improve practices is of paramount importance as the pandemic may be here to stay for some time and that, such populations are more vulnerable due to related demographics.

Conflict of Interest

The authors declare that no competing interests exist.

References

1. Lee ACC, Kozuki N, Cousens S, et al. Estimates of burden and consequences of infants born small for gestational age in low and middle income countries with INTERGROWTH-21 st standard: Analysis of CHERG datasets. *BMJ*. 2017;358. doi:10.1136/bmj.j3677

2. Budholiya P, Ali AW, Gunwan D, Sahil S, Tyagi CK, Sharma H. COVID-19: A Global Pandemic of 21st Century. *J Drug Deliv Ther.* 2020;10(3-s). doi:10.22270/jddt.v10i3-s.4088

3. Azlan AA, Hamzah MR, Sern TJ, Ayub SH, Mohamad E. Public knowledge, attitudes and practices towards COVID-19: A cross-sectional study in Malaysia. *PLoS One*. 2020;15(5). doi:10.1371/journal.pone.0233668

4. Heger F, Moshammer H. COVID-19: the Austrian experience. *Asian Pacific J Environ Cancer*. 2020;3(S1). doi:10.31557/apjec.2020.3.s1.3-4

5. Kamau N, Njiru H. Water, sanitation and hygiene situation in Kenya's urban slums. *J Health Care Poor Underserved*. 2018;29(1). doi:10.1353/hpu.2018.0022

6. Taksande A, Panwar RAS, Saqqaf SA, Rao R, Meshram R. Study of Knowledge, Attitude and Practice (KAP) towards COVID-19 Pandemic in Rural Area. *Med Sci.* 2020;24(106).

7. Agadjanian V, Zotova N. Sampling and surveying hard-to-reach populations for demographic research: A study of female labor migrants in Moscow, Russia. *Demogr Res.* 2012;26. doi:10.4054/DemRes.2012.26.5

8. C.L. M, J. G, S. R, et al. Risk of exposure to fecal contamination for adults and children in slum, non-slum, and high-income neighborhoods across Dhaka, Bangladesh using the SaniPath exposure assessment tool. *Am J Trop Med Hyg.* 2018;99(4 Supplement).

9. Patel A. Preventing COVID-19 Amid Public Health and Urban Planning Failures in Slums of Indian Cities. *World Med Heal Policy.* 2020;12(3). doi:10.1002/wmh3.351

10. Subasinghe W. Quality of Life Study on Slum Dwellers (With Special Reference to Sri Lanka). *Int J Sci Res Innov Technol.* 2015;2(3).

11. Ssemugabo C, Halage AA, Namata C, Musoke D, Ssempebwa JC. A socio-ecological perspective of the facilitators and barriers to uptake of water, sanitation and hygiene interventions in a slum setting in kampala, uganda: A qualitative study. *J Water Sanit Hyg Dev.* 2020;10(2). doi:10.2166/washdev.2020.124

12. Brauer M, Zhao JT, Bennitt FB, Stanaway JD. Global access to Handwashing: Implications for COVID-19 control in low-income countries. *Environ Health Perspect.* 2020;128(5). doi:10.1289/EHP7200

13. Mahdi H, Alqahtani A, Barasheed O, et al. Hand hygiene knowledge and practices among domestic hajj pilgrims: implications for future mass gatherings amidst COVID-19. *Trop Med Infect Dis.* 2020;5(4). doi:10.3390/tropicalmed5040160

14. Al ahdab S. A cross-sectional survey of knowledge, attitude and practice (KAP) towards COVID-19 pandemic among the Syrian residents. *BMC Public Health.* 2021;21(1). doi:10.1186/s12889-021-10353-3

15. Singh S, Singh RK. Awareness, Attitude and Practices towards COVID-19 among People of Bihar during Lockdown 1.0: A Cross-Sectional Study. *Int J Sci Healthc Res.* 2020;5(2).

16. Zhong BL, Luo W, Li HM, et al. Knowledge, attitudes, and practices towards COVID-19 among chinese residents during the rapid rise period of the COVID-19 outbreak: A quick online cross-sectional survey. *Int J Biol Sci.* 2020;16(10). doi:10.7150/ijbs.45221

17. Kadam S, Pati S, Chauhan AS. A study on knowledge and practice of hand washing among slum children and their mothers in Bhubaneswar, Odisha. *Indian J Public Heal Res Dev.* 2014;5(3). doi:10.5958/0976-5506.2014.00276.9

18. Pati S, Kadam SS, Chauhan AS. Hand hygiene behavior among urban slum children and their care takers in Odisha, India. *J Prev Med Hyg.* 2014;55(2). doi:10.15167/2421-4248/jpmh2014.55.2.431

19. De Vita MV, Scolfaro C, Santini B, et al. Malnutrition, morbidity and infection in the informal settlements of Nairobi, Kenya: An epidemiological study. *Ital J Pediatr.* 2019;45(1). doi:10.1186/s13052-019-0607-0

20. Aiello AE, Coulborn RM, Perez V, Larson EL. Effect of hand hygiene on infectious disease risk in the community setting: A meta-analysis. *Am J Public Health.* 2008;98(8). doi:10.2105/AJPH.2007.124610

21. Cabrera A, Martins C, Cunha IF. Television coverage of the Covid-19 pandemic in Portugal: An exploratory study. *Media J.* 2020;20(37). doi:10.14195/2183-5462_37_10

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ORIGINAL

Comparion between General and Spinal Anesthesia for Lumbar Disc Surgery: A Randomized Clinical Trial

Comparación entre anestesia general y raquídea para la cirugía discal lumbar: Un ensayo clínico aleatorizado

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Abstract

Introduction: Lumbar disc surgery is most often performed under general anesthesia (GA). However, spinal anesthesia (SA) can also be a successful alternative in lumbar disc surgery. The present study was conducted to compare the complications of general and spinal anesthesia in patients with lumbar discectomy.
Material and Methods: Fifty patients were randomly allocated into two groups of general (25 patient) and spinal anesthesia (25 patient). The pain severity (based on visual analogue scale [VAS]), the use of analgesics, blood pressure (BP), heart rate (HR), blood loss, respiratory rate (RR), patient satisfaction, nausea, vomiting, and shivering in recovery room were recorded.
Results: The mean pain severity score, postoperative use of analgesics, intraoperative blood loss and recovery time in the spinal anesthesia group were significantly lower than general anesthesia group (P<0.001). Intraoperative HR and BP changes, nausea, vomiting, and shivering in recovery room were significantly lower in spinal anesthesia group (p<0.05, p<0.001). The patient satisfaction was significantly high in the spinal anesthesia group (p<0.001).
Conclusions: spinal anesthesia is safe and seems to be more effective. Some advantages of SA include lower pain severity score and the use of analgesics, reduced amount of blood loss during the surgery and fewer postoperative complications.

Keywords: Anesthesia, Lumbar Surgery, Pain, Blood Loss.

Resumen

Introducción: La cirugía discal lumbar se realiza con mayor frecuencia bajo anestesia general (AG). Sin embargo, la anestesia raquídea (AC) también puede ser una alternativa satisfactoria en la cirugía discal lumbar. El presente estudio se realizó para comparar las complicaciones de la anestesia general y espinal en pacientes con discectomía lumbar.
Material y métodos: Cincuenta pacientes fueron asignados aleatoriamente a dos grupos de anestesia general (25 pacientes) y raquídea (25 pacientes). Se registraron la intensidad del dolor (según la escala analógica visual (EAV), el uso de analgésicos, la presión arterial (PA), la frecuencia cardiaca (FC), la pérdida de sangre, la frecuencia respiratoria (FR), la satisfacción del paciente, las náuseas, los vómitos y los escalofríos en la sala de recuperación.
Resultados: La puntuación media de la gravedad del dolor, el uso postoperatorio de analgésicos, la pérdida de sangre intraoperatoria y el tiempo de recuperación en el grupo de anestesia raquídea fueron significativamente inferiores a los del grupo de anestesia general (p<0,001). Los cambios intraoperatorios de la FC y la PA, las náuseas, los vómitos y los escalofríos en la sala de recuperación fueron significativamente menores en el grupo de anestesia raquídea (p<0,05, p<0,001). La satisfacción del paciente fue significativamente alta en el grupo de anestesia raquídea (p<0,001).
Conclusiones: la anestesia raquídea es segura y parece ser más eficaz. Algunas ventajas de la anestesia espinal son una menor puntuación de la intensidad del dolor y del uso de analgésicos, una menor pérdida de sangre durante la intervención y menos complicaciones postoperatorias.

Palabras clave: anestesia, cirugía lumbar, dolor, pérdida de sangre.

Background

Lumbar pain is the second major cause of consultation with physicians in the US and leads to the disability of at least 7 million people. The estimated cost of treatment for back pain is above $50 billion in addition to 93 million lost workdays in the year[1-5].

After lumbar herniation, lumbar laminectomy and discectomy with an annual statistics of 300,000 to 400,000 cases, is one of the most major surgeries with a prevalence of 10 to 40% in neurosurgery. These figures are reported to be about 13000 in the UK and over 250000 in the US[1,6-8]. Laminectomy can be performed under general anesthesia (GA) or spinal anesthesia (SA)[9,10]. However, GA is the most common method for lumbar disc surgery[10,11].

A safe anesthetic method should have characteristics such as maintaining stable hemodynamic, both rapid onset and reversal of effects, decreasing the length of stay in recovery room, reducing the demand for blood transfusion, postoperative pain, nausea, vomiting, and opioid use for analgesia[9,11]. However, recent studies show contradictory results and there is no single agreement for the appropriate anesthetic method in the lumbar disc surgery[12].

Objectives

The literature review indicated that there are controversial results regarding the effect of GA verses SA on laminectomy outcome[13]. Evidence shows that patients under spinal anesthesia have fewer complications and more satisfied compared to general anesthesia. This issue is consistent with the results of a number of conducted studies[14]. Previous researchers emphasized that further studies must be performed before reaching a unified conclusion. To the best of our knowledge, this study aimed to compare the outcomes of spinal versus general anesthesia in patients with lumbar laminectomy or discectomy.

Methods

Study protocol

This is a randomized controlled trial (RCT) performed at the one of the teaching hospitals affiliated to Ilam University of Medical Sciences (Imam Khomeini hospital).

Patient characteristics:

In this RCT, 50 patients aged 20-60 years with American Society of Anesthesiologist (ASA) physical status I or II who were scheduled for elective laminectomy or discectomy were enrolled in this study. The patients underwent either GA or SA.

Patients were randomly divided two groups of general or spinal anesthesia with 25 patients in each group using sealed envelopes technique. To avoid the effect of confounding variables, all procedures were performed with the same anesthesiologist and neurosurgeon.

Anesthesia procedure

Patients in GA group received 2-3 mg/kg intravenous propofol, 1-1.5 mcg/kg intravenous fentanyl, and0.6 mg/kg intravenous rocuronium bromide,2-3% sevoflurane and 50% N2O in O2 for maintenance of anesthesia. Ventilation mode: CMV, VT: 10 cc/kg, Breaths per minute: 12-14. Patients in SA group received 15 mg intrathecal bupivacaine 0.5% at L3 - L4 or L4 - L5 space in a sitting position (To prevent high spinal, we used 15 mg intrathecal bupivacaine for all patients with different height and weight). We used the Visual Analogue Scale (VAS) to determine severity of pain. The pain severity was assessed at 1, 4, 8, 12, and 24 hours after surgery. The patient's blood loss (during operation), mean blood pressure (BP), heart rate (HR), respiratory rate (RR), oxygen saturation (SPO2), urinary retention, and morphine consumption (IM) were recorded. NSAID according to patients need were administrated. The complications such as nausea, vomiting, and shivering in recovery room were recorded.

The exclusion criteria were contraindications to SA (such as patient's refusal, coagulopathy, infection at the needling site, and hypovolemia), severe spinal stenosis, history of cardiovascular disease, neuromuscular, seizure, or intracranial hypertension, renal or metabolic disease, bleeding abnormalities and drug or alcohol abuse.

Ethical Consideration

This study is approved under the ethical approval code of (IR. MEDILAM.RE.1394.39) and informed written consent was obtained from all subjects. Clinical Trial Code: (IRCT2015062222870N1) .

Validity and Reliability

Content validity was applied to assign the validity of the questionnaire. Cronbach's alpha test was applied to assign the reliability of questionnaire. The reliability of the questionnaire was 0.89.

Statistical analysis

According to Kolmogorov-Smirnov test, data were normally distributed and therefore, parametric tests were used ($P > 0.05$). Descriptive statistics (frequency, percent, mean, and standard deviation [SD]), independent t-test, chi-square test, Monte Carlo test, Fishers Exact test, Confidence Interval, Relative Risk, and Repeated Measurement were performed to analyze the results. P-Value < 0.05 was considered significant. Data were analyzed using the statistical software SPSS Ver.16.

Results

Characteristics were presented in **table I** and showed that demographic information (age and sex) and duration of surgical procedure were not different between the two groups (P > 0.5) (**Table I**).

Postoperative analgesia, blood loss, BP/S, BP/D and PR in the SA group were significantly lower than the GA group (P < 0.001) (**Table II**).

Independent t-test showed that the pain severity in the SA group was significantly lower than the GA group at different time intervals (P < 0.001) (**Table III**). Repeated measurement analysis showed that the average pain intensity in the groups were significantly different at various intervals (P < 0.001) (**Figure 1**).

At 1, 4, and 8 hours after surgery, the pain severity in GA group was significantly higher than the SA group. In the spinal group the postoperative VAS score at 1 hour was lower than one and stayed low (VAS < 2) at 4 and 8 hours after surgery. This suggests that the SA method has effectively controlled the pain severity (**Figure 1**).

In the SA group, one patient (4%) experienced vomiting, while eight patients (32%) in the general group experienced vomiting. The incidence of vomiting in the GA group was eight times more than the SA group (RR=8, 95% CI= 1.08-58.8). **Table II** shows that the incidence of nausea and shivering in the SA group was significantly lower than the GA group, but the incidence of headache after surgery in the GA group was significantly lower than the SA group (P < 0.05) (**Table IV**/ **Figure 2**).

Table I: Comparison of baseline characteristics and surgery duration of patients in spinal and general groups.

Patients Characteristics	Spinal group(n=25)	General group (n=25)	P- value
Age / year (mean ±sd)	50±4.7	51±5.3	0.40
Sex M/F n(%)	20 (80%)/5(20%)	19(76%)/6(24%)	0.90
Surgery duration/min (mean ±sd)	83.6±3.6	85.4±3.3	0.05

Table II: Postoperative outcomes in the two groups.

Patients Characteristics	Spinal group(n=25)	General group (n=25)	P- value
Anesthesia duration/ min (mean ±sd)	115.6±11.8	133±9.6	0.000
Recovery time/ min (mean ±sd)	26±11	38±9	0.000
Morphine consumption /mg (mean ±sd)	3.7±1.2	8±2.5	0.000
Blood loos / ml (mean ±sd)	317±10.9	424±5.9	0.000
BPS/ mm (mean ±sd)	115±28	135±47	0.000
BPD/ mm (mean ±sd)	68.6±34	87.4±39	0.000
PR/ per/ min (mean ±sd)	79.6±21	91.8±37	0.000

Table III: Adverse effects in patients in spinal and general anesthesia groups.

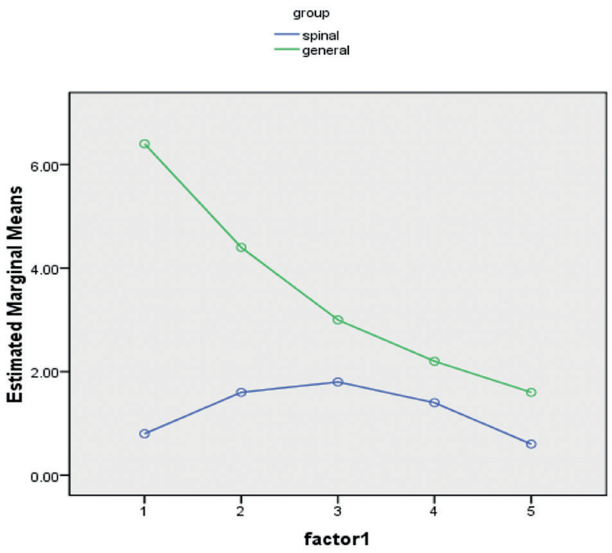
Parameter		Groups		Test	
		General (25), n(%)	Spinal (25), n(%)	RR (95% CI)	p-value
Vomiting	Yes	8 (32)	1 (4)	8 (1.08-58.8)***	0.012*
	No	17 (68)	24 (96)		
Nausea	Yes	12 (48)	3 (12)	4 (1.14-12.5)***	0.005**
	No	13 (52)	22 (88)		
Shivering	Yes	11 (44)	4 (16)	2.75 (1.01-7.46)***	0.031**
	No	14 (56)	21 (84)		
Headache	Yes	2 (8)	15 (60)	7.5 (1.9-29)****	0.001**
	No	23 (92)	10 (40)		
Urinary retention	yes	2 (8)	1 (4)	1.43 (1.09-5.35)***	0.025**
	No	23 (92)	24 (96)	1.85 (1.01-6.45)***	0.046**

*P- value computed using exact test instead of Mont Carlo test ** P- value computed using Chi-square test
*** Spinal group considered as references group **** General group considered as references group

Table IV: Severity of pain at various intervals in spinal and general anesthesia groups.

Pain score by VAS, h	General group (n=25) [M± SD]		Spinal group(n=25) [M± SD]		p-value
1 h after intervention	6.4±0.15		0.8±0.15		0.001
4 h after intervention	4.4±0.16		1.6±0.16		0.001
8 h after intervention	3±0.16		1.8±0.16		0.001
12 h after intervention	2.2±0.09		1.4±0.09		0.001
24 h after intervention	2.2±10	0.6±10	0.001		

Figure 1: Comparison of pain severity between spinal and general group at one, 4, 8, 12 and 24 hours after anesthesia.

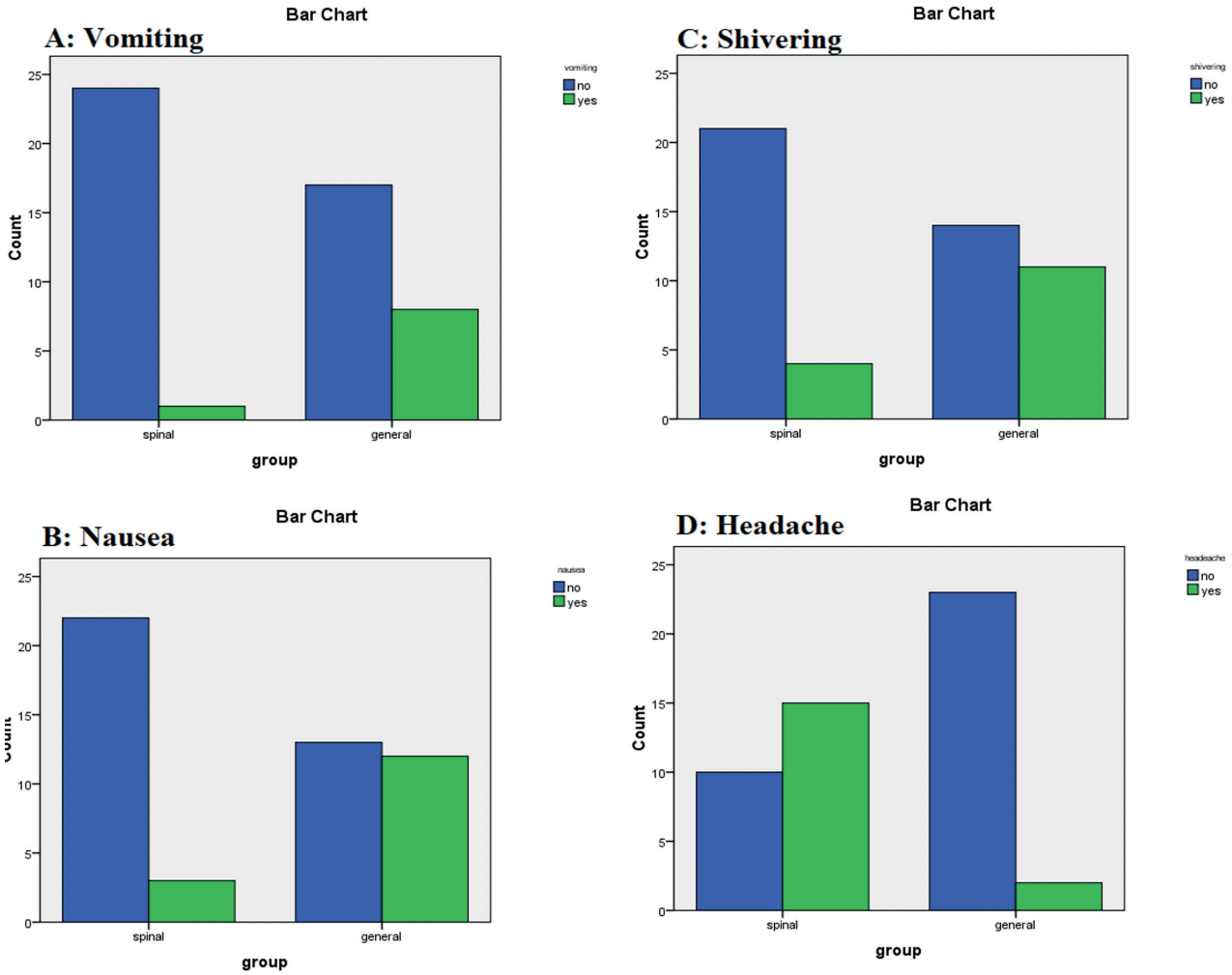


Discussion

Lumbar disc surgery is most commonly performed under general anesthesia. Nevertheless, spinal or epidural anesthesia is also a safe and successful alternative in lumbar surgery[15]. GA may have complications such as postoperative pain, blood loss, nausea, vomiting, and increase in the duration of recovery period[11,16].

The ability to perform long-term surgery in prone position without any airway disruption and patient's satisfaction are the main benefits of using GA[17]. Alternatively, regional anesthesia may decrease the amount of intraoperative blood loss, incidence of pulmonary and cardiac complications. It may decrease peripheral venous pressure to provide appropriate postoperative pain control and may decrease the length of inpatient stays and the overall costs. It may also lead to appropriate postoperative pain control[9-12, 18-21].

Figure 2: Comparison of side effects of general and spinal anesthesia.



Previous medical literature indicates inconsistency regarding the superiority of GA to SA in lumbar surgery. Our results show that patients undergoing lumbar surgery with SA have fewer complications and it has more advantages compared with GA. In addition, the satisfaction of patients and surgeons was significantly higher in SA group compared with GA group, which is consistent with previous studies[11,17,22-24], but inconsistent with the study of Sadrolsadat et al.[14].

Usually patients experience severe pain after lumbar disc surgery[25,26]. The results of previous studies indicate that compared to general anesthesia, spinal anesthesia had less complications in patients who are candidates for disc surgery[11,17,22-24]. In their study among 400 patients undergoing spinal or GA for lumbar disc surgery, McLain et al. (2005) concluded that SA was better and more effective than GA. They showed that SA might lead to reduced incidence of nausea and morphine use, shorter anesthesia duration and fewer adverse effects[22]. Tetzlaff et al. (1998) concluded that SA with fewer adverse effects could be determined as an effective alternative to GA for lumbar surgery[23]. Attari et al. (2011) concluded that SA decreases blood loss, BP, HR changes, and postoperative analgesia use. Furthermore, the satisfaction of surgeon and patient was significantly higher in SA group[17].

Demirel et al. (2003) conducted a study among patients undergoing discectomy or laminectomy. They found that epidural anesthesia was more successful than GA with fewer episodes of hypertension and less blood loss[24].

In their study, Khajavi et al (2013) compared GA with combined epidural/GA for lumbar disc surgery, and concluded that patients in combined epidural/GA group had less blood loss, hypotension, lower use of anesthetic medications during surgery, lower prevalence of tachycardia and hypertension and morphine consumption in the recovery room[11].

In their prospective study, Sadrolsadat et al. (2009) concluded that as opposed to previous studies that showed spinal anesthesia was better than general anesthesia for patients under lumbar surgery, SA does not offer any advantage over general anesthesia, and GA has many advantages over SA[14].

The mechanism of less blood loss after SA in lumbar disc surgery is due to two factors. The first mechanism is vasodilatation due to blockade of the sympathetic pathway. The second mechanism is spontaneous ventilation which reduces the intrathoracic pressure and resulting in less dilation of the epidural veins. This is another important factor for less blood loss after SA[17].

In our study, the mean arterial BP and HR changes compared to the baseline value were significantly lower in SA group compared with GA group. This mechanism is due to the better prevention of stress hormones by SA than GA[27-29]. Patients in SA group had less pain and morphine use was significantly lower compared with GA group. Reduction of pain score and morphine use after surgery can be explained by two mechanisms. The first hypothesis is the preventive effect of spinal anesthesia that reduces the pain severity by blockade of the afferent nociceptor sensitization pathway. The second process is possibly the remaining sensory block in spinal anesthesia group. This issue is caused by the delay in sensory recovery following motor recovery[17].

Conclusions

In conclusion, SA is a safe, effective, and successful method compared to GA for patients undergoing lumbar disc surgery. Some advantages of SA include decreasing pain severity score and analgesia use, reduced amount of blood loss during the surgery and fewer postoperative complications.

Limitations

The major limitation of the study was the small sample size, which is tried to be compensated in future studies.

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Conflict of Interest

There is no conflict of interest.

References

1. Rahimzadeh P, Sharma V, Imani F, Faiz HR, Ghodraty MR, Nikzad-Jamnani AR , et al . Adjuvant Hyaluronidase to Epidural Steroid Improves the Quality of Analgesia in Failed Back Surgery Syndrome: A Prospective Randomized Clinical Trial. Pain Physician 2014; 17: 75-82.

2. Amr YM. Effect of Addition of Epidural Ketamine to Steroid in Lumbar Radiculitis: One-Year Follow-Up. Pain Physician 2011; 14:475-481.

3. Manchikanti L, Singh V, Datta S, Cohen SP, Hirsch JA. Comprehensive review of epidemiology, scope, and impact of spinal pain. Pain Physician 2009; 12:E35- E70

4. Manchikanti L, Boswell MV, Singh V, Benyamin RM, Fellows B, Abdi S, et al . Comprehensive evidence-based guidelines for interventional techniques in the management of chronic spinal pain. Pain Physician 2009; 12:699-802.

5. Kim SB, Lee KW, Lee JH, Ah Kim M, Woo An B. The Effect of Hyaluronidase in Interlaminar Lumbar Epidural Injection for Failed Back Surgery Syndrome. Ann Rehabil Med 2012; 36: 466-473.

6. Gottschalk A, Freitag M, Tank S, Burmeister MA, Kreil S, Kothe R, et al. Quality of postoperative pain using an intraoperatively placed epidural catheter after major lumbar spinal surgery. Anesthesiology. 2004 Jul;101(1):175-80.

7. Raw DA, Beattie JK, Hunter JM. Anaesthesia for spinal surgery in adults. Br J Anaesth. 2003;91:886–904.

8. Gianesello L, Pavoni V, Barboni E, Galeotti I, Nella A. Perioperative Pregabalin for Postoperative Pain Control and Quality of Life After Major Spinal Surgery . J Neurosurg Anesthesiol 2011: 0 (0); 1-6.

9. Moudgil V, Bajwa BS. Lumbar Spine Surgery Outcome: Effect of Regional Anaesthesia Global Journal of Medical Research 2014 ; 14 (4): 4-10.

10. Vural C, Yorukoglu D.Comparison of Patient Satisfaction and Cost in Spinal and General Anesthesia for Lumbar Disc Surgery. Turk Neurosurg 2014, Vol: 24(3); 380-384

11. Khajavi MR, Asadian MA, Imani F, Etezadi F, Shariat Moharari R, Amirjamshidi A. General anesthesia versus combined epidural/general anesthesia for elective lumbar spine disc surgery: A randomized clinical trial comparing the impact of the two methods upon the outcome variables. Surgical Neurology International 2015; February 22: IP: 62.102.131.64

12. Karaman S, Karaman T, Dogru S, Sahin A, Arici S, Tapar H. Retrospective Evaluation of Anesthesia Approaches for Lumbar Disc Surgery. J Anesth Clin Res 2014, 5 (4) :1-3.

13. Moudgil V, Bajwa BS. Lumbar Spine Surgery Outcome: Effect of Regional AnaesthesiaGlobal Journal of Medical Research 2014 ; 14 (4): 4-10.

14. Sadrolsadat SH, Mahdavi AR, Moharari RS, Khajavi MR, Khashayar P, Najafi A, et al. A prospective randomized trial comparing the technique of spinal and general anesthesia for lumbar disk surgery: a study of 100 cases. Surg Neurol 2009 ;71(1):60-5.

15. Kara I, Celik JB, OC B, Apilliogullari S1, Karabagli H. Comparison of Spinal and General Anesthesia in Lumbar Disc Surgery. Journal of Neurological Sciences 2011; 28(4):487-96.

16. Gulur P, Nishimori M, Ballantyne JC. Regional anaesthesia versus general naesthesia, morbidity and mortality.Best Pract Res Clin Anaesthesiol. 2006;20:249-63.

17. Attari M, Mirhosseini A, Honarmand A, Safavi M. Spinal anesthesia versus general anesthesia for elective lumbar spine surgery: A randomized clinical trial. J Res Med Sci 2011;16(4):524-9.

18. Papadopoulos EC, Girardi FP, Sama A, Pappou IP, Urban MK, Cammisa FP Jr. Lumbar microdiscectomy under epidural anesthesia: A comparison study. Spine J 2006;6:561-4.

19. Nicassio N, Bobicchio P, Umari M, Tacconi L .Lumbar microdiscectomy under epidural anaesthesia with the patient in the sitting position: a prospective study. J Clin Neurosci , 2010, 17: 1537-1540.

20. De Rojas JO, Syre P, Welch WC .Regional anesthesia versus general anesthesia for surgery on the lumbar spine: a review of the modern literature. Clin Neurol Neurosurg, 2014, 119: 39-43.

21. Weinstein JN, Lurie JD, Tosteson TD, Skinner JS, Hanscom B, Tosteson AN, et al. Surgical vs nonoperative treatment for lumbar disk herniation: The Spine Patient Outcomes Research Trial (SPORT) observational cohort: JAMA 2006; 296:2451-9

22. McLain RF, Kalfas I, Bell GR, Tetzlaff JE, Yoon HJ, Rana M. Comparison of spinal and general anesthesia in lumbar laminectomy surgery: a case-controlled analysis of 400 patients. J Neurosurg Spine 2005; 2(1): 17-22.

23. Tetzlaff JE, Dilger JA, Kodsy M, al Bataineh J, Yoon HJ, Bell GR. Spinal anesthesia for elective lumbar spine surgery. J Clin Anesth 1998; 10(8): 666-9.

24. Demirel CB, Kalayci M, Ozkocak I, Altunkaya H, Ozer Y, Acikgoz B. A prospective randomized study comparing perioperative outcome variables after epidural or general anesthesia for lumbar disc surgery. J Neurosurg Anesthesiol 2003;15:185-92.

25. Abrishamkar S, Aminmansour B, Arti H. The effectiveness of computed tomography scans versus magnetic resonance imaging for decision making in patients with low back pain and radicular leg pain. Journal of Research in Medical Sciences, 2006; 11(6): 351-4.

26. Vasigh A, Najafi F, Jaafarpour M, Khajavikhan J, Khani A. The Effect of Sevoflurane Plus Propofol on Pain and Complications after Laminectomy: A Randomized Double Blind Clinical Trial. Journal of Clinical and Diagnostic Research. 2017 Apr, Vol-11(4): UC05-UC08.

27. Hebl JR, Horlocker TT, Kopp SL, Schroeder DR. Neuraxial blockade in patients with preexisting spinal stenosis, lumbar disk disease, or prior spine surgery: efficacy and neurologic complications. Anesth Analg 2010; 111(6): 1511-9.

28. Basaranoglu G, Erkalp K, Saidoglu L, Aydas D, Ozdemir H, Teker M. Selective spinal anesthesia for limb amputation above knee level. J Clin Anesth 2011; 23(2): 169.

29. Limongi JA, Lins RS. Cardiopulmonary arrest in spinal anesthesia. Rev Bras Anestesiol 2011; 61(1): 110-20.

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ORIGINAL

The efficiency of artificial neural network (ANN) for diagnosis of obesity and hypertension

La eficacia de la red neuronal artificial (RNA) para el diagnóstico de la obesidad y la hipertensión

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Abstract

Aim & Background: Obesity and hypertension are health problems in any society. The aim of this study was to evaluate the sensitivity, specificity and accuracy of artificial neural network (ANN) for the diagnosis of obesity and hypertension. Material & ***Methods:*** For this study, demographic information about 500 students aged 7-18 years was recorded in the ANN program. The recorded demographic information consisted of 11 input variables and 3 output variables. Input variables included age, sex, weight, height, waist circumference, body mass index, waist-to-height ratio, abdominal obesity, physical activity, genetics, and unhealthy eating behaviors, while output variables included obesity, systolic blood pressure, and diastolic blood pressure. In this study, Levenberg-Marquardt and Conjugate Gradient algorithms were used to training the network.
Results: The results showed that the sensitivity, specificity and accuracy of ANN based on experimental data in the diagnosis of obesity were equal to 0.941, 1 and 0.990, respectively; for high systolic blood pressure were 0.800, 1 and 0.970 and for high diastolic blood pressure were 0.875, 1 and 0.980, respectively. In addition, it was found that the sensitivity, specificity and accuracy of ANN based on the obtained total data in the diagnosis of obesity were equal to 0.945, 0.997 and 0.992, respectively; for high systolic blood pressure were 0.857, 0.993 and 0.970, respectively and for high diastolic blood pressure were 0.810, 0.997 and 0.900, respectively.
Conclusion: Based on the results of the present study, it can be concluded that ANN designed to diagnose obesity, systolic and diastolic blood pressure has high accuracy, so the use of ANN to diagnose other similar diseases was suggested.

Keywords: Artificial Neural Network, Health, Obesity, Hypertension, Efficiency, Iran.

Resumen

Objetivo y antecedentes: La obesidad y la hipertensión son problemas de salud en cualquier sociedad. El objetivo de este estudio fue evaluar la sensibilidad, la especificidad y la precisión de la red neuronal artificial (RNA) para el diagnóstico de la obesidad y la hipertensión.
Material y métodos: Para este estudio, se registró la información demográfica de 500 estudiantes de entre 7 y 18 años en el programa RNA. La información demográfica registrada constaba de 11 variables de entrada y 3 de salida. Las variables de entrada incluían la edad, el sexo, el peso, la altura, el perímetro de la cintura, el índice de masa corporal, la relación cintura-estatura, la obesidad abdominal, la actividad física, la genética y los comportamientos alimentarios poco saludables, mientras que las variables de salida incluían la obesidad, la presión arterial sistólica y la presión arterial diastólica. En este estudio, se utilizaron los algoritmos de Levenberg-Marquardt y de Gradiente Conjugado para entrenar la red.
Resultados: Los resultados mostraron que la sensibilidad, la especificidad y la precisión de la RNA basada en datos experimentales en el diagnóstico de la obesidad fueron iguales a 0,941, 1 y 0,990, respectivamente; para la presión arterial sistólica alta fueron 0,800, 1 y 0,970 y para la presión arterial diastólica alta fueron 0,875, 1 y 0,980, respectivamente. Además, se comprobó que la sensibilidad, la especificidad y la precisión de la RNA basada en los datos totales obtenidos en el diagnóstico de la obesidad eran iguales a 0,945, 0,997 y 0,992, respectivamente; para la presión arterial sistólica alta eran 0,857, 0,993 y 0,970, respectivamente y para la presión arterial diastólica alta eran 0,810, 0,997 y 0,900, respectivamente.
Conclusiones: En base a los resultados del presente estudio, se puede concluir que la RNA diseñada para diagnosticar la obesidad y la presión arterial sistólica y diastólica tiene una alta precisión, por lo que se sugirió el uso de la RNA para diagnosticar otras enfermedades similares.

Palabras clave: Red Neural Artificial, Salud, Obesidad, Hipertensión, Eficiencia, Irán.

Introduction

Obesity is a major public health problem, not only in developed countries but also in developing countries such as Iran, and has many medical and psychological consequences for children and adolescents[1]. Obesity is now so prevalent in the world's population that it is replacing nutrition and infectious diseases as the most important cause of disease. In particular, obesity is associated with diseases such as diabetes, heart disease, certain forms of cancer and sleep-disordered breathing and is determined by a body mass index higher than 30 kg/m^2 [2].

According to the World Health Organization, overweight and obesity are the abnormal accumulation of fat in the body that harms human health. In children and adolescents, the Body Mass Index (BMI) is used to measure overweight and obesity[3]. The BMI of each person is defined as the division of weight per kilogram by height squared in meters. Obesity lasts from childhood to adulthood and is significantly associated with increased blood pressure in adulthood. In addition, the level of blood pressure in childhood is the best predictor of blood pressure in adulthood[4-6]. Circulation throughout the body is done by the pressure created in the blood vessels of the body. Blood pressure is mostly related to heart rate and flexibility in the walls of the arteries. There are two types of blood pressure, such as systolic and diastolic. Systolic is the highest blood pressure and diastolic is the lowest blood pressure[7]. Despite the great variety in blood pressure, the general population in children and adolescents is called diastolic pressure of 80 mmHg or higher and systolic pressure of 120 mmHg or higher, hypertension[8].

High blood pressure is an important risk factor for heart and kidney failure. Since the most common sign and symptom in patients with high blood pressure is asymptomatic in them, its prevention can lead to the prevention of complications. There is a direct correlation between mean systolic and diastolic blood pressure and BMI; In other words, body mass index is an important predictor of hypertension[9,10]. In a similar study in Puerto Rican adolescents, a statistically significant relationship was observed between mean systolic and diastolic blood pressure and obesity[11]. Also, the study of the relationship between BMI, waist size, waist-to-height ratio and hypertension among Lithuanian adolescents aged 12-15 years, shows that BMI parameters and waist circumference are more strongly associated with hypertension and then the parameter Waist-to-height size more accurately predict hypertension[12]. Another study showed that waist size could be an important factor in predicting hypertension in Chinese children and adolescents aged 7-17 years. Also, BMI along with waist size had a greater effect on predicting blood pressure in children and adolescents[13].

Obtaining an estimate of the prevalence of obesity among children is necessary in order to assess the need for preventive measures and identify high-risk groups. Despite the global prevalence of obesity, there are limited reports from developing countries on the prevalence of obesity among children. In addition, in some studies, abdominal obesity and obesity and the combined effect of both factors in increasing blood pressure have been identified[14-16]. A study of Greek adolescents aged 6-18 years showed that overweight and obesity can be controlled by modifying behavior and following the Mediterranean lifestyle, which includes the Mediterranean diet, physical activity and active lifestyle[17].

Recently, many researches have used artificial intelligence tools, especially artificial neural network (ANN), to diagnose and predict diseases in the medical field. The high capacity of ANN, which is inspired by biological computing networks, has led to their rapid expansion. Recently, some attempts to predict the percentage of excess body fat in adults with the approach of artificial neural networks have been reported[18-20]. The aim of this study was to evaluate the sensitivity, specificity and accuracy of ANN for the diagnosis of obesity and hypertension in students aged 7-18 years.

Material & Methods

This study is a descriptive-analytical study that is predicted by artificial neural network (ANN). In this study, ANN predicts and evaluates the status of obesity and hypertension in children and adolescents based on input variables. The statistical population of this study was 500 students aged 7-18 years. The researcher-made questionnaire[21] related to the objectives of the present study was completed by a specialist physician and researchers.

The questionnaire included various information such as age, gender, weight, height, waist circumference, body mass index (BMI), and waist to height ratio, abdominal obesity, physical activity, genetics, unhealthy eating behaviors, obesity, systolic blood pressure and diastolic blood pressure. Unhealthy eating behaviors include the daily consumption of fast food, cakes, cookies, chips, puffs, sugary drinks and soft drinks by children and adolescents, which can lead to obesity and high blood pressure. Unhealthy eating behaviors are scaled at three levels: low, medium and high[22,23]. Specifications for 11 input variables (including: age, sex, weight, height, waist circumference, abdominal obesity, BMI, waist-to-height ratio, physical activity, genetics, and unhealthy eating behaviors) and three output variables (including: obesity, systolic blood pressure and diastolic blood pressure) are shown in **table I**.

Table I: Specifications of input and output variables in the present study.

Variable name (symbol)	Variable type (Input / Output)	Mean	Minimum	Maximum
Age (I-1)	Input	12.59	7.05	19
Gender (I-2)	Input	0.52	0	1
Weight (I-3)	Input	42.06	15.7	103.2
Height (I-4)	Input	148.2	102	195
Waist size (I-5)	Input	68.5	27.5	111.5
Abdominal obesity(I-6)	Input	0.2	0	1
Body mass index (BMI) (I-7)	Input	18.7	10.45	44.65
Waist to height ratio (I-8)	Input	0.47	0.2	0.76
Physical activity (I-9)	Input	3.06	0	6.5
Genetics (I-10)	Input	2.09	1	4
Unhealthy eating behaviors (I-11)	Input	0.89	0	2.5
Obesity (I-12)	Output	0.11	0	1.1
Systolic blood pressure (I-13)	Output	100.57	61	153
Diastolic blood pressure (I-14)	Output	65.1	35	95

Finally, using the ANN toolbox in Matlab software, the entered data was analyzed. About 80% of the available data, ie 400 students, were used for education and the remaining 20% of the data, ie 100 people, were used for ANN testing. Finally, using Sigmolide tangent stimulus warping and two scaled conjugate gradient algorithms and Lunberg Marquardt, network training was performed and then the results were compared with each other. To determine the network with the best structure, trial and error method was used and networks with different number of neurons were trained.

Results

The results of the network with scaled conjugate gradient algorithm (SCGA) and Levenberg-Marquart algorithm (LMA) for output variables including obesity, systolic blood pressure, and diastolic pressure are presented. Regarding the output variable of obesity, comparison of network results showed that these variables with SCGA and LMA had 17 and 15 hidden neurons, respectively. While these values were 18 and 15 for systolic blood pressure output and 17 and 17 neurons for diastolic blood pressure, respectively. The accuracy values of the two algorithms (SCGA and LMA) for the designed network with the three output variables examined in **table III** are presented. In addition, the sensitivity, specificity and accuracy of the selected neural network are obtained based on the turbulence matrix of the experimental data and the whole data set for obesity outcomes, high systolic blood pressure, and high diastolic blood pressure, which were shown in **tables IV** and **V**. The results showed that the sensitivity, specificity and accuracy of ANN based on experimental data in the diagnosis of obesity were equal to 0.941, 1 and 0.990, respectively; for high systolic blood pressure were 0.800, 1 and 0.970 and for high diastolic blood pressure were 0.875, 1 and 0.980, respectively (**Table IV**). In addition, it was found that the sensitivity, specificity and accuracy of ANN based on the obtained total data in the diagnosis of obesity were equal to 0.945, 0.997 and 0.992, respectively; for high systolic blood pressure were 0.857, 0.993 and 0.970, respectively and for high diastolic blood pressure were 0.810, 0.997 and 0.900, respectively (**Table V**).

Table II: Network results by SCG and LMA algorithms for output variables.

Variable name	Algorithm type	Number of hidden layer neurons	Regression	Mean Squared Error	Gradient
Obesity	SCGA LMA	17 15	0.98123 0.99435	0.006148 0.000962	0.0038214 0.0031865
Systolic blood pressure	SCGA LMA	18 15	0.87721 0.92521	0.007804 0.0069324	0.013254 0.013952
Diastolic blood pressure	SCGA LMA	17 17	0.90234 0.92346	0.019251 0.019332	0.008449 0.007825

Table III: Designed network accuracy with two algorithms for obesity, systolic blood pressure and diastolic blood pressure.

Algorithm type	Output variables		
	Obesity	Systolic blood pressure	Diastolic blood pressure
SCGA LMA	0.9916 0.9948	0.9564 0.9821	0.9445 0.9674

Table IV: Designed network accuracy with two algorithms for obesity, systolic blood pressure and diastolic blood pressure.

ANN prediction	Control (Healthy)	Disease
Disease (Obesity)	0	16
Control (Healthy)	83	1
Disease (Systolic blood pressure)	0	12
Control (Healthy)	85	3
Disease (Obesity)	0	14
Control (Healthy)	84	2

Table V: Designed network accuracy with two algorithms for obesity, systolic blood pressure and diastolic blood pressure.

ANN prediction	Control (Healthy)	Disease
Disease (Obesity)	1	52
Control (Healthy)	444	3
Disease (Systolic blood pressure)	3	70
Control (Healthy)	415	12
Disease (Obesity)	1	81
Control (Healthy)	399	19

Discussion

Obesity and high blood pressure are the common health problems in Iranian adolescents. In addition, in recent years, the use of ANN in medical sciences with the aim of promoting health, has greatly expanded[24-28]. The main purpose of this study was to evaluate the sensitivity, specificity and accuracy by ANN for the diagnosis of obesity and hypertension in students aged 7-18 years.

Various studies have shown that the input parameters used in the design of this network have the greatest impact on the prediction of hypertension and obesity in children and adolescents. Askary Kachoosangy et al. (2015) reported that there was significant association between increased BMI and hypertension. Maintaining normal weight and BMI is recommended as a priority to prevent high blood pressure[29]. Also the results of the study of Yuan et al. (2017) showed that BMI and waist circumference variables are directly related to blood pressure in Chinese adolescents, although according to the results of this study, BMI variable is better than waist circumference variable to diagnose pediatric hypertension[30]. Based on the findings of the study Khaji et al. (2016) which was performed on fifth grade elementary school children in Tehran, it was found that the prevalence of overweight and obesity in them is about 10% and 6%, respectively. In addition, the results of that study showed that different weight groups have significant differences in terms of blood pressure, which indicates that blood pressure has a significant relationship with weight[31].

Many previous studies have demonstrated the effective function of the Multi-Layer Perceptron (MLP) neural network in diagnosing and predicting diseases such as obesity and hypertension. In the study of Huang et al. (2010), which evaluated the effectiveness of ANN application and logistic regression model on residents over 35 years of age in rural China, found that ANN more accurately assesses the risk of hypertension[32]. In a study by Samant and Rao (2010) that evaluated the ability of ANN designed with the Lunberg-Marquardt algorithm to predict the probability of hypertension in a community of healthy and sick people (with a history of hypertension) in India, the maximum accuracy of ANN designed in that study was 92.85%[33]. A study by Ture et al. (2005) were performed to compare classification methods (three types of decision trees, four statistical algorithms and two neural networks) to predict the risk of hypertension. The results of that study showed that the MLP and Radial Basic Function (RBF) neural networks had the best performance among the mentioned classification methods with 89.29% and 86.36% accuracy, respectively[34]. Duran et al. (2019) used ANN with four input variables including age, height, weight and waist circumference to diagnose and predict obesity in children, which achieved an accuracy of 92%[35], while in the present study with 11 input variable with 95% accuracy, ANN was designed to diagnose and predict obesity and hypertension in children and adolescents. This shows that more effective factors are used in determining obesity and hypertension, with much more accurate diagnosis and prediction. Considering that in the present study, 11 effective variables in obesity and hypertension were used, the number of quantitative variables was used in the previous research; therefore, the results of the present study had a higher accuracy.

The results of present study showed that the sensitivity, specificity and accuracy of ANN based on experimental data in the diagnosis of obesity were equal to 0.941, 1 and 0.990, respectively; for high systolic blood pressure were 0.800, 1 and 0.970 and for high diastolic blood pressure were 0.875, 1 and 0.980, respectively. In addition, it was found that the sensitivity, specificity and accuracy of ANN based on the obtained total data in the diagnosis of obesity were equal to 0.945, 0.997 and 0.992, respectively; for high systolic blood pressure were 0.857, 0.993 and 0.970, respectively and for high diastolic blood pressure were 0.810, 0.997 and 0.900, respectively.

In the present study, it was shown that having 11 input variables, a system can be designed to predict obesity and blood pressure in students. The system designed in the present study is more accurate than previous studies in which they used fewer parameters to predict blood pressure and obesity. Also, the results of the present study showed that ANN designed to provide appropriate results for the diagnosis and prognosis of obesity and systolic and diastolic blood pressure in students. The results of the present study showed that this system predicts obesity, high systolic blood pressure and high diastolic blood pressure in students with 99, 97 and 98% accuracy, respectively.

In addition, based on the results of the present study, it was found that high blood pressure and obesity are the common health problems in children and adolescents. Also, the rate of hypertension in obese students is significantly higher than other adolescents with lower weight. According to the results of the present study, about 85% of obese adolescents have high blood pressure. In addition, the prevalence of risk factors for cardiovascular disease is higher in obese individuals with high blood pressure. Therefore, the need to design educational programs in the field of lifestyle improvement through social, cultural and nutritional effects and provide the correct pattern of food consumption and physical activity can be appropriate strategies to promote community health.

Conclusion

Based on the results, it can be concluded that the use of more input parameters predicts obesity and hypertension in children and adolescents with higher accuracy. Although using more effective variables complicates the analysis process, this can be done with intelligent tools

such as ANN. Based on the results of the present study, it can be concluded that ANN is designed to diagnose obesity and hypertension, so the use of ANN to diagnose other similar diseases was suggested.

Conflict of Interest

There is no conflict of interest.

References

1. Mirmiran P, Sherafat Kazemzadeh R, Jalali Farahani S, Azizi F. Childhood obesity in the Middle East: a review. EMHJ-Eastern Mediterranean Health Journal, 16 (9), 1009-1017, 2010.

2. Caprio S. Treating child obesity and associated medical conditions. The Future of Children. 2006: 209-24.

3. Ferenci T, Kovacs L. Predicting body fat percentage from anthropometric and laboratory measurements using artificial neural networks. Applied Soft Computing. 2018; 67:834-9.

4. Weisell RC. Body mass index as an indicator of obesity. Asia Pacific journal of clinical nutrition. 2002; 11:S681-4.

5. Dua S, Bhuker M, Sharma P, Dhall M, Kapoor S. Body mass index relates to blood pressure among adults. North American journal of medical sciences. 2014; 6(2):89.

6. Assadi F. Childhood hypertension: A problem of epidemic proportion. International Journal of Preventive Medicine. 2014 Mar 7:1-3.

7. Kaplan NM. Kaplan's clinical hypertension. Lippincott Williams & Wilkins; 2010.

8. Kasper DL, Fauci AS, Hauser S, Longo DL, Jameson JL, Loscalzo J. Parkinson's disease and other movement disorders. Harrison's Principles of Internal Medicine. 19th ed. New York, NY: McGraw-Hill Education. 2015.

9. Seravalle G, Grassi G. Obesity and hypertension. Pharmacological research. 2017; 122:1-7.

10. Baig M, Gazzaz ZJ, Gari MA, Al-Attallah HG, Al-Jedaani KS, Mesawa AT, et al. Prevalence of obesity and hypertension among University students' and their knowledge and attitude towards risk factors of Cardiovascular Disease (CVD) in Jeddah, Saudi Arabia. Pakistan journal of medical sciences. 2015; 31(4):816.

11. Venegas HL, Pérez CM, Suárez EL, Guzmán M. Prevalence of obesity and its association with blood pressure, serum lipids and selected lifestyles in a Puerto Rican population of adolescents 12-16 years of age. Puerto Rico Health Sciences Journal. 2003; 22(2).

12. Kuciene R, Dulskiene V. Associations between body mass index, waist circumference, waist-to-height ratio, and high blood pressure among adolescents: a cross-sectional study. Scientific Reports. 2019; 9(1):1-1.

13. Wang M, Sun J, Ma C, Xi B. A3672 Role of waist circumference in predicting elevated blood pressure among children and adolescents with normal body mass index. Journal of Hypertension. 2018; 36:e290.

14. Golan M, Weizman A. Familial approach to the treatment of childhood obesity: conceptual model. Journal of nutrition education. 2001; 33(2):102-7.

15. Chhatwal J, Verma M, Riar SK. Obesity among pre-adolescent and adolescents of a developing country (India). Asia Pacific journal of clinical nutrition. 2004; 13(3).

16. Mohammadi M, Mirzaei M. The effect of obesity, abdominal obesity and joint effect of them on high blood pressure in men of Mazandaran Province, Iran (population attributable fraction study): brief report. Tehran University Medical Journal TUMS Publications. 2017; 74(10):735-40.

17. Katsagoni CN, Psarra G, Georgoulis M, Tambalis K, Panagiotakos DB, Sidossis LS, EYZHN Study Group. High and moderate adherence to Mediterranean lifestyle is inversely associated with overweight, general and abdominal obesity in children and adolescents: The MediLIFE-index. Nutrition Research. 2020; 73:38-47.

18. Ferenci T, Kovacs L. Predicting body fat percentage from anthropometric and laboratory measurements using artificial neural networks. Applied Soft Computing. 2018; 67: 834-9.

19. Kupusinac A, Stokić E, Doroslovački R. Predicting body fat percentage based on gender, age and BMI by using artificial neural networks. Computer methods and programs in biomedicine. 2014; 113(2):610-9.

20. Shao YE. Body fat percentage prediction using intelligent hybrid approaches. The Scientific World Journal. 2014; 2014.

21. Motlagh ME, Ziaodini H, Qorbani M, Taheri M, Aminaei T, Goodarzi A, et al. Methodology and early findings of the fifth survey of childhood and adolescence surveillance and prevention of adult noncommunicable disease: the CASPIAN-V study. International journal of preventive medicine. 2017; 8.

22. Payab M, Kelishadi R, Qorbani M, Motlagh ME, Ranjbar SH, Ardalan G, et al. Association of junk food consumption with high blood pressure and obesity in Iranian children and adolescents: the CASPIAN-IV Study. Journal de pediatria. 2015; 91:196-205.

23. Kelishadi R, Poursafa P. A review on the genetic, environmental, and lifestyle aspects of the early-life origins of cardiovascular disease. Current problems in pediatric and adolescent health care. 2014; 44(3):54-72.

24. Amato F, López A, Peña-Méndez EM, Vaňhara P, Hampl A, Havel J. Artificial neural networks in medical diagnosis. Journal of applied biomedicine. 2013; 11(2):47-58.

25. Tajbakhsh N, Shin JY, Gurudu SR, Hurst RT, Kendall CB, Gotway MB, et al. Convolutional neural networks for medical image analysis: Full training or fine tuning?. IEEE transactions on medical imaging. 2016; 35(5):1299-312.

26. Brameier M, Banzhaf W. A comparison of linear genetic programming and neural networks in medical data mining. IEEE Transactions on Evolutionary Computation. 2001; 5(1):17-26.

27. Hinton GE, Salakhutdinov RR. Reducing the dimensionality of data with neural networks. Science. 2006; 313(5786):504-7.

28. Lakhani P, Sundaram B. Deep learning at chest radiography: automated classification of pulmonary tuberculosis by using convolutional neural networks. Radiology. 2017; 284(2):574-82.

29. Askary Kachoosangy R, Habibi E, Hosseini L. The Investigation of Relationship between Hypertension and High Body Mass Index in 30-60-Year Population of Shahid Motahary Hospital, Marvdasht in 1391. Journal of Sabzevar University of Medical Sciences. 2015; 22(3):206-12.

30. Yuan P, Qian ZM, Vaughn M, Huang J, Ward P, Zhu Y, et al. Comparison of body mass index with abdominal obesity for identifying elevated blood pressure in children and adolescents: The SNEC study. Obesity Research & Clinical Practice. 2017; 11(4):406-13.

31. Khaji A, Khodaii S, Faeghi A, Azizi S, Firoozian A, Jafari J. Blood pressure and obesity in young adolescents in Tehran. Iranian Journal of Pediatrics 2006; 16(1): 45 – 50.

32.Huang S, Xu Y, Yue L, Wei S, Liu L, Gan X, et al. Evaluating the risk of hypertension using an artificial neural network method in rural residents over the age of 35 years in a Chinese area. Hypertension Research. 2010; 33(7):722-6.

33. Samant R, Rao S. Evaluation of artificial neural networks in prediction of essential hypertension. International Journal of Computer Applications. 2013; 81(12).

34. Ture M, Kurt I, Kurum AT, Ozdamar K. Comparing classification techniques for predicting essential hypertension. Expert Systems with Applications. 2005; 29(3):583-8.

35. Duran I, Martakis K, Rehberg M, Semler O, Schoenau E. Diagnostic performance of an artificial neural network to predict excess body fat in children. Pediatric Obesity. 2019; 14(2):e12494.

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ORIGINAL

Relationship between values of 7 NAFLD scales and different RCV scales in 219,477 Spanish workers

Relación entre valores de 7 escalas de NAFLD y diferentes escalas de RCV en 219.477 trabajadores españoles.

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Abstract

Introduction: Cardiometabolic diseases are highly prevalent and constitute the leading cause of morbidity and mortality worldwide. Non-alcoholic fatty liver disease (NAFLD) is also very prevalent. The aim of this study is to assess the relationship between different NAFLD risk scales and cardiovascular risk (CVR) scales.
Material and methods: Descriptive, cross-sectional study in 219477 Spanish workers in which the relationship between NAFLD and liver fibrosis risk scales (FLI, HSI, ZJU, FLD, FSI, LAP and BARD score) and CVR scales (REGICOR, SCORE, DORICA, ERICE and vascular age) was assessed.
Results: In our study there is a direct relationship between the increase in the values of the CVR scales and the increase in the risk values of NAFLD and hepatic fibrosis. The value of the CVR scales for predicting the presence of high risk values of NAFLD and liver fibrosis scales using ROC curves is not very high.
Conclusions: There is a good relationship between the values of both types of scales although the predictive value is not good.

Keywords: NAFLD, liver fibrosis, cardiovascular risk.

Resumen

Introducción: Las enfermedades cardiometabólicas son muy prevalentes y constituyen la primera causa de morbimortalidad en todo el mundo. La enfermedad del hígado graso no alcohólico (NAFLD) también es muy prevalente. El objetivo de este estudio es valorar la relación entre diferentes escalas de riesgo de NAFLD y escalas de riesgo cardiovascular (RCV).
Material y métodos: Estudio descriptivo y transversal en 219477 trabajadores españoles en el que se valora la relación entre escalas de riesgo de NAFLD y fibrosis hepática (FLI, HSI, ZJU, FLD, FSI, LAP y BARD score) con escalas de RCV (REGICOR, SCORE, DORICA, ERICE y edad vascular).
Resultados: En nuestro estudio existe una relación directa entre el incremento de los valores de las escalas de RCV y el incremento de los valores de riesgo de NAFLD y fibrosis hepática. El valor de las escalas de RCV para predecir la presencia de valores de alto riesgo de las escalas de NAFLD y fibrosis hepática empleando las curvas ROC no es muy alto.
Conclusiones: Existe buena relación entre los valores de ambos tipos de escalas aunque el valor predictivo no es bueno.

Palabras clave: NAFLD, fibrosis hepática, riesgo cardiovascular.

Introduction

The term non-alcoholic fatty liver disease (NAFLD) is used to refer to a broad group of liver disorders ranging from an initial phase called simple steatosis to more serious conditions such as steatohepatitis and even cirrhosis. Histologically, the lesions that appear in NAFLD are similar to those caused by alcohol consumption, although by definition NAFLD develops only in people who do not drink alcohol or only drink alcohol sporadically.

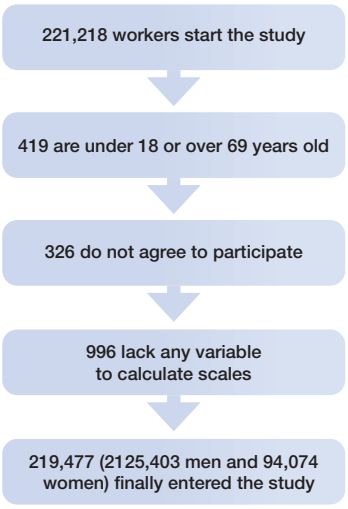
NAFLD was first described in the 1950s by Zelman[1] and was correctly characterized by Ludwig et al2 thirty years later[2]. Thirty years later, it is currently a clinical condition that attracts the attention of healthcare professionals due to its high prevalence, especially in Western countries[3]. Recently, it has been shown that NAFLD can lead to death, not only due to the chronic liver disease[4] it causes, but also as a consequence of alterations in lipid metabolism and increased cardiovascular risk.

The aim of the present study was to assess the relationship between different NAFLD and liver fibrosis risk scales and some cardiovascular risk scales.

Material and methods

A descriptive, cross-sectional study was carried out in 219,477 Spanish workers from different regions and work sectors, mostly in public administration, health, hospitality, construction and commerce. The workers included in the study were selected among those who attended occupational health checkups carried out between January 2017 and December 2019. See flow diagram in **figure 1**.

Figure 1: Flow chart of participants in the study.



Inclusion criteria:

- Age between 18 and 69 years.
- Acceptance to participate in the study.
- Authorization to use the data obtained for epidemiological purposes.
- Belonging to one of the companies included in the study and not being on temporary disability at the time of the study.

The anthropometric (height, weight and waist circumference), analytical and clinical determinations were performed by the different occupational health professionals of the participating companies after standardization of the processes to avoid interobserver bias.

Weight (in kilograms) and height (in centimeters) were determined with a SECA 700 scale-measuring device. Waist circumference was measured with the person in a standing position, upper extremities hanging, feet together and abdomen relaxed. It was placed parallel to the ground at the level of the last floating rib.

Blood pressure was obtained while seated and after a 10-minute rest at rest. Three measurements were obtained one minute apart and the mean was calculated.

Blood analysis was performed after fasting for no less than 12 hours. Cholesterol, triglycerides and glycemia were obtained using enzymatic techniques while HDL was obtained using precipitation techniques. LDL was calculated by applying the Friedewald formula (total cholesterol -HDL-c- triglycerides/5), which is only applicable when triglycerides do not exceed a value of 400.

Seven risk scales were calculated for non-alcoholic fatty liver disease and liver fibrosis:

- Fatty Liver Index (FLI)[6]

$$FLI = (e^{0.953*\log_e(\text{triglycerides}) + 0.139*BMI + 0.718*\log_e(GGT) + 0.053*\text{waist circumference} - 15.745}) / (1 + e^{0.953*\log_e(\text{triglycerides}) + 0.139*BMI + 0.718*\log_e(GGT) + 0.053*\text{waist circumference} - 15.745}) \times 100$$

The cut-off point to consider high risk is 60.

- Hepatic steatosis index (HSI)[7]
HSI = 8 × AST/ALT + BMI + 2 if diabetes, + 2 if female.
The cut-off point to consider high risk is 36.

- Zhejian University index (ZJU index)[8]
ZJU = BMI + Blood glucose (mmol L) + Triglycerides (mmol L) +3 AST/ALT +2 if female.
The cut-off point to consider high risk is 38.

- Fatty liver disease index (FLD)[9]
FLD = BMI+Triglycerides+3 × (AST/ALT) +2 × Hyperglycemia (present=1; absent=0).
The cutoff point to consider high risk is 37.

- Framingham Steatosis Index (FSI)[10]
FSI = -7.981 + 0.011 x age - 0.146 x sex (female =1, male = 0) + 0.173 x BMI + 0.007 x triglycerides + 0.593 x hypertension (yes = 1, no =0) + 0.789 x diabetes (yes = 1, no =0) + 1.1 x AST/ALT ratio ≥1.33 (yes = 1, no =0).

- Lipid accumulation product (LCP)[11]
Men: (waist (cm) - 65) x (triglycerides (mMol)).
Women: (waist (cm) - 58) x (triglycerides (mMol)).
The cut-off point to consider high is 42.7.

- BARD score[12] It is a risk scale for liver fibrosis.

BMI from 28 (1 point), AST/ALT from 0.8 (2 points), diabetes mellitus (2 points). Values between 2-4 points indicate high risk.

Six cardiovascular risk scales are calculated:

- Registro Gironí del Cor (REGICOR)[13].

This is a scale used to determine the possibility of suffering a cerebrovascular event, fatal or otherwise, during the next decade of life. It is applicable between 35 and 74 years of age. Values below 5% are considered low, between 5% and 9% moderate, from 10% to 14% high, and from 15% and above very high.

- Systematic Coronary Risk Evaluation (SCORE)[14]
Estimates the probability of presenting a fatal cerebrovascular event in the next 10 years. It is applicable between 40 and 65 years of age. Values are considered low up to 3%, moderate between 4% and 5%, and high after 5%.

- Dyslipidemia Obesity and Cardiovascular Risk in Spain (DORICA)[15]
Evaluates the risk of presenting a cerebrovascular event in the following decade. It is applicable between 20 and 64 years of age. Risk is considered low if it is less than 5%, slight between 5% and 9%, moderate between 10% and 19%, high between 20% and 39%, and very high above 40%.

- Spanish Cardiovascular Risk Equation (ERICE)[16]
It also calculates the risk of presenting a cerebrovascular event in the following decade. It is applicable between 30 and 80 years of age. It is considered low if it is less than 5%, mild between 5% and 9%, moderate between 10% and 14%, moderate-high between 15%-19%, high between 20%-29% and very high after 30%.

- Framingham vascular age and SCORE[17].
Both are obtained from tables and assess the aging of the vascular tree. A very useful concept is that of ALLY (avoidable lost life years), which is the avoidable years of life lost, corresponding to the difference between the individual's biological age and vascular age[18].

Smoker is any person who has smoked at least one cigarette (or its equivalent in another type of consumption) in the last 30 days or has quit less than 12 months ago.

The social class is determined based on the proposal of the Spanish Society of Epidemiology, which is based on the 2011 National Classification of Occupations[19]. Three groups are established: class I (directors, managers and university professionals), class II (intermediate occupations and self-employed workers) and class III (manual workers).

Results

The mean age of the sample was over 40 years (41.8 years in men and 39.9 years in women), with the majority group being between 30 and 49 years of age. The anthropometric, clinical and analytical variables in all cases show more unfavorable values in men. The social class most represented in the study is class III. Approximately one out of every three workers included in the study was a smoker. All the data can be consulted in **table I**.

Table II shows how all the NAFLD and liver fibrosis risk scales increase their mean values as the values of the different scales that assess cardiovascular risk increase. In all cases, the mean values of the NAFLD and liver fibrosis risk scales are higher in men.

Table III shows that the prevalence of high values of the NAFLD and liver fibrosis risk scales is also higher as the values of the cardiovascular risk scales increase. As with the mean values, higher values are observed in men in all cases.

Table IV shows the results of the multivariate analysis by multinomial logistic regression. The risk of presenting elevated values for all the nonalcoholic fatty liver disease and liver fibrosis risk scales increases as the cardiovascular risk scales increase. The greatest increases are seen with the DORICA scale.

Figure 2 and **table V** show the areas under the curve with their 95% confidence intervals of the cardiovascular risk scales for predicting the presence of high values of the nonalcoholic fatty liver disease and liver fibrosis risk scales. In general, the areas under the curve found are not high and only DORICA and ALLY Framingham vascular age for FLI and BARD score and ERICE for BARD score exceed 70%.

Table I: Characteristics of the population.

	Men n=125,403 Mean (SD)	Women n=94,074 Mean (SD)	p
Age	41.8 (10.5)	39.9 (10.5)	<0.0001
Height	175.2 (6.8)	162.3 (6.3)	<0.0001
Weight	82.6 (15.0)	68.0 (14.7)	<0.0001
SBP	126.1 (15.6)	115.4 (15.5)	<0.0001
DBP	77.3 (11.1)	72.3 (10.5)	<0.0001
Cholesterol	195.6 (37.9)	192.1 (35.5)	<0.001
HDL-c	52.1 (9.8)	57.2 (10.3)	<0.0001
LDL-c	118.4 (35.1)	116.3 (33.5)	<0.001
Tryglicerides	125.7 (76.0)	93.1 (45.6)	<0.0001
Glycaemia	93.4 (21.5)	88.3 (16.0)	<0.0001
AST	29.0 (17.5)	18.7 (11.6)	<0.0001
ALT	24.4 (13.3)	18.2 (7.9)	<0.0001
GGT	32.7 (31.8)	18.8 (16.3)	<0.0001
Creatinine	0.86 (0.17)	0.68 (0.14)	<0.0001
	%	%	p
18-29 years	14.4	19.4	<0.0001
30-39 years	26.6	28.9	
40-49 years	33.6	32.0	
50-59 years	21.5	16.8	
60-69 years	3.9	2.9	
Social class I	6.1	7.5	<0.0001
Social class II	14.5	20.5	
Social class III	79.4	72.0	
Non smokers	67.5	66.7	<0.001
Smokers	32.5	33.3	

SBP systolic blood pressure. DBP diastolic blood pressure. HDL High density lipoprotein. LDL Low density lipoprotein. AST aspartate transaminase. **ALT** alanine transaminase. **GGT** gamma-glutamyl transferase.

Table II: Mean values of NAFLD and liver fibrosis risk scales according to values of cardiovascular risk scales by sex.

		FLI	HSI	ZJU	FLD	FSI	LAP	BARD
Men	**n**	**mean (SD)**	**mean (SD)**	**mean (SD)**	**mean (SD)**	**mean (SD)**	**mean (SD)**	**mean (SD)**
REGICOR low	85617	41.0 (26.6)	37.1 (6.7)	37.4 (5.6)	32.3 (5.3)	0.21 (0.19)	34.5 (29.0)	1.2 (1.1)
REGICOR moderate	21321	43.1 (26.8)	37.5 (6.6)	37.9 (5.7)	32.7 (5.3)	0.23 (0.20)	35.8 (29.7)	1.3 (1.1)
REGICOR high-very high	2103	43.3 (27.6)	37.5 (6.6)	38.0 (5.8)	32.8 (5.4)	0.24 (0.21)	36.5 (31.9)	1.4 (1.1)
SCORE low	56202	42.8 (26.2)	37.3 (6.6)	37.7 (5.5)	32.5 (5.2)	0.22 (0.19)	35.8 (29.6)	1.2 (1.0)
SCORE moderate	10860	47.8 (26.4)	38.1 (6.6)	38.9 (5.8)	33.4 (5.3)	0.29 (0.21)	39.3 (31.0)	2.0 (1.0)
SCORE high	6567	51.5 (25.8)	38.5 (6.4)	39.6 (5.7)	33.9 (5.2)	0.34 (0.21)	41.3 (30.4)	2.2 (0.9)
ERICE low-mild	93513	40.4 (26.4)	36.9 (6.7)	37.2 (5.5)	32.1 (5.3)	0.20 (0.18)	34.4 (29.7)	1.1 (1.0)
ERICE moderate	11280	51.4 (25.9)	39.0 (6.6)	39.8 (5.8)	34.2 (5.3)	0.33 (0.21)	39.8 (26.5)	2.2 (1.0)
ERICE high-very high	2604	52.0 (25.3)	39.3 (6.0)	40.2 (5.5)	34.4 (5.0)	0.36 (0.20)	41.6 (31.1)	2.2 (0.9)
DORICA low-mild	100614	38.3 (26.1)	36.6 (6.7)	36.8 (5.4)	31.8 (5.2)	0.19 (0.17)	32.1 (26.9)	1.0 (1.0)
DORICA moderate	15294	53.3 (26.1)	38.9 (6.6)	39.9 (5.9)	34.4 (5.5)	0.33 (0.21)	45.9 (37.7)	2.0 (1.0)
DORICA high-very high	2187	61.7 (25.0)	39.9 (6.8)	42.0 (6.5)	35.9 (5.5)	0.44 (0.23)	57.4 (41.2)	2.4 (1.0)
ALLY VA Framingham <10 years	74928	36.9 (25.0)	36.2 (6.3)	36.5 (5.1)	31.5 (4.9)	0.18 (0.16)	30.9 (25.1)	1.0 (1.0)
ALLY VA Framingham ≥10 years	32469	53.3 (26.6)	39.4 (7.0)	40.0 (6.0)	34.5 (5.6)	0.32 (0.22)	45.6 (36.7)	1.8 (1.1)
ALLY VA SCORE <10 years	50418	41.7 (25.9)	37.1 (6.4)	37.5 (5.4)	32.3 (5.1)	0.21 (0.18)	34.7 (28.4)	1.2 (1.0)
ALLY VA SCORE ≥10 years	23211	50.0 (26.4)	38.4 (6.9)	39.2 (5.8)	33.7 (5.4)	0.31 (0.21)	41.4 (32.7)	1.8 (1.1)
Women	**n**	**mean (SD)**	**mean (SD)**	**mean (SD)**	**mean (SD)**	**mean (SD)**	**mean (SD)**	**mean (SD)**
REGICOR low	63018	20.0 (22.5)	36.6 (6.9)	37.2 (6.1)	30.3 (5.8)	0.15 (0.16)	19.7 (18.3)	0.7 (0.8)
REGICOR moderate	13551	21.5 (23.5)	37.0 (6.9)	37.6 (6.3)	30.7 (6.0)	0.17 (0.18)	20.6 (17.8)	0.8 (0.9)
REGICOR high-very high	1371	22.0 (23.9)	37.1 (7.0)	37.6 (6.4)	30.7 (6.1)	0.17 (0.17)	20.9 (18.7)	0.8 (0.9)
SCORE low	46626	21.8 (22.8)	37.1 (6.7)	37.7 (5.9)	30.8 (5.7)	0.17 (0.17)	20.9 (18.8)	0.9 (0.9)
SCORE moderate	1479	32.5 (26.3)	39.8 (7.2)	40.5 (6.2)	33.2 (5.9)	0.28 (0.21)	28.4 (23.1)	1.8 (0.8)
SCORE high	414	34.8 (28.9)	39.8 (7.6)	40.7 (6.8)	33.3 (6.6)	0.32 (0.22)	29.9 (24.7)	1.9 (0.8)
ERICE low-mild	73515	20.3 (22.7)	36.6 (6.8)	37.2 (6.1)	30.3 (5.9)	1.15 (0.16)	19.8 (18.4)	0.7 (0.8)
ERICE moderate	2136	32.3 (25.4)	41.4 (6.8)	41.0 (6.2)	33.4 (5.7)	0.28 (0.18)	29.6 (17.3)	1.8 (0.8)
ERICE high-very high	153	34.0 (27.5)	40.7 (7.3(	41.3 (6.8)	33.8 (6.3)	0.29 (0.22)	30.1 (24.7)	1.9 (0.8)
DORICA low-mild	84063	19.3 (22.2)	36.3 (6.8)	36.9 (6.0)	30.1 (5.8)	0.14 (0.16)	19.1 (17.7)	0.6 (0.8)
DORICA moderate	2586	39.7 (28.4)	41.1 (7.4)	42.4 (7.0)	34.8 (6.5)	0.34 (0.24)	35.8 (29.2)	2.0 (0.9)
DORICA high-very high	75	60.3 (29.4)	45.3 (8.4)	49.6 (8.1)	39.9 (7.6)	0.52 (0.28)	58.3 (41.0)	2.6 (0.8)
ALLY VA Framingham <10 years	61797	17.4 (20.3)	35.9 (6.5)	36.5 (5.6)	29.7 (5.5)	0.13 (0.14)	17.6 (15.6)	0.6 (0.7)
ALLY VA Framingham ≥10 years	14007	35.1 (27.7)	40.5 (7.3)	41.2 (6.7)	33.9 (6.4)	0.28 (0.22)	31.2 (25.8)	1.4 (1.0)
ALLY VA SCORE <10 years	42006	20.9 (22.2)	36.9 (6.6)	37.5 (5.8)	30.6 (5.6)	0.16 (0.16)	20.2 (18.0)	0.8 (0.9)
ALLY VA SCORE ≥10 years	6513	30.3 (26.8)	39.2 (7.2)	39.9 (6.5)	32.7 (6.2)	0.26 (0.22)	27.5 (24.1)	1.5 (1.0)

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Table III: Prevalence of high values of NAFLD and liver fibrosis risk scales according to values of cardiovascular risk scales by sex.

		FLI high	HSI high	ZJU high	FLD high	LAP high	BARD high
Men	**n**	**%**	**%**	**%**	**%**	**%**	**%**
REGICOR low	85617	26.6	51.2	39.7	59.8	43.1	35.5
REGICOR moderate	21321	28.8	53.5	43.4	63.3	45.5	41.1
REGICOR high-very high	2103	31.0	54.5	44.3	63.7	46.2	41.2
SCORE low	56202	27.9	53.0	42.0	65.1	45.3	37.2
SCORE moderate	10860	34.6	60.4	52.3	63.4	51.1	64.3
SCORE high	6567	41.0	62.9	58.1	64.8	56.5	72.9
ERICE low-mild	93513	25.6	50.0	38.4	63.5	42.3	31.9
ERICE moderate	11280	39.7	65.7	57.7	62.6	56.0	71.8
ERICE high-very high	2604	40.6	70.2	64.2	65.4	56.9	74.8
DORICA low-mild	100614	23.1	48.2	35.7	62.4	39.1	29.3
DORICA moderate	15294	42.2	64.7	59.4	62.5	60.5	65.9
DORICA high-very high	2187	56.4	69.8	72.0	56.0	72.8	82.6
ALLY VA Framingham <10 years	74928	20.6	45.7	33.1	64.1	37.4	28.1
ALLY VA Framingham ≥10 years	32469	43.1	67.0	59.2	61.7	59.7	58.2
ALLY VA SCORE <10 years	50418	26.5	52.1	40.6	65.7	43.8	37.5
ALLY VA SCORE ≥10 years	23211	38.0	61.2	54.3	63.2	54.5	59.4
Women	**n**	**n**	**%**	**%**	**%**	**%**	**%**
REGICOR low	63018	8.7	46.8	37.3	46.6	29.7	15.7
REGICOR moderate	13551	10.6	48.9	39.5	46.6	31.2	20.6
REGICOR high-very high	1371	10.7	51.2	40.9	45.1	31.9	19.5
SCORE low	46626	9.5	50.9	41.2	50.5	32.0	21.8
SCORE moderate	1479	17.4	69.8	62.1	60.0	49.3	58.4
SCORE high	414	24.6	66.7	64.5	45.7	51.4	64.5
ERICE low-mild	73515	9.0	46.8	37.4	46.5	29.5	15.6
ERICE moderate	2136	15.7	73.3	64.7	54.9	50.6	60.8
ERICE high-very high	153	20.2	80.4	68.6	57.4	51.0	61.5
DORICA low-mild	84063	8.4	44.9	35.4	45.1	28.0	13.5
DORICA moderate	2586	26.8	75.5	71.9	51.7	59.6	67.3
DORICA high-very high	75	52.0	88.0	92.0	72.1	88.0	92.0
ALLY VA Framingham <10 years	61797	6.4	42.1	32.4	45.0	24.8	11.1
ALLY VA Framingham ≥10 years	14007	22.3	72.1	64.3	54.9	53.7	43.0
ALLY VA SCORE <10 years	42006	8.7	49.7	39.9	50.1	30.8	19.8
ALLY VA SCORE ≥10 years	6513	17.2	64.2	55.7	54.8	45.0	45.6

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Table IV: Multinomial logistic regression.

	FLI high OR (95% CI)	HSI high OR (95% CI)	ZJU high OR (95% CI)	FLD high OR (95% CI)	LAP high OR (95% CI)	BARD high OR (95% CI)
REGICOR low	1	1	1	1	1	1
REGICOR moderate	1.08 (1.02-1.17)	1.09 (1.00-1.19)	1,08 (1.02-1.15)	1.09 (1.05-1.15)	1.06 (1.02-1.11)	1.11 (1.06-1.17)
REGICOR high-very high	1.27 (1.17-1.38)	1.14 (1.07-1.22)	1.17 (1.09-1.25)	1.22 (1.14-1.30)	1.14 (1.07-1.22)	1.30 (1.21-1.40)
SCORE low	1	1	1	1	1	1
SCORE moderate	1.21 (1.15-1.26)	1.34 (1.29-1.38)	1.31 (1.26-1.35)	1.05 (1.00-1.10)	1.05 (1.01-1.09)	1.30 (1.25-1.34)
SCORE high	1.31 (1.26-1.36)	1.47 (1.43-1.51)	1.46 (1.42-1.50)	1.25 (1.16-1.34)	1.35 (1.30-1.40)	1.47 (1.42-1.52)
ERICE low-mild	1	1	1	1	1	1
ERICE moderate	1.09 (1.03-1.116)	1.23 (1.12-1.36)	1.18 (1.08-1.30)	1.14 (1.04-1.25)	1.06 (1.01-1.11)	1.04 (1.00-1.09)
ERICE high-very high	1.27 (1.15-1.40)	1.84 (1.67-2.04)	1.62 (1.47-1.78)	1.17 (1.06-1.28)	2.45 (2.20-2.72)	1.23 (1.12-1.35)
DORICA low-mild	1	1	1	1	1	1
DORICA moderate	1.79 (1.63-1.96)	1.16 (1.04-1.28)	1.65 (1.49-1.83)	1.29 (1.22-1.35)	1.63 (1.44-1.84)	1.88 (1.70-2.09)
DORICA high-very high	3.14 (2.84-3.47)	1.39 (1.25-1.54)	2.53 (2.28-2.82)	1.35 (1.28-1.41)	3.24 (2.87-3.67)	3.37 (3.03-3.76)
ALLY VE Framingham <10 years	1	1	1	1	1	1
ALLY VE Framingham ≥10 years	2.49 (2.41-2.58)	2.41 (2.34-2.49)	2.48 (2.41-2.55)	1.02 (1.00-1.05)	1.99 (1.93-2.05)	2.33 (2.27-2.40)
ALLY VE SCORE <10 years	1	1	1	1	1	1
ALLY VE SCORE ≥10 years	1.08 (1.04-1.13)	1.06 (1.01-1.12)	1.12 (1.05-1.19)	1.05 (1.01-1.09)	1.20 (1.15-1.24)	1.17 (1.08-1.26)

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Figure 2: ROC curve.

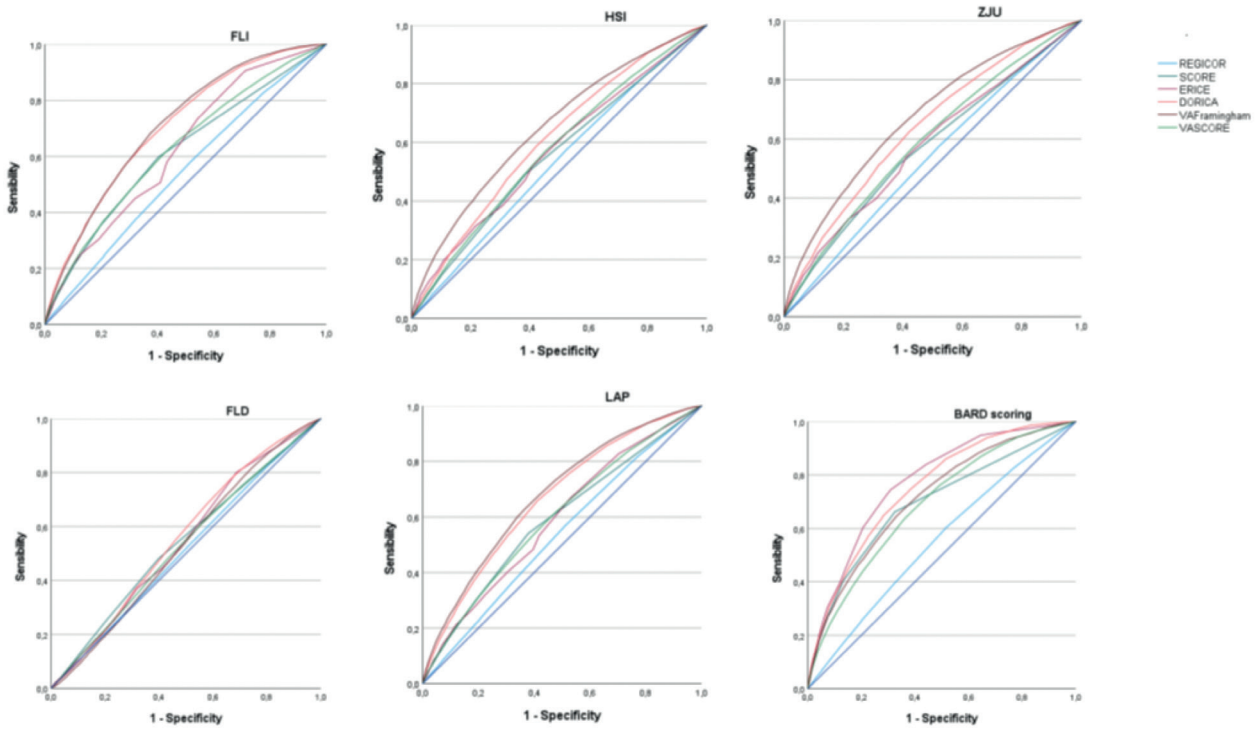

Table V: Areas under the curve (ROC curves).

	FLI high AUC (95% CI)	HSI high AUC (95% CI)	ZJU high AUC (95% CI)	FLD high AUC (95% CI)	LAP high AUC (95% CI)	BARD high AUC (95% CI)
REGICOR	0.541 (0.537-0.545)	0.531 (0.527-0.534)	0.534 (0.530-0.537)	0.511 (0.508-0.515)	0.536 (0.533-0.539)	0.554 (0.551-0.557)
SCORE	0.613 (0.609-0.617)	0.556 (0.553-0.560)	0.572 (0.568-0.575)	0.541 (0.538-0.545)	0.588 (0.585-0.592)	0.695 (0.692-0.698)
ERICE	0.625 (0.622-0.629)	0.571 (0.567-0.574)	0.579 (0.575-0.582)	0.545 (0.542-0.549)	0.590 (0.587-0.593)	0.774 (0.772-0.777)
DORICA	0.704 (0.701-0.707)	0.610 (0.607-0.613)	0.637 (0.634-0.640)	0.558 (0.555-0.561)	0.665 (0.662-0.668)	0.752 (0.749-0.755)
ALLY VA Framingham	0.709 (0.706-0.712)	0.651 (0.648-0.654)	0.674 (0.671-0.677)	0.530 (0.527-0.533)	0.678 (0.675-0.681)	0.715 (0.712-0.718)
ALLY VA SCORE	0.626 (0.623-0.630)	0.574 (0.571-0.578)	0.592 (0.589-0.596)	0.529 (0.526-0.533)	0.596 (0.593-0.599)	0.691 (0.688-0.694)

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Discussion

In our study, the mean values and the prevalence of high values for all the NAFLD and liver fibrosis risk scales analyzed increase as the cardiovascular risk scales increase.

Multivariate analysis showed that the variable that most increased the risk of presenting elevated values of the different non-alcoholic fatty liver disease and liver fibrosis risk scales was the DORICA scale followed by vascular age with the Framingham model. The areas under the curve of all the cardiovascular risk scales show low values that only in some cases exceed 70%.

We have not found studies like ours that assess the relationship between NAFLD and liver fibrosis risk scales with cardiovascular risk scales but there is abundant literature showing the relationship between NAFLD and cardiovascular disease.

A review by Targher et al[20] concluded that there is increasing evidence that NAFLD is strongly associated with an increased risk of severe cardiovascular disease such as cardiomyopathy, cardiac valvular calcifications, and arrhythmias, independent of traditional cardiovascular risk factors.

A subsequent review by Kasper et al[21] also obtained similar results, indicating that increasing evidence suggests that individuals with NAFLD are at increased risk of developing hypertension, coronary artery disease, cardiomyopathy and cardiac arrhythmias, which will lead to increased cardiovascular morbidity and mortality.

A review by Caussy et al[22] provided evidence that NAFLD could be considered an independent risk factor for cardiovascular disease based on its relationship with diabetes mellitus. People with diabetes and NAFLD were found to have a higher risk of cardiovascular disease than diabetics without NAFLD, suggesting a possible synergistic effect of both conditions on cardiovascular risk. This synergy could be explained because both entities share several pathophysiological pathways.

Strengths and limitations

The strengths of the study include the large sample size, more than 200,000 individuals, and the large number of NAFLD and liver fibrosis risk and cardiovascular risk scales used. The main limitation is that no objective diagnostic techniques for NAFLD or liver fibrosis other than the risk scales were used.

Conclusions

Taking into account the results obtained in our study, we can conclude that in this Spanish working population there is a direct relationship between the values of the different NAFLD and liver fibrosis risk scales and the values of the cardiovascular risk scales. The power of the cardiovascular risk scales to predict the presence of elevated values of the different NAFLD and liver fibrosis scales is low and only in some cases moderate.

Conflict of Interest

The authors declare that no competing interests exist.

References

1. Zelman S. The liver in obesity. AMA Arch Intern Med. 1952 Aug;90(2):141-56. doi: 10.1001/archinte.1952.00240080007002.

2. Ludwig J, Viggiano TR, McGill DB, Oh BJ. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. Mayo Clin Proc. 1980 Jul;55(7):434-8.

3. Le MH, Yeo YH, Li X, Li J, Zou B, Wu Y, et al. 2019 Global NAFLD Prevalence: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2022 Dec;20(12):2809-2817.e28. doi: 10.1016/j.cgh.2021.12.002.

4. Younossi ZM, Paik JM, Al Shabeeb R, Golabi P, Younossi I, Henry L. Are there outcome differences between NAFLD and metabolic-associated fatty liver disease? Hepatology. 2022 Nov;76(5):1423-1437. doi: 10.1002/hep.32499.

5. Yi M, Peng W, Feng X, Teng F, Tang Y, Kong Q, et al. Extrahepatic morbidities and mortality of NAFLD: an umbrella review of meta-analyses. Aliment Pharmacol Ther. 2022 Oct;56(7):1119-1130. doi: 10.1111/apt.17165.

6. Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol. 2006 Nov 2;6:33. doi: 10.1186/1471-230X-6-33.

7. Wang C, Cai Z, Deng X, Li H, Zhao Z, Guo C, et al. Association of Hepatic Steatosis Index and Fatty Liver Index with Carotid Atherosclerosis in Type 2 Diabetes. Int J Med Sci. 2021 Jul 23;18(14):3280-3289. doi: 10.7150/ijms.62010.

8. Li L, You W, Ren W. The ZJU index is a powerful index for identifying NAFLD in the general Chinese population. Acta Diabetol. 2017 Oct;54(10):905-911. doi: 10.1007/s00592-017-1024-8.

9. Lee I, Cho J, Park J, Kang H. Association of hand-grip strength and non-alcoholic fatty liver disease index in older adults. J Exerc Nutrition Biochem. 2018 Dec 31;22(4):62-68. doi: 10.20463/jenb.2018.0031.

10. Long MT, Pedley A, Colantonio LD, Massaro JM, Hoffmann U, Muntner P, et al. Development and Validation of the Framingham Steatosis Index to Identify Persons With Hepatic Steatosis. Clin Gastroenterol Hepatol. 2016 Aug;14(8):1172-1180.e2. doi: 10.1016/j.cgh.2016.03.034.

11. Sheng G, Lu S, Xie Q, Peng N, Kuang M, Zou Y. The usefulness of obesity and lipid-related indices to predict the presence of Non-alcoholic fatty liver disease. Lipids Health Dis. 2021 Oct 10;20(1):134. doi: 10.1186/s12944-021-01561-2.

12. Xiao G, Zhu S, Xiao X, Yan L, Yang J, Wu G. Comparison of laboratory tests, ultrasound, or magnetic resonance elastography to detect fibrosis in patients with nonalcoholic fatty liver disease: A meta-analysis. Hepatology. 2017 Nov;66(5):1486-1501. doi: 10.1002/hep.29302.

13. Jané BA, Ramírez-Manent JI, Bote SA, Sbert PR, González San Miguel HM, Lopez González ÁA. Determination of cardiovascular risk in 192,711 underweight and normal weight workers. Turk J Med Sci. 2022 Aug;52(4):926-933. doi: 10.55730/1300-0144.5392.

14. Rubín-García M, Vitelli-Storelli F, Toledo E, Castro-Barquero S, Tresserra-Rimbau A, Martínez-González MÁ, et al. Polyphenol intake and cardiovascular risk in the PREDIMED-Plus trial. A comparison of different risk equations. Rev Esp Cardiol (Engl Ed). 2022 May;75(5):401-411. doi: 10.1016/j.rec.2021.06.013.

15. Cinza Sanjurjo S, Prieto Díaz MÁ, Llisterri Caro JL, Barquilla García A, Rodríguez Padial L, Vidal Pérez R, et al. Prevalencia de obesidad y comorbilidad cardiovascular asociada en los pacientes incluidos en el estudio IBERICAN. Semergen. 2019 Jul-Aug;45(5):311-322. doi: 10.1016/j.semerg.2018.11.003.

16. Mohebbi V, Aramayo A, Morales J. Determination of scales related to cardiovascular risk and fatty liver in 5.370 Spanish farmers. Academic Journal of Health Sciences 2021;36 (2):26-33. doi: 10.3306/AJHS.2021.36.02.26

17. Cuende JI. Vascular Age Versus Cardiovascular Risk: Clarifying Concepts. Rev Esp Cardiol (Engl Ed). 2016 Mar;69(3):243-6. doi: 10.1016/j.rec.2015.10.019.

18. Cuende JI. Vascular Age, RR, ALLY, RALLY and Vascular Speed, Based on SCORE: Relations Between New Concepts of Cardiovascular Prevention. Rev Esp Cardiol (Engl Ed). 2018 May;71(5):399-400. English, Spanish. doi: 10.1016/j.rec.2017.02.043.

19. Domingo-Salvany A, Bacigalupe A, Carrasco JM, Espelt A, Ferrando J, Borrell C, et al. Propuestas de clase social neoweberiana y neomarxista a partir de la Clasificación Nacional de Ocupaciones 2011. Gac Sanit. 2013 May-Jun;27(3):263-72. doi: 10.1016/j.gaceta.2012.12.009.

20. Targher G, Byrne CD, Tilg H. NAFLD and increased risk of cardiovascular disease: clinical associations, pathophysiological mechanisms and pharmacological implications. Gut. 2020 Sep;69(9):1691-1705. doi: 10.1136/gutjnl-2020-320622.

21. Kasper P, Martin A, Lang S, Kütting F, Goeser T, Demir M, et al. NAFLD and cardiovascular diseases: a clinical review. Clin Res Cardiol. 2021 Jul;110(7):921-937. doi: 10.1007/s00392-020-01709-7.

22. Caussy C, Aubin A, Loomba R. The Relationship Between Type 2 Diabetes, NAFLD, and Cardiovascular Risk. Curr Diab Rep. 2021 Mar 19;21(5):15. doi: 10.1007/s11892-021-01383-7.

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ORIGINAL

Prevalence of sacroiliac joint dysfunction in patients with chronic low back pain

Prevalencia de disfunción de la articulación sacroilíaca en pacientes con dolor lumbar crónico

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Abstract

Background: Sacroiliac joint dysfunction (SIJD) is generally occurring in the event of pain in the sacroiliac region in the form of abnormal movement in this region. therefore, the aim of the present study was to determine the prevalence of SIJD in LBP patients.
Methods: The present study was performed on SIJD patients. A total of 190 patients were included in the present study using convenience sampling method. eligible patients that referred to specialized clinics and offices of orthopedic and neurosurgery physicians were identified and the study objectives were explained to them. After obtaining the patients' consent, the necessary diagnostic tests were performed to evaluate SIJ-related problems. They were then statistically evaluated if they had this syndrome. The data was analyzed using the SPSS16.
Results: Results showed that out of 190 LBP patients, 82 (43.2%) had SIJ and 108 (56.8%) did not have such syndrome. Table I showed the demographic characteristics of patients with and without SIJ. The results showed no statistically significant difference between all demographic characteristics of patients (except for gender, employment and physical activity status). Also, the amount of pain in standing is equal to 74 (38.9), in walking is equal to 129 (67.9) and in climbing stairs is equal to 83 (43.7), in getting out of a car is equal to 113 (59.5%) and in the state of rising from a chair was also equal to 78 (41.1%).
Conclusions: Due to the high prevalence of the joint in SIJD patients, it is suggested to perform therapeutic interventions and rehabilitation in these patients.

Key words: Sacroiliac joint dysfunction, Chronic low back pain, Pain.

Resumen

Antecedentes: La disfunción de la articulación sacroilíaca (DISAS) suele producirse si hay dolor en la región sacroilíaca manifestándose como movimientos anormales en esta región.El objetivo del presente estudio es determinar la prevalencia de la disfunción de la articulación sacroilíaca en pacientes con dolor lumbar.
Métodos: El presente estudio se realizó en pacientes con DISAS. Se identificó a los pacientes elegibles que acudieron a clínicas especializadas y consultas de médicos traumatólogos y neurocirujanos y se les explicaron los objetivos del estudio. Tras obtener el consentimiento de los pacientes, se realizaron las pruebas diagnósticas necesarias para evaluar los problemas relacionados con la articulación sacroilíaca. A continuación, se evaluó estadísticamente si presentaban este síndrome. Los datos se analizaron con el programa SPSS 16.0.
Resultados: Los resultados mostraron que de 190 pacientes con dolor lumbar, 82 (43,2%) tenían DISAS y 108 (56,8%) no tenían dicho síndrome. La tabla I mostró las características demográficas de los pacientes con y sin DISAS. Los resultados no mostraron diferencias estadísticamente significativas entre todas las características demográficas de los pacientes (excepto el sexo, el empleo y el estado de actividad física). Además, la cantidad de personas con dolor al estar de pie fue de 74 (38,9%), al caminar 129 (67,9%), al subir escaleras 83 (43,7%), al salir de un coche113 (59,5%) y en el estado de levantarse de una silla también era igual a 78 (41,1%).
Conclusiones: Debido a la alta prevalencia de DISAS, se sugiere realizar intervenciones terapéuticas y de rehabilitación en estos pacientes.

Palabras clave: Disfunción de la articulación sacroilíaca, Lumbalgia crónica, Dolor.

Background

The sacroiliac joint (SIJ) is the largest axial joint in the body with an average surface area of about 17.5 cm, which supports the upper body when walking or standing and is not very mobile[1,2]. There are currently no specific computed tomography findings for the diagnosis of sacroiliac joint dysfunction (SIJD) and degenerative findings are common in asymptomatic people[3]. SIJ is supported by a network of muscles that help deliver regional muscular forces to the pelvic bones. So that some of these muscles are functionally attached to the SIJ ligaments and their function can affect joint mobility. Age-related changes in the SIJ begin during puberty and continue throughout life. These changes are accelerated in the third and fourth decades of life and may manifest themselves with superficial irregularities up to and including joint limitations[4,5].

SIJ is responsible for transferring and distributing distributed loads to the lower limbs, facilitating labor, limiting limb rotation, and providing stability with little movement[4]. SIJD is generally occurs in the event of pain in the sacroiliac region in the form of abnormal movement in this region. SIJD symptoms include low-back pain (LBP), leg sciatica pain, thigh or hip pain, transient numbness, or foot burning[6-8]. SIJD is one of the causes of chronic pain that may often not be diagnosed properly, so, it is estimated that SIJD accounts for about 15-30% of chronic LBP, which is due to the prevalence of chronic LBP, this number is a very important statistic[4,9].

One of the major challenges of the health system is chronic pain, which is very complex and has severe symptoms and complications. In fact, experiencing pain is an unpleasant experience that can affect other aspects of life[10-13]. Considering the pain overlapping in different parts of the body, physicians may mistakenly diagnose SIJ pain in other parts of the body and design the related treatment accordingly. Therefore, identifying SIJ pain is so important[14]. This pain is significantly more common in SIJD patients, but complete statistics and information are not available in this regard. One of these types of pain is LBP pain. LBP plays a major role in the burden of social diseases and years lived with disability (YLD). LBP is the main cause of retirement and can lead to changes in the patient's lifestyle, mental health disorders and obesity by causing economic losses as well as reducing the quality of life[15,16].

Objectives

SIJ-related problems are very important and it is necessary to pay attention to this group of people. On the other hand, problems related to patients' pain are among the priorities of the medical staff. Therefore, the aim of the present study was to determine the prevalence of SIJD in LBP patients.

Methods

Participants and Design

The present study was performed on SIJD patients in Ilam. A total of 190 patients were included in the present study using convenience sampling method.

Inclusion and Exclusion criteria

Inclusion criteria included participants aged between 18 and 65 years, consent to participate in the study and at least 3 months of chronic LBP according to the opinion of a specialist and clinical examinations. Exclusion criteria also included disc herniation, structural anomaly, history of surgery or tumor in the lumbar region, pregnant women, traumatic L.B.P, disc herniation, history of advanced and professional exercise for at least six months, joint degenerative disorders, history of chronic diseases affecting pain (including cancer, polyneuropathy, diabetes, osteoporosis and other related diseases), inability or lack of cooperation when performing clinical examinations and diagnostic tests, osteoporosis, pelvic or spinal fractures.

SIJD diagnosis method

Specific Gillet test, supine to sit test, compression test, sitting flexion test, (FABER) patrice test, distraction test, Gaenslen's test and Yeoman's test were used to determine the SIJ involvement[16-18]. Since the result of one test is not sufficient to diagnose SIJ-related problems, therefore, several diagnostic tests were used and if the result of three tests was positive, SIJD was confirmed[18-22]. To investigate the pain states, we used questions that were raised Telli et al.'s study. These included five questions in the field of pain-causing states, which were answered using Yes-No format[23].

Study method

Eligible patients that referred to specialized clinics and offices of orthopedic and neurosurgery physicians were identified and the study objectives were explained to them. After obtaining the patients' consent, the necessary diagnostic tests were performed to evaluate SIJ-related problems. They were then statistically evaluated if they had this syndrome. Patients were assured that their information would be kept confidential and that their cooperation or non-cooperation would not affect provision of the desired services and the necessary medical services will be provided to them in the best possible way.

Data analysis

The data was analyzed using the SPSS16.

Results

Results showed that out of 190 LBP patients, 82 (43.2%) had SIJ and 108 (56.8%) did not have such syndrome.

Table I showed the demographic characteristics of patients with and without SIJ. The results showed no statistically significant difference between all demographic characteristics of patients (except for gender, employment and physical activity status).

Results showed, the amount of pain in standing is equal to 74 (38.9), in walking is equal to 129 (67.9) and in climbing stairs is equal to 83 (43.7), in getting out of a car is equal to 113 (59.5%) and in the state of rising from a chair was also equal to 78 (41.1%).

Also, although level of pain was different in SIJD and non-SIJD patients in most items, this level was not statistically significant. However, this difference was statistically significant in the case of Item "getting out of a car", and pain level was higher in SIJD patients than other patients (p = 0.000) (**Table II**).

Table I: Comparison of Demographic Data Between SJD and No SJD.

-		No N (%)	No SJD	SJD	P-value
Sex	Male Female	93(48.9) 97(51.1)	66(61.1) 42(38.9)	27(32.9) 55(67.1)	0.000
Occupation	Yes No	22(11.6) 168(88.4)	18(16.7) 90(83.3)	4(4.9) 78(95.1)	0.012
Marital status	Marital status Single	104(54.7) 86(45.3)	59(54.6) 49(45.4)	45(54.9) 37(45.1)	0.97
Activity	Yes No	58(30.5) 132(69.5)	39(36.1) 69(63.9)	19(23.2) 63(76.8)	0.055
Education level	Reading and writing Diploma University	51(26.8) 118(62.1) 21(11.1)	29(26.9) 66(61.1) 13(12)	22(26.8) 52(63.4) 8(9.8)	0.797
Age					

Table II: Comparison of Pain Characteristics Between SJD and No SJD Groups.

-			No	No SJD	SJD
Pain on	**Prolonged standing**	Yes No	74(38.9) 116(61.1)	38(35.2) 70(64.8)	36(43.9) 46(56.1)
	Getting out of a car	Yes No	113(59.5) 77(40.5)	52(48.1) 56(51.9)	61(74.4) 21(25.6)
	Walking some distance	Yes No	129(67.9) 61(32.1)	72(66.7) 36(33.3)	57(69.5) 25(30.5)
	Climbing stairs	Yes No	83(43.7) 107(56.3)	45(41.7) 63(58.3)	38(46.3) 44(53.7)
	Rising from a chair	Yes No	78(41.1) 112(58.9)	35(32.4) 73(67.6)	43(52.4) 39(47.6)

Discussion

Result showed, out of 190 LBP patients, 82 (43.2%) had SIJD and 108 (56.8%) did not have SIJD. In previous studies, Ramirez et al. showed that the SIJD prevalence was 40% among 136 LBP patients in Brazil[24]. Wieczorek et al. also observed SIJD prevalence in 51 patients (60.7%)[25]. Similarly, Rawat et al. reported that was 13.3% of LBP patients had SIJD[26]. Other studies also investigated the prevalence of SIJD in different study populations. The SIJD prevalence was also reported to be was 30% among Indian students in a study by Sivakumar et al.[27]. Madani et al. also reported that SIJD prevalence was 72.3% among patients with lumbar disc hernia (LDH) in Tehran, Iran[20], which are consistent with the results of the present study, which confirm the significant prevalence of SIJD in patients.

Results of comparing demographic characteristics of patients with and without SIJD showed that no significant difference between the two groups of patients in terms of all demographic variables except for gender, occupation and physical activity. In fact, the employment rate of SIJD patients was reported to be 4.9% compared to patients without SIJD (16.7%). The daily physical activity of SIJD patients was much lower than that of patients without SIJD, which is consistent with the results of a study by Dehghan Manshadi et al. in Hamedan, Iran where the level of physical activity was 24% and 50% in the SIJD and non-SIJD groups, respectively[28].

According to the findings, the prevalence of SIJD was higher in women than men. Various studies have investigated the SIJD status in LBP patients and other patients. Wieczorek et al. showed that the LBP prevalence was higher in women (67.2%) than men[25]. Telli et al.[23] also showed that the SIJD prevalence was 63.2% among women, which is consistent with the results of the present study. Other relevant studies have investigated the relationship between the SIJD prevalence and

gender. For example, Telli et al.[23] investigated that the SIJD prevalence among LDH women and showed that SIJD affects 75.6. % of them, while the same prevalence was 57.1% in the non-SIJD group (P<0.005). Sivakumar et al. also investigated the SIJD prevalence among 590 students and found that the prevalence of this disorder in female students (n=347, 59%) was higher than male students (n=243, 41%)[27].

Conclusions

Due to the high prevalence of the joint in SIJD patients, it is suggested to perform therapeutic interventions and rehabilitation in these patients.

Conflict of Interests

No conflict of interest.

Ethical Approval

R.MEDILAM.REC.1401

References

1. Lee S, Kim S, Lee S: European spine journal: official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society. Eur Spine J 2007, 16(3)):431-7.

2. Tonosu J, Oka H, Watanabe K, Abe H, Higashikawa A, Kawai T, Yamada K, Nakarai H, Tanaka S, Matsudaira K: Characteristics of the spinopelvic parameters of patients with sacroiliac joint pain. Scientific Reports 2021, 11(1):1-5.

3. Eno J-JT, Boone CR, Bellino MJ, Bishop JA: The prevalence of sacroiliac joint degeneration in asymptomatic adults. JBJS 2015, 97(11):932-6.

4. Cohen SP: Sacroiliac joint pain: a comprehensive review of anatomy, diagnosis, and treatment. Anesthesia & Analgesia 2005, 101(5):1440-53.

5. Joukar A, Elgafy H, Agarwal AK, Duhon B, Goel VK: The Sacroiliac Joint: A Review of Anatomy, Biomechanics, Diagnosis, and Treatment Including Clinical and Biomechanical Studies (In Vitro and In Silico). Handbook of Spine Technology 2021:349-74.

6. Cohen SP, Benzon HT: Pain originating from the buttock: sacroiliac joint syndrome and piriformis syndrome. In: Essentials of Pain Medicine. edn.: Elsevier Inc.; 2011: 330-9.

7. Hayden JA, Van Tulder MW, Tomlinson G: Systematic review: strategies for using exercise therapy to improve outcomes in chronic low back pain. Annals of internal medicine 2005, 142(9):776-85.

8. Arslan A, Ahmad A, Muhammad SB, Asghar M: Prevalence of Sacroiliac Joint Dysfunction Among Females In Lahore: A Cross Sectional Study. Pakistan Journal of Physical Therapy (PJPT) 2021.

9. Chopp JN, Fischer SL, Dickerson CR: The specificity of fatiguing protocols affects scapular orientation: Implications for subacromial impingement. Clinical Biomechanics 2011, 26(1):40-5.

10. Hatefi M, KomLakh K: Investigation of the effect of Duloxetine on pain status of patients with spinal cord injuries: A systematic review of drug therapy. Eurasian Chemical Communications 2022, 4(3):256-62.

11. Hatefi M, Komlakh K, Nouri L: Investigating the effect of methylprednisolone pulse on the treatment of back pain. Romanian Journal of, 125(2):264.

12. Komlakh K, Karbasfrushan A: The effect of Pregabalin on the pain status of patients with disc and spinal surgeries: A systematic review of drug therapy. EURASIAN CHEMICAL COMMUNICATIONS 2022, 4(11):1147-55.

13. Vasigh A, Tarjoman A, Borji M: The effect of spiritual-religious interventions on patients' pain status: systematic review. Anaesthesia, Pain & Intensive Care 2018, 22(4).

14. Deer TR, Rupp A, Budwany R, Bovinet CJ, Chatas JW, Pyles ST, Azeem N, Li S, Naidu R, Antony A: Pain relief salvage with a novel minimally invasive posterior sacroiliac joint fusion device in patients with previously implanted pain devices and therapies. Journal of Pain Research 2021, 14:2709.

15. Peck J, Urits I, Peoples S, Foster L, Malla A, Berger AA, Cornett EM, Kassem H, Herman J, Kaye AD: A comprehensive review of over the counter treatment for chronic low back pain. Pain and Therapy 2021, 10(1):69-80.

16. Vickers NJ: Animal communication: when i'm calling you, will you answer too? Current biology 2017, 27(14):R713-R715.

17. Ribeiro RP, Guerrero FG, Camargo EN, Pivotto LR, Aimi MA, Loss JF, Candotti CT: Construct validity and reliability of tests for sacroiliac dysfunction: standing flexion test (STFT) and sitting flexion test (SIFT). Journal of Osteopathic Medicine 2021, 121(11):849-56.

18. Laslett M, Young SB, Aprill CN, McDonald B: Diagnosing painful sacroiliac joints: A validity study of a McKenzie evaluation and sacroiliac provocation tests. Australian Journal of Physiotherapy 2003, 49(2):89-97.

19. Young S, Aprill C, Laslett M: Correlation of clinical examination characteristics with three sources of chronic low back pain. The spine journal 2003, 3(6):460-5.

20. Rezaeian ZS, Alifard F, Goodarzi Z, Karimi A, Asghari-Jafarabadi M: Prevalence of sacroiliac dysfunction among patients with Low back pain referring to hospitals in Isfahan (a pilot study). Journal of Research in Rehabilitation Sciences 2008, 4(1).

21. McKenzie R, May S: The lumbar spine: mechanical diagnosis and therapy, vol. 1: Orthopedic Physical Therapy; 2003.

22. Madani SP, Dadian M, Firouznia K, Alalawi S: Sacroiliac joint dysfunction in patients with herniated lumbar disc: a cross-sectional study. Journal of back and musculoskeletal rehabilitation 2013, 26(3):273-9.

23. Telli H, Hüner B, Kuru Ö: Determination of the prevalence from clinical diagnosis of sacroiliac joint dysfunction in patients with lumbar disc hernia and an evaluation of the effect of this combination on pain and quality of life. Spine 2020, 45(8):549.

24. Ramirez C, Sanchez L, Oliveira B: Prevalence of sacroiliac joint dysfunction and sacroiliac pain provocation tests in people with low back pain. Annals of Physical and Rehabilitation Medicine 2018, 61:e152.

25. Wieczorek A, Campau E, Pionk E, Gabriel-Champine ME, Ríos-Bedoya CF: A Closer Look into the Association between the Sacroiliac Joint and Low Back Pain. Spartan Medical Research Journal 2021, 6(1).

26. Dr.Sudhir Kumar Rawat DAV, Dr.Arvind Kumar, Dr Munir Upadhyay, Dr Amit Patel, Dr Mikir Soni, Dr Jainish Patel. A STUDY OF PREVALENCE OF SACROILIAC JOINT DISEASE IN CHRONIC IDIOPATHIC LOW BACK PAIN PATIENTS.International Journal of Advanced Research (2016), Volume 4, Issue 2, 1471-7. In.

27. Sivakumar S, Kamalakannan M, Arun B, Kalpana A, Prakash J, Pradeep KV: Prevalence of sacroiliac joint dysfunction in college students. Biomedicine 2021, 41(2):293-6.

28. Dehghan Manshadi F, Haj-valie G, Heydari Moghadam R, Khademi Kalantar K, Yavari kia A, Karami M: The relationship between anterior knee pain and dysfunction of the sacroiliac joint. Journal of Ergonomics 2015, 3(1):10-6.

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ORIGINAL

Hyperbilirubinemia is a predictor of appendiceal perforation in children: A meta-analysis

La hiperbilirrubinemia es un factor predictivo de perforación apendicular en niños: Un metaanálisis

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Abstract

Objective: In this meta-analysis, our goal was to examine the diagnostic utility of bilirubin in identifying complicated from uncomplicated pediatric appendicitis.

Materials and methods: Using the databases Embase, PubMed, Scopus, and Cochrane, we carried out a thorough literature search up to 2022. Studies comparing complicated appendicitis (CA) and simple appendicitis (SA) in terms of hyperbilirubinemia in the pediatric population were included.

Results: A total of 5 studies with 2740 acute appendicitis patients (1097 complicated appendicitis and 1643 simple appendicitis) were included in this meta-analysis. Five studies have discussed the diagnostic value of total bilirubin (TB). When compared to simple appendicitis, complicated appendicitis had a significantly higher TB count (I^2=94%), (WMD=0.18, 95% CI -0.00 to 0.37; P=0.05), DB count (I^2=0%), (WMD=0.11, 95% CI 0.04 to 0.18; P=0.002), and IB count (I^2= not applicable), (WMD=0.04, 95% CI 0.01 to 0.07; P=0.02).

Conclusions: In conclusion, in this meta-analysis, total bilirubin, direct bilirubin, and indirect bilirubin values were higher in complicated appendicitis compared to simple appendicitis. Both total bilirubin and direct bilirubin can be used as diagnostic parameters in childhood appendicitis to differentiate complicated appendicitis from simple appendicitis.

Key words: Appendicitis, children, direct hyperbilirubinemia, hyperbilirubinemia.

Resumen

Objetivo: En este metanálisis, nuestro objetivo fue examinar la utilidad diagnóstica de la bilirrubina para identificar la apendicitis pediátrica complicada frente a la no complicada.

Materiales y métodos: Utilizando las bases de datos Embase, PubMed, Scopus y Cochrane, realizamos una búsqueda bibliográfica exhaustiva hasta 2022. Se incluyeron estudios que compararan apendicitis complicada (AC) y apendicitis simple (AS) en términos de hiperbilirrubinemia en la población pediátrica.

Resultados: Se incluyeron en este metanálisis un total de 5 estudios con 2740 pacientes con apendicitis aguda (1097 complicada y 1643 simple). Cinco estudios han discutido el valor diagnóstico de la bilirrubina total (TB). En comparación con la apendicitis simple, la apendicitis complicada tuvo un recuento de TB significativamente mayor (I^2=94 %), (DMP=0,18, IC del 95 %: -0,00 a 0,37; P=0,05), recuento de DB (I^2=0 %), (DMP = 0,11, IC del 95 %: 0,04 a 0,18; P = 0,002) y recuento de BI (I^2 = no aplicable), (DMP = 0,04, IC del 95 %: 0,01 a 0,07; P = 0,02).

Conclusiones: Tanto la bilirrubina total como la directa pueden usarse como parámetros de diagnóstico en la apendicitis infantil para diferenciar la apendicitis complicada de la apendicitis simple.

Palabras clave: Apendicitis, niños, hiperbilirrubinemia directa, hiperbilirrubinemia.

Introduction

One of the most typical causes of acute abdomen is acute appendicitis[1]. This disease has a perforation risk of up to 20% and a lifetime incidence of about 7%[1,2]. Early diagnosis can occasionally be difficult, despite the well-known classical signs and clinical features of acute appendicitis. Acute appendicitis is primarily diagnosed based on clinical symptoms, with radiological examinations being reserved for specific patients. A perforation, which can be linked to considerable morbidity and even fatality, may occur if acute appendicitis is not diagnosed at an early stage[3,4].

The Alvarado score and the RIPASA score are only two of the several screening and scoring instruments that have been developed to help in the diagnosis of acute appendicitis[1]. However, scoring methods like these have come under fire for lacking sensitivity and specificity as well as failing to foretell the severity of acute appendicitis. In addition, a number of blood tests are utilized to gauge the severity of appendicitis. However, a raised WBC count has no prognostic utility in identifying uncomplicated appendicitis from complicated appendicitis[1-4]. Blood cells (WBC) counts are typically elevated in patients with appendicitis. Many researchers are still interested in finding a method or marker that can predict the diagnosis of acute appendicitis and distinguish between uncomplicated and severe appendicitis with good sensitivity and specificity[5-7]. A straightforward, affordable, and easily calculable measure of subclinical inflammation is bilirubin. Although elevated blood bilirubin has been found to be a possible indicator of appendix perforation, its sensitivity and specificity are insufficient[8-10].

In this meta-analysis, our goal was to examine the diagnostic utility of bilirubin in identifying complicated from uncomplicated pediatric appendicitis.

Materials and Methods

Search Strategy

Using the databases Embase, PubMed, Scopus, and Cochrane, we carried out a thorough literature search up to 2022. Appendicitis, pediatric appendicitis, perforated appendicitis, gangrenous appendicitis, hyperbilirubinemia, direct bilirubin, elevated bilirubin, and children were the search phrases used. Furthermore, we searched also "simple appendicitis, complicated appendicitis, un-complicated appendicitis, non-complicated appendicitis, pediatric appendicitis, appendicitis in children, hyperbilirubinemia in appendicitis, serum bilirubin, laboratory marker for appendicitis". References and reviews were searched manually for further relevance.

Study Selection

Studies comparing complicated appendicitis (CA) and simple appendicitis (SA) in the pediatric population were included.

Inclusion criteria:[1] clinical studies comparing CA and SA, and[2] raw data including some of the following: total bilirubin, direct bilirubin, and indirect bilirubin.
Exclusion criteria:[1] no comparative case series as a control;[2] studies could not provide usable raw data or duplicate publications.

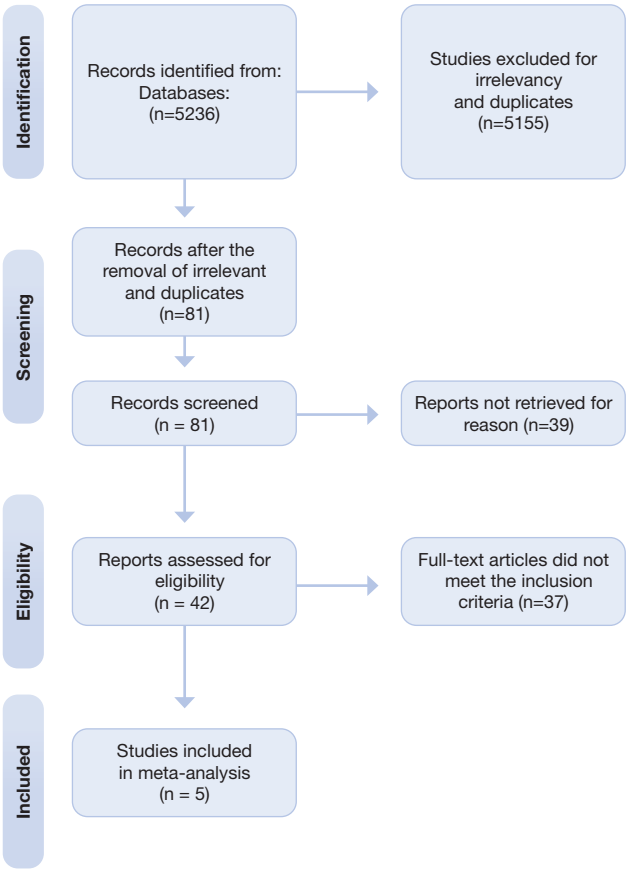
Data Extraction

Two authors independently reviewed the included studies (SA and MA). We extracted information on sample size, study design, and year of publication. Population data were obtained, including the type of appendicitis, and bilirubin values.

Risk of Bias Assessment

The risk of bias in the included studies was evaluated using the ROBINS-I (Risk Of Bias in Non-randomized Studies—of Interventions) method. The reviewers also evaluated the overall risk of bias across all studies for each relevant outcome and considered that information when making decisions about the "quality of evidence."

Table I: PRISMA flow diagram of study selection.



Statistical Analysis

For the statistical data analysis, Review Manager (RevMan) software version 5.4 was used. Both continuous and dichotomous variables were evaluated using measured mean differences and risk ratios. The I^2 statistic was employed to quantify the amount of statistical heterogeneity, and the Chi-square test was utilized to determine it. Significance was set at $P \leq 0.05$. We applied a random effect model.

Reporting

PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analysis) was used to report the findings of this systematic review.

Results

Using a PRISMA flow diagram, **table I** presents an overview of the selection procedure of 42 studies identified during the initial search strategy were retrieved for full-text review, and 5 studies[8,9,10,11,12] with 2740 acute appendicitis patients (1097 complicated appendicitis and 1643 simple appendicitis) who met the inclusion criteria were selected.

Risk of Bias

Table II provides a summary of the ROBINS-I tool's risk of bias evaluation. A "moderate" risk of bias existed in three articles with regard to "Bias due to confounding." Given their retrospective character, all studies had a "moderate" risk of bias in the other categories.

Table II: Risk of Bias (ROBINS-I Tool).

Author	Year	Bias due to confounding	Bias for other domains
Chen et al.	2021	**Moderate:** Age under 3 years	Moderate
Güngör et al.	2021	**Moderate:** Age difference between groups	Moderate
Koirala et al.	2022	**Moderate:** Difference of number by gender	Moderate
Noh et al.	2012	**Moderate:** Age difference between groups	Moderate
Yang et al.	2019	**Moderate:** Age difference between groups	Moderate

Figure 1: The value of total bilirubin.

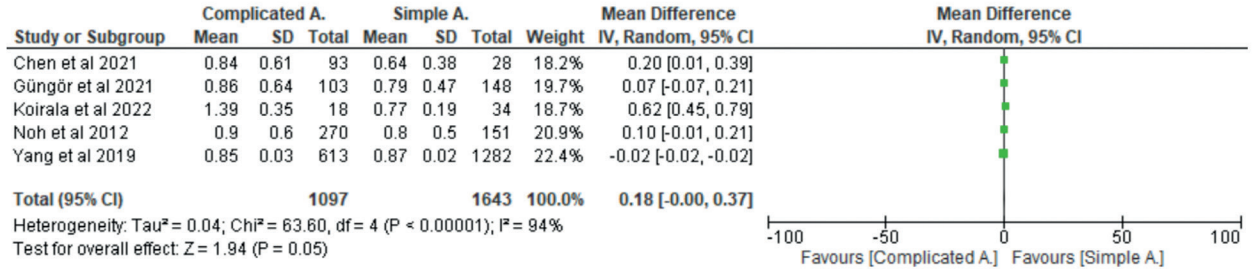


Figure 2: The value of direct bilirubin.

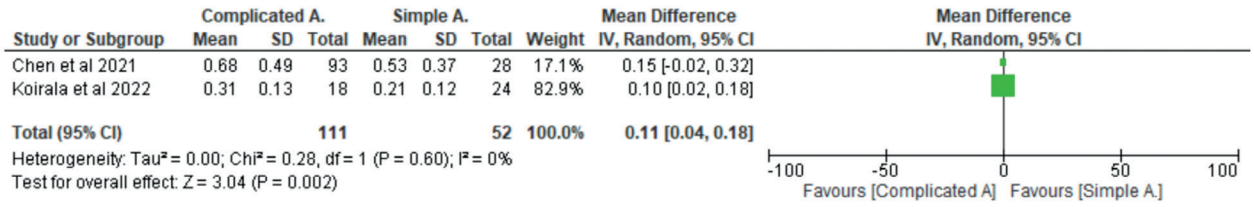
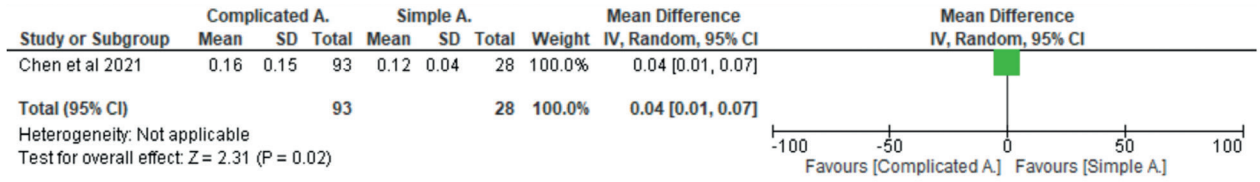


Figure 3: The value of indirect bilirubin.



Outcomes
A total of 5 studies were included in this meta-analysis. All of these studies were retrospective comparative studies To be used to distinguish complicated appendicitis from simple appendicitis; 5 studies evaluating total bilirubin, 2 direct bilirubin, and 1 study of indirect bilirubin were included in this meta-analysis.

Total bilirubin
Five studies have discussed the diagnostic value of total bilirubin (TB). When compared to simple appendicitis, complicated appendicitis had a significantly higher TB count (I^2=94%), (WMD=0.18, 95% CI -0.00 to 0.37; P=0.05; **Figure 1**).

Direct Bilirubin
Although three studies documented the diagnostic value of direct bilirubin (DB), only two studies (111 patients in CA group and 52 patients in SA group) were suitable for meta-analysis. However, the CA group had a significantly higher DB when compared to SA group (I^2=0%), (WMD=0.11, 95% CI 0.04 to 0.18; P=0.002; **Figure 2**).

Indirect Bilirubin
Only 1 study (93 patients in CA group and 28 patients in SA group) was suitable for meta-analysis investigating the effects of indirect bilirubin (IB). It is found that CA group had a significantly higher IB when compared to the SA group (I^2= not applicable), (WMD=0.04, 95% CI 0.01 to 0.07; P=0.02; **Figure 3**).

Discussion

Since all studies included in this meta-analysis had a moderate risk of bias, no studies were excluded due to bias.

In many previous studies, the effects and results of laboratory blood parameters on the differential diagnosis, diagnostic features, treatment, and complications of simple appendicitis and complicated appendicitis were examined[11,12]. Especially in recent years, relative parameters such as neutrophil-lymphocyte ratio and platelet-lymphocyte ratio have come to the fore[13-16].

The main goal of this study is to establish whether or not hyperbilirubinemia is a valid indicator of appendiceal perforation. The meta-analysis of previous studies emphasized that hyperbilirubinemia can be used to predict perforated appendicitis in adult patients[17]. There are studies suggesting that hyperbilirubinemia in children can be used in the differential diagnosis of complicated appendicitis and acute appendicitis, as in adults[10-12]. But there is no meta-analysis on this subject. However, this meta-analysis is the first meta-analysis suggesting that hyperbilirubinemia (both total, indirect and direct) can be used in the differential diagnosis of complicated and simple appendicitis in the pediatric population.

According to the study by Koirala et al., it shows that both direct and total bilirubin can be used in the differential diagnosis of complicated and simple appendicitis[8]. Similar results were found in the study by Chen et al. In the study by Chen et al., the mean of direct bilirubin in the complicated appendicitis group was almost twice that of appendicitis in the simple appendicitis group[9]. On the other hand, according to a study conducted by Güngör et al. in 2021, the mean total bilirubin in the complicated appendicitis group was almost twice as high as the total bilirubin in the simple appendicitis group[12]. It is noteworthy that the number of patients in this study is considerably higher than in equivalent studies. However, as a result, when complicated appendicitis and simple appendicitis were compared in our study, total bilirubin (p=0.05), direct bilirubin (p=0.002), and indirect bilirubin (p=0.02) values were higher in the complicated appendicitis group.

Conclusions

In conclusion, in this meta-analysis, total bilirubin, direct bilirubin, and indirect bilirubin values were higher in complicated appendicitis compared to simple appendicitis. Both total bilirubin and direct bilirubin can be used as diagnostic parameters in childhood appendicitis to differentiate complicated appendicitis from simple appendicitis.

Conflict of interest
The authors declare no conflict of interest

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References

1. Krzyzak M, Mulrooney SM. Acute Appendicitis Review: Background, Epidemiology, Diagnosis, and Treatment. Cureus. 2020 Jun 11;12(6):e8562.

2. Risteski T, Sokolova R, Memeti S, Simeonov R. Laparoscopic versus open appendectomy in pediatric patients: Operative and postoperative experience. J Clin Tri Exp Invest. 2022;1(2):49-55.

3. Basuguy E, Okur MH, Arslan S, Aydoğdu B, Akdeniz S, Azizoğlu M. Çocuklarda torakoport yardımlı laparoskopik apendektomi sonuçlarımız. Dicle Med J. 2020;47(3):727-34.

4. Falchi D, Bakır AC, Risteski T, Abu Tziam H, Yüksel S, Inal Azizoğlu S. Diagnostic Value of The Ischemia Modified Albumin and Pentraxin 3 In Pediatric Appendicitis: A Meta Analysis. J Clin Tri Exp Invest. 2022;1(1):1-9.

5. Oztan MO, Aksoy Gokmen A, Ozdemir T, Müderris T, Kaya S, Koyluoglu G. Pentraxin-3: A strong novel biochemical marker for appendicitis in children. Am J Emerg Med. 2019;37(10):1912-16.

6. Arslan S, Aydogdu B, Arslan MS, Zeytun H, Okur MH, Basuguy E, et al. Analysis of Risk Factors for Appendicitis in Children: A Multicenter Epidemiological Study. Dicle Med J. 2016;43(4):556-60.

7. Halaseh SA, Kostalas M, Kopec C, Nimer A. Bilirubin as a Predictor of Complicated Appendicitis in a District General Hospital: A Retrospective Analysis. Cureus. 2022;14(9):e29036.

8. Koirala DP, Gupta AK, Dahal GR, Shrestha BM, Shrestha S, Neupane S, et al. Role of hyperbilirubinaemia as a predictor of complicated appendicitis in paediatric population. Afr J Paediatr Surg. 2022;19:61-4.

9. Chen Y, Wang Z, Xiao D, Zeng H, Ma X. Predicting the Severity of Acute Appendicitis of Young Children (<3 Years Old): Development and Assessment of a New Prediction Nomogram. Front Pediatr. 2021;9:763125.

10. Yang J, Liu C, He Y, Cai Z. Laboratory Markers in the Prediction of Acute Perforated Appendicitis in Children. Emerg Med Int. 2019;2019:4608053.

11. Noh H, Chang SJ, Han A. The diagnostic values of preoperative laboratory markers in children with complicated appendicitis. J Korean Surg Soc. 2012;83(4):237-41

12. Güngör A, Göktuğ A, Güneylioğlu MM, Yaradılmış RM, Bodur I, Öztürk B, et al. Utility of biomarkers in predicting complicated appendicitis: can immature granulocyte percentage and C-reactive protein be used? Postgrad Med. 2021;133(7):817-21.

13. Catal O, Ozer B, Sit M, Erkol H. Is appendectomy a simple surgical procedure? Cir Cir. 2021;89(3):303-8

14. Ozdemir H, Sunamak O. Comparison of the non-absorbable polymer clips, knot-tying, and loop ligature appendiceal stump closure methods in laparoscopic appendectomy. Cir Cir. 2022;90(2):193-6.

15. Esquivel-Esquivel N, Horta-Baas G. Neutrophil-to-lymphocyte ratio in the diagnosis of acute appendicitis. Assessment of its diagnostic accuracy. Arch Argent Pediatr. 2022;120(5):317-24.

16. Ayeni A, Mahmood F, Mustafa A, Mcleish B, Kulkarni V, Singhal S, et al. Predicting the Severity of Acute Appendicitis in Children Using Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR). Cureus. 2022;14(8):e28619.

17. Gavriilidis P, de'Angelis N, Evans J, Di Saverio S, Kang P. Hyperbilirubinemia as a Predictor of Appendiceal Perforation: A Systematic Review and Diagnostic Test Meta-Analysis. J Clin Med Res. 2019;11(3):171-8.

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ORIGINAL

Cáncer y vacunas. Presente y futuro

Cancer and vaccines. Present and future

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Resumen

Introducción: En el último siglo, las vacunas han sido la herramienta sanitaria más eficaz en salud pública para reducir la mortalidad y morbilidad de las enfermedades infecciosas. En la prevención y tratamiento del cáncer, la tendencia actual se orienta hacia un tratamiento personalizado en el que se incluyen las vacunas junto con otros tratamientos novedosos, como la inmunoterapia.
Metodología: Se realiza una revisión bibliográfica, en diciembre de 2022, en las bases de datos de PubMed/Medline, de artículos científicos publicados en línea hasta la fecha, sin acotar periodo de búsqueda, utilizando como palabras clave y términos MeSH: *cancer and vaccines; Cancer and therapeutic vaccines; colorectal cancer, Skin cáncer, Breast cancer, Prostate cancer, Kidney cancer, Lung cancer; Cancer and preventive vaccines HPV, Hepatitis B.*
Resultados: Los resultados obtenidos en la búsqueda con el concepto genérico (cáncer y vacunas) y, de forma concreta, los relacionados con la utilización terapéutica de las vacunas en cáncer, casi duplican los referidos al uso preventivo. Destacan las referencias a cáncer de pulmón, de piel y de mama y, en uso preventivo, las de virus del papiloma y hepatitis B.
Conclusión: El desarrollo de vacunas para el tratamiento del cáncer es un reto, ya que la intervención vacunal debe combatir un sistema inmunitario que ha sido restringido por mecanismos que sostienen la respuesta inmunitaria y frenado por los que mantienen la enfermedad en un intento de autotolerancia. Los resultados en curso de este tipo de vacunas son prometedores.

Palabras clave: cáncer, vacunas terapéuticas, vacunas preventivas, inmunoterapia.

Abstract

Introduction. In the last century, vaccines have been the most effective public health tool to reduce mortality and morbidity from infectious diseases. In cancer prevention and treatment, the current trend is towards personalized treatment, including vaccines along with other novel treatments such as immunotherapy.
Methodology. A literature review was carried out in December 2022 in the PubMed/Medline databases of scientific articles published online to date, without limiting the search period, using the following keywords and MeSH terms: *cancer and vaccines; Cancer and therapeutic vaccines; colorectal cancer, Skin cancer, Breast cancer, Prostate cancer, Kidney cancer, Lung cancer; Cancer and preventive vaccines HPV, Hepatitis B.*
Results. The results obtained in the search with the generic concept (cancer and vaccines) and, specifically, those related to the therapeutic use of vaccines in cancer almost double those referring to preventive use. The references to lung, skin and breast cancer and, in preventive use, those for papillomavirus and hepatitis B stand out.
Conclusion. The development of vaccines for cancer treatment is challenging, as vaccine intervention must combat an immune system that has been constrained by mechanisms that sustain the immune response and held back by those that maintain the disease in an attempt at self-tolerance. The expected future results of such vaccines are promising.

Keywords: cancer, prophylactic cancer vaccine, therapeutic cancer vaccine, immunotherapy.

Introducción

En el último siglo, las vacunas han sido la herramienta sanitaria más eficaz en salud pública para reducir la mortalidad y morbilidad de las enfermedades infecciosas. Sin embargo, muchas enfermedades aún no pueden prevenirse mediante vacunación, dejando un campo abierto a la investigación. En algunas patologías, los ensayos clínicos y las nuevas tecnologías abren nuevas posibilidades para hacer frente, como medidas preventivas o terapéuticas, a más enfermedades en el siglo XXI, con el desarrollo de vacunas, ya sea como adyuvantes, vectores, vacunas de ácidos nucléicos o diseño de antígenos[1].

En el campo del tratamiento del cáncer, la tendencia actual en las actuaciones sanitarias se orienta de forma creciente hacia un tratamiento personalizado, en el que se incluyen las vacunas. Las dificultades asociadas a la falta de potencia y amplitud antigénica se reducen con el uso de la nanotecnología biomimética, que permitirá superar estos obstáculos dentro de una perspectiva de medicina personalizada[2].

Metodología

Se realiza una búsqueda, en diciembre de 2022, en las bases de datos de PubMed/Medline, de artículos científicos publicados en línea hasta la fecha de la búsqueda sin acotar periodo de tiempo, utilizando como palabras clave y términos MeSH los que se muestran en la tabla.

Se seleccionaron 46 artículos originales, revisiones sistemáticas y artículos de revisión relacionados con la vacunación preventiva y terapéutica en cáncer. Se excluyeron estudios con información no relevante, comentando 27 de estos artículos por su mayor interés para los autores, todos ellos de los últimos 5 años (**Tabla I**).

Tabla I: Resultados de la búsqueda bibliográfica.

Descriptor de búsqueda	Resultados obtenidos
Cancer and vaccines	68.516 resultados
Cancer and preventive vaccines	23.292 resultados
Cancer and therapeutic vaccines	48.988 resultados
Colorectal cancer and therapeutic vaccines	1.753 resultados
Skin cancer and therapeutic vaccines	2.431 resultados
Breast cancer and therapeutic vaccines	2.384 resultados
Prostate cancer and therapeutic vaccines	1.867 resultados
Kidney cancer and therapeutic vaccines	1.060 resultados
Lung cancer and therapeutic vaccines	3.019 resultados
HPV and cancer and preventive vaccines	7.910 resultados
Hepatitis B and cancer and preventive vaccines	1.329 resultados

Fuente: https://pubmed.ncbi.nlm.nih.gov/ Fecha de búsqueda 13/12/2022

Resultados

Son cuantiosos los resultados obtenidos en la búsqueda de la bibliografía científica con el concepto genérico (cáncer y vacunas) y, de forma concreta, los relacionados con la utilización terapéutica de las vacunas en cáncer casi duplican los referidos al uso preventivo. En cuanto al tipo de cáncer, destacan los que relacionan el uso terapéutico de las vacunas con el cáncer de pulmón, el de piel y el de mama. En el uso preventivo de las vacunas en cáncer destacan las publicaciones referidas al virus del papiloma humano y su relación con el cáncer de cuello uterino.

Artículos comentados

El objetivo de las vacunas contra el cáncer es dirigir el sistema inmunitario para facilitar la erradicación de las células cancerosas. Los recientes avances tecnológicos han puesto de manifiesto una nueva biología que puede ayudar a lograr un mejor conocimiento en la selección y administración de antígenos y en el seguimiento de las respuestas humanas tras la vacunación permitiendo, de este modo, enfoques más agresivos y novedosos[3].

Las vacunas contra el cáncer se pueden dividir en dos tipos: preventivas o terapéuticas.

- Las **vacunas preventivas** disponibles comercialmente bloquean la infección de los agentes causantes del virus del papiloma humano, el virus de la hepatitis B o el virus de Epstein-Barr y se dirigen a la prevención del cáncer de cuello de útero[4], cáncer de ano tanto en mujeres como en hombres[5-6], el cáncer de hígado[7] y el cáncer nasofaríngeo y gástrico[8].

- Las **vacunas terapéuticas** para el tratamiento del cáncer se basan en su capacidad para estimular la respuesta del sistema inmunitario a las células cancerosas, que suele ser baja. Este grupo de vacunas son de reciente aparición y muchas de ellas se encuentran en fase experimental. Es el caso de los ensayos clínicos en vacunas terapéuticas contra el cáncer de mama, pulmón, colon, piel, riñón y próstata, entre otros[9].

Nos centraremos en estas últimas por las opciones de presente y futuro que plantean de curación o cronificación de la enfermedad y, con ello, la posibilidad de retorno al trabajo y recuperación de las actividades de la vida diaria perdidas durante la enfermedad. Son estos aspectos de especial relevancia en salud laboral.

Las vacunas terapéuticas contra el cáncer han supuesto un avance en la inmunoterapia contra esta enfermedad y comparten el objetivo de crear y amplificar las respuestas de células T específicas del tumor, pero aún quedan obstáculos importantes que resaltar

Se han investigado numerosas estrategias para superar los mecanismos inmunosupresores del microambiente tumoral (TME) y contrarrestar el escape del tumor. En un esfuerzo por amplificar las respuestas de células T específicas de tumores, se utiliza cada vez más una

estrategia heteróloga de administración de antígenos de inducción y refuerzo para las vacunas basadas en virus. Los sistemas de nanopartículas se han mostrado prometedores como vectores de suministro de vacunas contra el cáncer en la investigación preclínica. T-win es otra plataforma dirigida tanto a las células tumorales como al TME, que utiliza vacunas basadas en péptidos que se involucran y activan las células T para atacar las moléculas inmunorreguladoras expresadas en las células inmunosupresoras y malignas. Actualmente están surgiendo algoritmos para la selección de neoantígenos y para seleccionar objetivos terapéuticamente relevantes para desarrollar terapias personalizadas. En conjunto, el campo de las vacunas terapéuticas contra el cáncer está evolucionando rápidamente, con la promesa de una posible sinergia con las inmunoterapias existentes para el tratamiento del cáncer a largo plazo[10].

En las vacunas terapéuticas contra el cáncer se trata tanto de actuar frente a los tumores existentes como de prevenir su reaparición. Predominantemente, la investigación se ha orientado hacia el contexto metastásico, basándose en una inmunoterapia activa en la que el sistema inmunitario humano pueda activarse para reconocer y destruir las células tumorales. Dada las dificultades que supone este escenario, se plantea dirigir los estudios a tumores clínicamente más accesibles, llegar a un consenso sobre los criterios de valoración biológicos más importantes y probar la capacidad de las vacunas para alcanzarlos para, finalmente, ampliar el conocimiento sobre cómo manipular el sistema inmunitario más allá de la estimulación inicial que proporciona una vacuna, comparando los resultados de distintos estudios[11].

El sistema inmunitario de los pacientes con cáncer metastásico está considerablemente comprometido, tanto por la inmunosupresión mediada por el tumor, como por el tratamiento. Aun cuando la enfermedad residual es mínima, las vacunas dirigidas contra antígenos asociados al tumor no logran erradicarlo en la inmensa mayoría de los casos.

La investigación en animales en relación con uso preventivo de vacunas en la fase más temprana posible de la carcinogénesis ha demostrado ser más eficaz para provocar una respuesta inmunitaria antitumoral con mejora en la supervivencia. Esto puede ser de utilidad en algunos cánceres humanos, como el adenocarcinoma de próstata y el cáncer de cuello de útero, que pueden detectarse en fases muy tempranas y para los que se dispone de vacunas terapéuticas, abriendo la posibilidad de administrarlas precozmente a pacientes diagnosticados de lesiones premalignas para detener la progresión de la enfermedad. La capacidad de inmunizar a los pacientes en las fases más tempranas de la carcinogénesis, cuando sus sistemas inmunitarios son plenamente competentes, puede provocar un cambio de paradigma en la forma de probar y utilizar clínicamente estas vacunas terapéuticas contra el cáncer[12].

Durante los últimos 20 años se han identificado varios antígenos asociados a tumores, algunos de los cuales se han utilizado con resultados alentadores como inmunoterapia contra diversos tipos de cáncer. Sin embargo, se ha de tener en consideración que las características de las células tumorales y el estado inmunológico frente al cáncer difieren mucho de un paciente a otro, por lo que el desarrollo de nuevos criterios y biomarcadores fiables para seleccionar a los pacientes y antígenos vacunales adecuados supondrá un gran avance en el desarrollo de vacunas contra el cáncer[13].

De forma general, las vacunas contra el cáncer suelen derivarse de las células tumorales del paciente o de los antígenos que se encuentran en su superficie, lo que puede ayudar al sistema inmunitario a identificar y eliminar estas células malignas. Muchas investigaciones se centran actualmente en el diseño de vacunas con la esperanza de activar el sistema inmunitario para que ataque a las células cancerosas de forma más eficaz, fiable y segura.

Se analizan a continuación con más detalle los resultados encontrados en el análisis bibliográfico en relación con el uso de vacunas terapéuticas en algunos de los tipos de cáncer más prevalentes:

- **El cáncer de mama** se ha convertido en el cáncer más diagnosticado en todo el mundo y su recaída y las metástasis siguen siendo un gran reto a pesar de los avances en quimioterapia, terapia endocrina y terapia dirigida a HER2 en las últimas décadas.

Aunque los avances clínicos en el campo de la terapia del cáncer de mama HER2-positivo han mejorado gracias a la comprensión de los mecanismos de regulación inmunitaria del microentorno tumoral, la resistencia al tratamiento y la recaída de la enfermedad siguen considerándose retos importantes en la práctica clínica. Cada vez hay más informes sobre la inducción de respuestas inmunitarias celulares y humorales en pacientes con cáncer de mama HER2-positivo y se presentan otros enfoques inmunoterapéuticos, como los inhibidores de CTLA-4, los inhibidores del punto de control inmunitario y los anticuerpos anti PD-1/PD-L1[14].

El objetivo de las vacunas contra el cáncer es inducir una respuesta inmunológica duradera para erradicar las células tumorales. Se han evaluado diferentes tipos de vacunas contra el cáncer de mama en ensayos clínicos, pero ninguna ha aportado beneficios significativos. Los estudios más recientes indican la posibilidad de aplicar vacunas en combinación con anticuerpos monoclonales anti-HER2 o el bloqueo de puntos de control inmunitarios[15].

• **El cáncer de pulmón** sigue siendo un reto sanitario. Los tres principales tratamientos convencionales, cirugía, quimioterapia y radioterapia, que se utilizan habitualmente para su tratamiento, no han evitado que siga siendo la principal causa de mortalidad relacionada con el cáncer. La inmunoterapia ha surgido como una terapia eficaz y en la actualidad existe un creciente uso como herramienta terapéutica. Comprender los pasos del reconocimiento inmunitario y la erradicación de las células cancerosas es vital para entender cómo puede utilizarse de forma óptima en las terapias actuales y con buenas perspectivas de futuro[16]. Los ensayos realizados con vacunas neoantígenas ofrecen nuevas oportunidades terapéuticas para el tratamiento del cáncer de pulmón[17].

La combinación de inmunoterapias, como las vacunas contra el cáncer y los inhibidores del punto de control inmunitario, así como la asociación con las tres terapias convencionales, puede allanar el camino hacia la inmunoterapia personalizada[18].

• **El cáncer colorrectal** es una de las principales causas de muerte por cáncer. A pesar de los avances en la terapia sistémica sigue acompañándose de una elevada mortalidad y son necesarios tratamientos más eficaces, especialmente para los pacientes con cáncer colorrectal metastásico. Los datos actuales apoyan el hecho de que los tumores colorrectales son inmunorresponsables y que un subgrupo de pacientes con enfermedad avanzada logrará beneficios a largo plazo con la inmunoterapia[19].

En los últimos años, se han producido avances significativos en las estrategias terapéuticas en este tipo de cáncer, incluida las vacunas, que en algunos casos han sido aprobadas para uso clínico y en otros se encuentran en ensayos clínicos en fase avanzada. En los ensayos clínicos de vacunas contra el cáncer hay varias consideraciones que deben tenerse en cuenta, como la ingeniería de las células presentadoras de antígenos, la toxicidad potencial de las zonas antigénicas, la farmacocinética y farmacodinámica de las vacunas y la monitorización de la respuesta inmunitaria de los pacientes. Por ello, la necesidad de superar los mecanismos de inmunosupresión/tolerancia inmunitaria es un paso crítico para el éxito de la introducción de vacunas terapéuticas y se requiere una mejor comprensión de los neoantígenos, los mecanismos de escape de la vigilancia inmunitaria tumoral y las interacciones huésped-tumor para desarrollar vacunas más eficaces y seguras en el futuro[20].

Los resultados obtenidos con la inmunoterapia en muchos tipos de tumores sólidos avanzados han hecho que cada vez sea mayor su utilización para el tratamiento del cáncer colorrectal como terapia de primera línea del cáncer metastásico y en estadios tempranos[21].

• **El cáncer de próstata** es el cuarto cáncer más frecuente en el mundo y su tratamiento se basa actualmente en la extirpación quirúrgica y/o la radioterapia y/o la hormonoterapia. En los últimos años, la inmunoterapia se ha convertido en una importante opción terapéutica contra el cáncer[22]. Las estrategias combinadas son las más prometedoras. Varios estudios finalizados y otros en curso han demostrado que la combinación de vacunas contra el cáncer o inhibidores de los puntos de control con diferentes agentes inmunoterapéuticos, terapia hormonal, radioterapia, agentes que actúan frente al ADN o quimioterapia, pueden potenciar las respuestas inmunitarias e inducir respuestas clínicas más drásticas y duraderas sin toxicidad significativa. El objetivo de la inmunoterapia en el cáncer de próstata no tiene por qué ser la erradicación completa de la enfermedad avanzada, sino el retorno a un equilibrio inmunológico con un estado indolente de la enfermedad. Actualmente se está trabajando en biomarcadores de la respuesta inmunitaria que abren un futuro esperanzador[23].

El cáncer de próstata es un tumor frío con una respuesta inmunitaria inadecuada al tratamiento. Las vacunas contra el cáncer, las citocinas y los inhibidores de los puntos de control son agentes inmunoterapéuticos que actúan dentro del ciclo de inmunidad del cáncer y el cáncer de próstata ofrece oportunidades y retos únicos para el desarrollo de fármacos inmunoterapéuticos convirtiendo un cáncer de próstata "frío" en "caliente" y haciéndolo así más susceptible a la inmunoterapia[24].

• **El cáncer renal** y particularmente el carcinoma de células renales claras, se ha considerado durante mucho tiempo que es sensible a las inmunoterapias. Con los recientes avances en inmunoterapia para tumores sólidos se espera que las inmunoterapias combinadas se conviertan en la opción de tratamiento de primera línea en el cáncer de riñón[25]. El panorama actual del tratamiento se está desplazando hacia los agentes inmunooncológicos, que ya han ganado terreno en la clínica como monoterapia con los inhibidores del punto de control inmunitario o es probable que lo hagan en un futuro próximo como combinación de ellos. El futuro promete nuevas combinaciones u otros agentes inmunooncológicos, como vacunas e inhibidores metabólicos de puntos de control inmunitario, con resultados beneficiosos[26].

El planteamiento actual de tratamiento del carcinoma renal de células claras es limitado. Los antígenos asociados a tumores, especialmente las vacunas de ARNm personalizadas basadas en neoantígenos, representan nuevas estrategias y manifiestan beneficios clínicos en tumores sólidos, pero sólo una pequeña proporción de pacientes podría beneficiarse de ellas, lo que requiere identificar antígenos eficaces y poblaciones adecuadas para facilitar la aplicación de vacunas de ARNm en la terapia del cáncer. Se han

identificado posibles neoantígenos eficaces para el desarrollo de vacunas de ARNm contra el carcinoma renal de células claras que podrían beneficiar especialmente a algunos subtipos[27].

• Finalmente, en **el cáncer de piel** destaca el aumento de la incidencia de melanoma, pero con disminución de la mortalidad. Un manejo mejorado, que parte del análisis del ganglio centinela, ha permitido reducir la morbilidad asociada mediante una cirugía de estadificación y el tratamiento de la enfermedad avanzada con el uso de terapia dirigida e inmunoterapia de punto de control[28].

En las últimas tres décadas se han llevado a cabo investigaciones sobre vacunas para el tratamiento del **melanoma metastásico** y la prevención de recidivas tras la resección, aunque los resultados obtenidos no han sido esperanzadores. Las vacunas celulares utilizadas pueden dividirse en autólogas, derivadas del propio tumor del paciente, y alogénicas. Las vacunas autólogas tienen la ventaja de contener todos los antígenos asociados al tumor potencialmente relevantes para ese paciente en particular. Sin embargo, son difíciles de obtener de la mayoría de los pacientes con enfermedad avanzada e imposibles de conseguir en pacientes tras la resección de toda la enfermedad clínicamente evidente. No existe consenso sobre cómo deben procesarse, conservarse, modificarse y administrarse los tumores para que sirvan como vacuna eficaz. La cantidad de tumor autólogo disponible rara vez es suficiente para producir más de dos o tres dosis de vacunación, y el tiempo transcurrido entre la extracción inicial del tumor y la disponibilidad final de la vacuna puede dar lugar a una progresión tumoral a intervalos que disminuye la probabilidad de eficacia de la vacuna. Todos estos inconvenientes limitan su aplicabilidad y también la capacidad de probar vacunas autólogas en ensayos prospectivos. Las vacunas alogénicas evitan muchos de estos problemas, pero pueden no contener todos los antígenos asociados al tumor presentes en el propio tumor del paciente. En particular, es poco probable que los neoantígenos creados por mutaciones en el tumor del paciente estén representados en una vacuna alogénica. Aunque las vacunas alogénicas pueden fabricarse en cantidades suficientes para permitir ensayos a gran escala, siguen existiendo importantes limitaciones en la fabricación y estandarización del producto vacunal[29].

Conclusiones

Recogiendo a modo de resumen lo incluido en el documento de revisión de vacunas Europa, 202230 podemos concluir afirmando que, cuando se trata de este tipo de opciones inmunizadoras, hay que considerar dos enfoques principales.

El primero es un enfoque profiláctico, orientado a la prevención de cánceres relacionados con una infección, como el cáncer de hígado consecuencia

Tabla II: Revisión de la cartera de vacunas para Europa-2022.

Tipo de cáncer	Características	Situación vacunal
Glioblastoma	- Tumor cerebral de crecimiento rápido y agresivo que puede provocar la muerte en seis meses o menos, si no se trata. - Incidencia de 3,21 por 100.000 habitantes. - El GBM presenta retos de tratamiento únicos debido a la localización de los tumores en el cerebro. - Aproximadamente un 40% de supervivencia en el primer año tras el diagnóstico y un 17% en el segundo año.	**Vacunas en proyecto: 1** Para: Adultos y adultos mayores Está en Fase II Tipo de Vacuna: Partícula similar al virus
Cáncer de Pulmón, colorrectal, páncreas	**Cáncer de pulmón** - El 2º cáncer más frecuente en todo el mundo - Más de 2,2 millones de nuevos casos de cáncer de pulmón en 2020 **Cáncer colorrectal** - El 3er cáncer más frecuente en todo el mundo - Más de 1,9 millones de nuevos casos de cáncer colorrectal en 2020 **Cáncer de páncreas** - El 12º cáncer más frecuente en todo el mundo - Más de 495.000 nuevos casos de cáncer de páncreas en 2020	**Vacunas en proyecto: 1** Para: Adultos Está en Fase I Tipo de Vacuna: mRNA
Cáncer de piel	- Tipo de cáncer más frecuente. - Los principales tipos de cáncer de piel son el carcinoma de células escamosas, el carcinoma basocelular y el melanoma. La mayoría de las muertes por cáncer de piel están causadas por melanoma. - Más de 150.000 nuevos casos de melanoma en 2020. - 8.100 millones de dólares de coste anual del tratamiento de los cánceres de piel en los Estados Unidos.	**Vacunas en proyecto: 1** Para: Adultos y adultos mayores Está en Fase II Tipo de Vacuna:mRNA
Tumor sólido	- Aproximadamente el 90% de los cánceres humanos adultos. Pueden desarrollarse en muchas partes del cuerpo humano. - Los tumores sólidos pueden ser no cancerosos (benignos), premalignos (células que tienen el potencial para volverse malignas) o malignos (cancerosos).	**Vacunas en proyecto: 2** Para: Adultos y adultos mayores Está en Fase I Tipo de Vacuna: ARNm Subunidad proteica

Fuente: Vaccines Europe pipeline review 2022. Ref[31-36]

de la infección por hepatitis B, los relacionados con la infección por el VPH (virus del papiloma humano) o el virus de Epstein-Barr.

El otro enfoque es curativo. El objetivo de las vacunas terapéuticas contra el cáncer es inducir la regresión tumoral, erradicar la enfermedad residual mínima, establecer una memoria antitumoral duradera y evitar reacciones inespecíficas o adversas.

El desarrollo de vacunas para el tratamiento del cáncer es un reto, ya que la intervención vacunal debe combatir un sistema inmunitario que ha sido restringido por mecanismos que sostienen la respuesta inmunitaria y frenado por los mecanismos que mantienen la enfermedad en un intento de autotolerancia.

Sin embargo, los resultados recientes de los ensayos clínicos en curso de este tipo de vacunas son prometedores.

Actualmente, los miembros de Vaccines Europe tienen en proyecto cinco vacunas contra distintos tipos de cáncer: glioblastoma, cáncer de mama, cáncer de pulmón, cáncer colorrectal, de páncreas y de piel, así como frente tumores sólidos (**Tabla II**).

Se abre así una nueva perspectiva en el abordaje del cáncer, tanto preventiva como curativa, en un marco de medicina personalizada que va a requerir adaptar las actuaciones sanitarias, sociales y laborales en aquellos casos en los que se logre una curación o cronificación del proceso oncológico que permita el retorno al trabajo de las personas que han padecido un cáncer y lo han superado.

Los médicos del ámbito de la salud laboral tendremos que participar activamente en la parte que nos concierne, tanto en la vacunación preventiva, como en la valoración de la aptitud laboral de la persona que retorna al trabajo cuando el resultado de las terapias administradas, entre las que se incluyen las vacunas terapéuticas así lo permitan. El objetivo es conseguir que el desempeño de la actividad laboral sea compatible con las posibles secuelas residuales que hayan podido quedar tras el proceso oncológico o por los tratamientos que se hayan seguido o que se deban mantener por la persona que retorna al trabajo, de forma que no implique riesgos de empeoramiento o recidiva del mismo cáncer o el desarrollo de otras neoplasias.

Conflicto de intereses

Los autores declaran no tener ningún conflicto de inereses.

Bibliografía

1. Delany I, Rappuoli R, De Gregorio E. Vaccines for the 21st century. EMBO Mol Med. 2014 Jun;6(6):708-20.

2. Zhou J, Kroll AV, Holay M, Fang RH, Zhang L. Biomimetic Nanotechnology toward Personalized Vaccines. Adv Mater. 2020 Apr;32(13):e1901255.

3. Sellars MC, Wu CJ, Fritsch EF. Cancer vaccines: Building a bridge over troubled waters. Cell. 2022 Jul 21;185(15):2770-88.

4. Martínez-Gómez X, Curran A, Campins M, Alemany L, Rodrigo-Pendás JÁ, Borruel N, Castellsagué X, Díaz-de-Heredia C, Moraga-Llop FA, Del Pino M, Torné A. Multidisciplinary, evidence-based consensus guidelines for human papillomavirus (HPV) vaccination in high-risk populations, Spain, 2016. Euro Surveill. 2019 Feb;24(7):1700857.

5. Méndez-Martínez R, Rivera-Martínez NE, Crabtree-Ramírez B, Sierra-Madero JG, Caro-Vega Y, Galván SC, de León DC, García-Carrancá A. Multiple human papillomavirus infections are highly prevalent in the anal canal of human immunodeficiency virus-positive men who have sex with men. BMC Infect Dis. 2014 Dec 16;14:671.

6. Cortés J, Gil A, Martinón F, Bosch FX, Ramón y Cajal JM. Vaccination against human papilloma virus in men: situation and proposals". Acad J Health Sci 2022; 37 (3): 166-70.

7. Pattyn J, Hendrickx G, Vorsters A, Van Damme P. Hepatitis B Vaccines. J Infect Dis. 2021 Sep 30;224(12 Suppl 2):S343-S351

8. Shechter O, Sausen DG, Gallo ES, Dahari H, Borenstein R. Epstein-Barr Virus (EBV) Epithelial Associated Malignancies: Exploring Pathologies and Current Treatments. Int J Mol Sci. 2022 Nov 19;23(22):14389.

9. Giarelli E. Cancer vaccines: a new frontier in prevention and treatment. Oncology (Williston Park). 2007 Oct;21(11 Suppl Nurse Ed):11-7; discussion 18.

10. Jou J, Harrington KJ, Zocca MB, Ehrnrooth E, Cohen EEW. The Changing Landscape of Therapeutic Cancer Vaccines-Novel Platforms and Neoantigen Identification. Clin Cancer Res. 2021 Feb 1;27(3):689-703.

11. Morse MA, Chui S, Hobeika A, Lyerly HK, Clay T. Recent developments in therapeutic cancer vaccines. Nat Clin Pract Oncol. 2005 Feb;2(2):108-13.

12. Gray A, Raff AB, Chiriva-Internati M, Chen SY, Kast WM. A paradigm shift in therapeutic vaccination of cancer patients: the need to apply therapeutic vaccination strategies in the preventive setting. Immunol Rev. 2008 Apr;222:316-27.

13. Sasada T, Itoh K. Current status and future perspective of cancer vaccine development. Gan To Kagaku Ryoho. 2011 Apr;38(4):503-8.

14. Arab A, Yazdian-Robati R, Behravan J. HER2-Positive Breast Cancer Immunotherapy: A Focus on Vaccine Development. Arch Immunol Ther Exp (Warsz). 2020 Jan 9;68(1):2.

15. Zhu SY, Yu KD. Breast Cancer Vaccines: Disappointing or Promising? Front Immunol. 2022 Jan 28;13:828386.

16. Steven A, Fisher SA, Robinson BW. Immunotherapy for lung cancer. Respirology. 2016 Jul;21(5):821-33.

17. Ding Z, Li Q, Zhang R, Xie L, Shu Y, Gao S, et al. Personalized neoantigen pulsed dendritic cell vaccine for advanced lung cancer. Signal Transduct Target Ther. 2021 Jan 20;6(1):26.

18. Kinoshita T, Terai H, Yaguchi T. Clinical Efficacy and Future Prospects of Immunotherapy in Lung Cancer. Life (Basel). 2021 Sep 30;11(10):1029.

19. Wrobel P, Ahmed S. Current status of immunotherapy in metastatic colorectal cancer. Int J Colorectal Dis. 2019 Jan;34(1):13-25.

20. Shahnazari M, Samadi P, Pourjafar M, Jalali A. Therapeutic vaccines for colorectal cancer: The progress and future prospect. Int Immunopharmacol. 2020 Nov;88:106944.

21. Fan A, Wang B, Wang X, Nie Y, Fan D, Zhao X, Lu Y. Immunotherapy in colorectal cancer: current achievements and future perspective. Int J Biol Sci. 2021 Sep 3;17(14):3837-49.

22. Silva D, Abreu-Mendes P, Mourato C, Martins D, Cruz R, Mendes F. Prostate cancer, new treatment advances - immunotherapy. Actas Urol Esp (Engl Ed). 2020 Sep;44(7):458-68.

23. Bilusic M, Madan RA, Gulley JL. Immunotherapy of Prostate Cancer: Facts and Hopes. Clin Cancer Res. 2017 Nov 15;23(22):6764-70.

24. Patel D, McKay R, Parsons JK. Immunotherapy for Localized Prostate Cancer: The Next Frontier? Urol Clin North Am. 2020 Nov;47(4):443-56.

25. Hammers H. Immunotherapy in kidney cancer: the past, present, and future. Curr Opin Urol. 2016 Nov;26(6):543-7

26. Bedke J, Stühler V, Stenzl A, Brehmer B. Immunotherapy for kidney cancer: status quo and the future. Curr Opin Urol. 2018 Jan;28(1):8-14.

27. Xu H, Zheng X, Zhang S, Yi X, Zhang T, Wei Q, Li H, Ai J. Tumor antigens and immune subtypes guided mRNA vaccine development for kidney renal clear cell carcinoma. Mol Cancer. 2021 Dec 6;20(1):159.

28. Curti BD, Faries MB. Recent Advances in the Treatment of Melanoma. N Engl J Med. 2021 Jun 10;384(23):2229-40.

29. Sondak VK, Sabel MS, Mulé JJ. Allogeneic and autologous melanoma vaccines: where have we been and where are we going? Clin Cancer Res. 2006 Apr 1;12(7 Pt 2):2337s-2341s.

30. Vaccines Europe pipeline review 2022.Disponible en: https://isanidad.com/wp-content/uploads/2022/12/Vaccines-Europe-pipeline-review-2022-1.pdf

31. American Association of Neurological Surgeons. Glioblastoma multiforme. Disponible en: https://www.aans.org/en/Patients/Neurosurgical-Conditions-and-Treatments/Glioblastoma-Multiforme (consultado el 12 de diciembre de 2022).

32. World Cancer Research Fund International. Cancer trends. Disponible en: https://www.wcrf.org/cancer-trends/ (consultado el 12 de diciembre de 2022).

33. National Cancer Institute. Skin Cancer (Including melanoma) Patent Version. Disponible en: https://www.cancer.gov/types/skin (consultado el 12 de diciembre de 2022).

34. Skin Cancer Foundation. Skin cancer facts & statistics. Disponible: https://www.skincancer.org/skin-cancer-information/skin-cancer-facts/ (consultado el 12 de diciembre de 2022).

35. World Cancer Research Fund International. Skin cancer statistics. Disponible en: https://www.wcrf.org/cancer-trends/skin-cancer-statistics/ (consultado el 12 de diciembre de 2022).

36. Thermo Fisher Scientific. Solid Tumor Research. Disponible en: https://www.thermofisher.com/be/en/home/life-science/cancer-research/solid-tumor-research.html (consultado el 12 de diciembre de 2022).

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ORIGINAL

Multicentric study on the effect of rectal Ozone on COVID-19: the Spanish and Slovakian experience

Estudio multicéntrico sobre el efecto del Ozono rectal en COVID-19: la experiencia española y eslovaca

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Abstract

Objective: To evaluate the effect of rectal Ozone (O_3) in severe COVID-19 pneumonia in two different cohorts differing in location (Madrid vs Zilina), ethnicity (Slovakian vs Spanish cohorts) and age.

Material and Methods: In a multicenter-study, 32 severe bilateral-COVID-19-pneumonia patients and (+) RT-PCR (reverse transcriptase polymerase chain reaction) SARS-CoV-2 were evaluated (16 from each cohort). Primary outcomes: a) clinical (O_2-saturation); b) biochemical (Lymphocyte-count, Fibrinogen, D-Dimer, Urea, Ferritin, LDH [lactate dehydrigenase], IL-6 and CRP [c-reactive protein]); and c) radiological improvement. Secondary outcomes: a) days-of-hospitalization, b) mortality-rate before discharge.The Ozone-protocol consisted of 10 sessions of intra-rectal Ozone, total dose 5.25 mg (150 mL volume, 35 µg/ml concentration). The Standard-of-care protocol included O_2 supply, antivirals (Remdesivir / Isoprinosine), corticosteroids (Dexamethasone / Metilprednisolone), monoclonal antibodies (Anakinra / Tocilizumab), antibiotics (Azytromicine), anticoagulants (Enoxaparine / Fraxiparine).

Results: Patients in Slovakian cohort were younger (53.38 vs 84.69 years). Grade of severity was worse in Spanish-cohort (4.78 vs 3.30 points). Length of stay was superior in Spanish-cohort (27.38 vs 10.07 days). Both cohorts improved O_2-saturation and Lymphocyte-count. Inflammation biomarkers (Fibrinogen, D-Dimer, Urea, Ferritin, LDH, CRP and IL-6) decreased in both cohorts. In Spanish-cohort, Urea and Ferritin improvement was not significant (p>0.05), while in Slovakian-cohort, Urea, Fibrinogen and LDH were not significant (p>0.05) Radiological signs of bilateral pneumonitis decreased on both cohorts. Mortality was similar between both cohorts (12.5%) but inferior if compared to an external control group (23%).

Conclusion: After Standard of care protocol, Rectal Ozone improved O_2-saturation, decreased inflammation biomarkers and improved Taylor's radiological scale in both cohorts. Although age, grade of severity and days of hospitalization were inferior in Slovakian cohort, mortality was similar in both cohorts, but inferior if compared to an external control cohort.

Keywords: Ozone, Ozone therapy, Pneumonia, COVID-19, SARS-CoV-2, Rectal insufflation.

Resumen

Objetivo. Evaluar el efecto del Ozono (O_3) rectal en la neumonía grave por COVID-19 en dos cohortes diferentes en cuanto a localización (Madrid vs Zilina), etnia (cohortes eslovaca vs española) y edad.

Material y métodos: En un estudio multicéntrico, se evaluaron 32 pacientes con neumonía bilateral grave por COVID-19 y (+) RT-PCR (reacción en cadena de la polimerasa con transcriptasa inversa) SARS-CoV-2 (16 de cada cohorte). Resultados primarios: a) clínicos (saturación de O_2); b) bioquímicos (recuento de linfocitos, fibrinógeno, dímero D, urea, ferritina, LDH [deshidrogenasa láctica], IL-6 y PCR [proteína c reactiva]); y c) mejoría radiológica. Resultados secundarios: a) días de hospitalización, b) tasa de mortalidad antes del alta. El protocolo de ozono consistió en 10 sesiones de ozono intra-rectal, dosis total de 5,25 mg (volumen de 150 ml, concentración de 35 µg/ml). El protocolo de cuidados estándar incluyó suministro de O_2, antivirales (Remdesivir / Isoprinosina), corticosteroides (Dexametasona / Metilprednisolona), anticuerpos monoclonales (Anakinra / Tocilizumab), antibióticos (Azitromicina), anticoagulantes (Enoxaparina / Fraxiparina).

Resultados: Los pacientes de la cohorte eslovaca eran más jóvenes (53,38 vs 84,69 años). El grado de gravedad fue peor en la cohorte española (4,78 frente a 3,30 puntos). La duración de la estancia fue superior en la cohorte española (27,38 frente a 10,07 días). Ambas cohortes mejoraron la saturación de O_2 y el recuento de linfocitos. Los biomarcadores de inflamación (fibrinógeno, dímero D, urea, ferritina, LDH, PCR e IL-6) disminuyeron en ambas cohortes. En la cohorte española, la mejoría de la Urea y la Ferritina no fue significativa (p>0,05), mientras que en la cohorte eslovaca, la Urea, el Fibrinógeno y la LDH no fueron significativos (p>0,05) Los signos radiológicos de neumonitis bilateral disminuyeron en ambas cohortes. La mortalidad fue similar en ambas cohortes (12,5%), pero inferior si se compara con un grupo de control externo (23%).

Conclusiones: Tras el protocolo de cuidados estándar, el ozono rectal mejoró la saturación de O_2, disminuyó los biomarcadores de inflamación y mejoró la escala radiológica de Taylor en ambas cohortes. Aunque la edad, el grado de gravedad y los días de hospitalización fueron inferiores en la cohorte eslovaca, la mortalidad fue similar en ambas cohortes, pero inferior si se compara con una cohorte de control externa.

Palabras clave: Ozono, Ozonoterapia, Neumonía, COVID-19, SARS-CoV-2, Insuflación rectal.

Introduction

Since the discovery of a new coronavirus on Wuhan, province of China, by December 2019, this new pandemic due to the new SARS-CoV-2 or COVID-19 virus has hit the economies and Sanitary Health Systems all over the world to an extent that the World Health Organization (WHO) has declared an exceptional situation of pandemic by the 3rd of March 2020[1].

To date, there is no effective treatment for the management of SARS-CoV-2 infection or COVID-19 disease. There are several clinical trials trying to find the most accurate treatment to fight against COVID-19 infection. Unfortunately, there is no evidence from controlled trials to recommend a specific treatment for suspected/confirmed COVID-19 patients[2].

In Spain, the pandemic situation in its first and second waves has saturated the Health System extremely that Material and Human Resources have been reorganized because of the shortage of them[3]; therefore, all medical activity has been focused and directed multidisciplinary to fight against this new pandemic situation. In that scenario, Ozone has been proposed as a complementary treatment to Internal Medicine Staff of our Hospital.

Currently, there are 9 clinical trials (CT) that postulate the potential use of Ozonized Autohemotherapy on the management of COVID-19 disease (1 CT from Brazil, 1 from Turkey, 2 CT from Italy, 2 CT from Spain and 3 CT from China); only 2 CT considers ozonized saline solution (1 CT from Spain and 1 CT from India); and 3 CT (2 CT from Cuba and 1 from India) consider rectal Ozone as an alternative for the management of COVID-19 infection. The studies from Cuba are still in phase of recruiting, and the study from India (Shah et al) has been recently published[4-7].

The Standard-of-care for COVID-19 is only supportive and acute respiratory distress syndrome (ARDS) will cause respiratory failure and finally death in COVID-19 patients. Although most patients will develop mild symptoms (fever, cough, myalgia and dyspnea); a small percentage of patients (15%) will develop a hyper inflammation or "cytokine storm" syndrome[8], and ARDS will constitute the leading cause of mortality, which occurs in 4.9% of patients[2]. Treatment of hyper inflammation will decrease the mortality rate[9]; therefore, we hypothesize that anti-inflammatory drug such as corticosteroids, monoclonal antibodies and even ozone could be recommended at this Stage.

Ozone (O_3) is capable of modulating pain and inflammation and recognized bactericidal, fungicidal, virucidal and anti-parasitic properties are attributed to ozone; a fact that is supported by clinical studies that come from countries where the practice of ozone therapies is well-regulated (Cuba, Italy, Germany, Russia, Turkey, India and Spain)[10,11]. Many water purification plants worldwide use ozone because of its germicidal effect[10]. Because of ozone biological properties, Fernández-Cuadros et al have postulated ozone as an alternative therapy for the management of the present SARS-CoV-2 pandemic[12]. Virucidal, immunomodulatory and vasodilator properties that favor O_2 transport to hypoxemic tissues postulate Ozone as a promising alternative in COVID-19 management[12].

Despite the preventive effect of vaccines on COVID-19 infection, there is no drug with anti-viral, anti-inflammatory and oxigenatory properties all in one as ozone does. Our study group postulated and further demonstrated ozone as a treatment once COVID-19 disease has started and viral spread, inflammation and hypoxia are hallmarks present in COVID-19 patients. In that sense, our Research Group has presented the preliminary results of rectal ozone for the management of mild-severe COVID-19, with very promising results[13,14]. Although our patients treated were older (mean age 83 years), there is no report of a similar study considering the treatment of younger patients, using the same protocol. There is a need to perform a multicenter study to evaluate our protocol in different groups and with different ages, that means in different cohorts, considering location, ethnicity and age, in order to recommend and to confirm the results observed previously in our country.

The objective of this article is to show the updated results of the effectiveness of a rectal ozone (O_3) protocol in a series of COVID-19 patients with severe bilateral pneumonia (Spanish cohort), and to compare them with another cohort of patients treated in another country (Slovakian cohort), in terms of clinical, biochemical and radiological variables. Mortality and Hospitalization time (length of stay) were also compared between cohorts. Cohorts differed on location (Madrid vs Zilina), ethnicity (Slovakian vs Spanish cohorts) and age.

Material and methods

A prospective, before-and-after, multicentric study was performed in 2 Hospitals, one in Hospital Universitario Santa Cristina, Madrid-Spain (16 patients), and another in FNsP Hospital (Faculty Hospital and Poliklinic), Zilina-Slovakia (16 patients). The study included a total of 32 severe COVID-19 patients, with clinical symptoms and RT-PCR (reverse transcriptase polymerase change reaction) positive for SARS-CoV-2. The study run from August 2020 to February 2021. All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki (1975), and the protocol was approved by the Ethics Committee of Santa Cristina University Hospital (15/4/20), by

Ethics Committee for Medical Investigation at Hospital Universitario la Princesa (25-06-20, acta CEIm 14/20, Registry number 4146), and by Zilina's Ethic Comission (17/1/2021). Three Committees authorized the study for ozone treatment for compassionate use in severe COVID-19 pneumonia (**Figure 1**).

Inclusion criteria: 1) patients 18 years and older; 2) with positive result on RT-PCR SARS-CoV-2; 3) with clinical signs of moderate-severe pneumonia (SpO2 <93% or PaO2/FiO2<300 mmHg, or moderate/severe respiratory symptoms); 4) with radiological signs of COVID-19 pneumonia [bilateral "ground glass image" (compatible with lung lesions) on chest X-ray (according to Taylor's scale)] [15]; 5) who required hospitalization due to moderate or severe respiratory symptoms; 6) who required O2-supply with non-mechanical ventilation; 7) whose patient/legal representative gave informed consent to participate in the trial.

Exclusion criteria: 1) Pregnancy or breast feeding; 2) Glucose 6-phosphate dehydrogenase (G6PD) deficiency (favism), rare in Spain; 3) Patients enrolled in other clinical studies. Comorbidities did not constitute a reason for exclusion in this study.

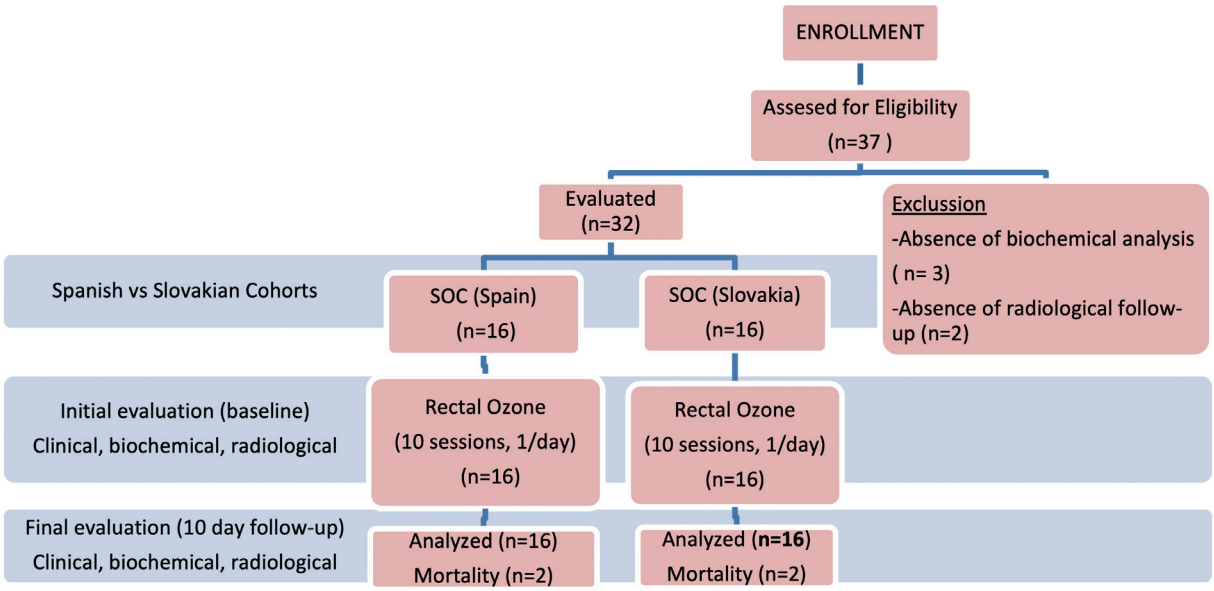
Once Standard-of-care (SOC) was completed (depending of the best available treatment on each country), no further clinical improvement was observed after Standard-of-care, and at this point, physicians considered that Ozone could be prescribed as compassionate use in COVID-19 treatment, the initial biochemical evaluation (leucocyte and lymphocyte count [Mindray BC-6000 kit], Ferritin [Abbott Alinity I kit], D-Dimer [IL ACL TOP 300 CTS kit], Fibrinogen [IL ACL TOP 300 CTS kit], CRP [C-reactive protein, Abbott Alinity c kit] and IL-6 [Snibe Maglumi 1000 kit]) and the initial radiography of the chest were performed. The procedure, indications and contraindications were explained to the patient and/or legal representative, and informed consent was signed prior to patient evaluation and treatment.

The Standard-of-care protocol in Spanish cohort included O_2-supply, antivirals (Remdesivir [200 mg/1day, the first day and 100 mg/day for 4 days]), corticosteroids [Dexamethasone 6 mg/day por 7 days] or Metilprednisolone [40 mg/day for 7 days]), antibiotics (Azytromicine [500 mg/day per 5 days]) and anticoagulants (Enoxaparine [40 mg SC [subcutaneous]/day, all hospitalization period], anti-IL-6 (Tocilizumab 8 mg/kg IV [intravenous] twice with an interval of 12 h, and up to a maximum of 800 mg per dose]) or anti-IL-1 (Anakinra 100 mg, single dose) and hyper immune serum (1 dose) if necessary.

The Standard-of-care protocol In Slovakian cohort included O_2-supply, antivirals (Remdesivir [200 mg IV/1 day, the first day and 100 mg/day for 4 days]; Isoprinosine 500 mg, 2 tablets/3 time/day in the case of lymphocytopenia), corticosteroids [Dexamethasone 8-24 mg IV/ 10-24 days], antibiotics [Azytromicine 500 mg/day for 6 days], anticoagulants [Fraxiparine, 1 dose per day if D Dimer > 1.0, 2 doses per day if D Dimer>2.0], and anti-IL-1 (Anakinra 100 mg, single dose in some cases).

The ozone protocol consisted in administering intra rectally a dose of 5,25 mg of ozone (rectal insufflation of 150 mL of Ozone at a 35 µg/mL concentration for 5 to 10 days), according to the severity of the patients. The supplies needed for ozone insufflation were: a) Ozonosan α-Plus® [Ozone Generator for Spanish cohort], or Ozofutura® [Ozone Generator for Slovakian cohort] ; b) Rectal probe;

Figure 1: Study protocol, enrollment, initial/final evaluation and follow-up in COVID-19 patients including both Spanish and Slovakian cohorts. SOC, Standard of care..



c) three silicone syringes of 50 mL capacity; and d) gel for lubrication of probe.

Prior to ozone administration, the patient was placed in the supine position (sedated patients) or lateral decubitus position (collaborative patients) with the lower limbs flexed. Three 50-mL silicone syringes of ozone were loaded with the corresponding concentration (35 µg/mL), and were slowly injected rectally through a 14 French rectal probe. The probe was previously lubricated with medical gel-type solution. The insufflation rate was of 1 mL / second.

The final evaluation was performed after of ozone protocol was completed. Clinical, biochemical analysis and chest radiographies were evaluated, and any adverse effects were recorded. Mortality and Hospitalization time were compared between both cohorts.

Chest Radiography was used to confirm diagnosis and to grade severity. Taylor Scale for Severe Acute Respiratory Infection grades severity (SARS), ranging from 1 to 5 degrees. Grade 1 is normal. Grade 2 shows patchy atelectasis, hyper inflammation or bronchial wall thickening. Grade 3 denotes focal alveolar consolidation but with no more than one segment or lobe involved. Grade 4 depicts multifocal consolidation and grade 5 shows diffuse alveolar consolidation[15].

For determination of sample size, the a priori power calculation was based on Taylor Scale, with an expected effect size of 0.2 between Groups at 10-days follow-up, a 2-time point of measurement (pretest-posttest evaluation) and a level of significance of 0.05 and a desired power of 0.80; all of which gave us a total sample size estimation of 30 patients. With an expected dropout of 10% during the study, a total of 32 patients were finally calculated (16 patients in each group).

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS®), Illinois, USA version 20.0. Frequencies and percentages were used to evaluate qualitative variables; while for the evaluation of quantitative variables, means/median and standard deviation were used. For evaluation of Taylor's Scale, median and Interquartile range (IQR) were used. The Wilcoxon test was the statistical tool used to evaluate a change before-and-after treatment in quantitative variables. The level of significance was 95% (p <0.05).

Results

This is a multicenter study where two cohorts of 16 patients each who were treated using homogeneous ozone protocol (Total dose 5.25 mg, 150 ml at a 35 µg/ml concentration, every day for up to 10 days.

Demographic Variables

In **table I**, we observe that the Slovakian cohort was younger than the Spanish cohort (53.38 vs 84.69 years, p=0.0001). Regarding COVID-19 severity, using Taylor scale as a radiological grading system, the Spanish cohort was more severe than the Slovakian cohort (4.78 vs 3.30, p=0.0001). No significant differences regarding sex were observed in both cohorts. The Length of Stay (LOS) was superior in the Spanish cohort (27.38 vs 10.07 days, p=0.0038). Number of Ozone sessions was similar in both cohorts (7.5 vs 6.43). No adverse events were observed in both cohorts. Mortality was similar in both cohorts (12.5%, p=0.7642). **Table I**.

Primary Outcomes (clinical, biochemical and radiological variables)

In **table II**, in the Spanish cohort, all variables improved on an overall view. The improvement was significant for Saturation of O_2, Lymphocytes, Fibrinogen, D-Dimer, LDH, CRP, IL-6 and Taylor Scale (p<0.05). On the contrary, the improvement was not significant for Leucocytes, Urea and Ferritin (p>0.05). **Table II**.

In **table III**, in the Slovakian cohort, all variables improved on an overall view. The improvement was significant for Saturation of O_2, Lymphocytes, D-Dimer, Ferritin, CRP, IL-6 and Taylor Scale (p<0.05). On the contrary, the improvement was not significant for Leucocytes, Fibrinogen, Urea and LDH (p>0.05). **Table III**.

In **table IV**, when both the Spanish and the Slovakian cohort were evaluated together, all variables improved on an overall view. The improvement was significant for Saturation of O2, Lymphocytes, Fibrinogen, D-Dimer, CRP, IL-6 and Taylor Scale (p<0.05). On the contrary, the improvement was not significant for Leucocytes, Urea and Ferritin (p>0.05). **Table IV**. **Figures 2** and **3**.

Table I: Demographic and clinical Variables in patients treated in Spain and Slovakia, after rectal Ozone insufflation (n=32).

Variable	Spanish Cohort	Slovakian Cohort	p
Taylor, median [IQR]	4.78 [0.3]	3.30 [0.82]	0,0001**
Age (years) mean ± SD	84,69 ± 12.23	53,38 ± 11.88	0,0001**
Male Sex n (%)	12(75%)	10(62.5%)	0.3342
Female Sex n (%)	4(25%)	6(37.5%)	0.2982
Length of Stay (days) mean ± SD	27,38 ± 15.96	10,07 ± 3.81	0,0038**
Number of Ozone sessions mean ± SD	7.5 ± 2.80	6.43 ± 1.71	0.1187
Adverse events	0	0	1
Mortality (%)	12.5	12.5	0.7642

*, p<0.05. %, percentage. **, p<0.01. IQR, Interquartile range. SD, standard deviation.

Table II: Main Variables in patients treated in Spain, after rectal Ozone insufflation (n=16).

VARIABLES	PRE-O3	POST-O3	P
CLINICAL			
Sat O_2 mean ± SD	89 ± 4.1	94.5 ± 3.4	0.0002**
BIOCHEMICAL			
Leucocytes cells/mL mean ± SD	8602 ± 3676	7823 ± 2568	0.4165
Lymphocytes cells/mL mean ± SD	985 ± 484	1278 ± 583	0.0403*
Fibrinogen mg/dL mean ± SD	713 ± 112	572 ± 163	0.0107*
D-Dimer ng/mL mean ± SD	3240 ± 2484	1343 v 1320	0.0110*
Urea mg/dL mean ± SD	67 ± 41	55 ± 24	0.1089
Ferritin ng/mL mean ± SD	989 ± 799	840 ± 1060	0.6043
LDH U/L mean ± SD	329 ± 111	241 ± 89	0.0209*
CRP mg/mL mean ± SD	8.9 ± 6.1	2.46 ± 3.7	0.0040**
IL6 pg/mL mean ± SD	85.07 ± 50.53	30.48 ± 38.10	0.0048**
RADIOLOGICAL			
Taylor median [IQR]	4.78[0.3]	3.0[0.0]	0.0001**

*, p<0.05. **, p<0.01. Sat O_2, Saturation of Oxygen. LDH, lactate dehydrogenase. CRP, C-reactive protein. IL-6, interleukin 6. . IQR, Interquartile range. SD, standard deviation.

Table III: Main Variables in patients treated in Slovakia, after rectal Ozone insufflation (n=16).

VARIABLES	PRE-O3	POST-O3	P
CLINICAL			
Sat O_2 mean ± SD	86 ± 6.99	94 ± 2.47	0.0001**
BIOCHEMICAL			
Leucocytes cells/mL mean ± SD	9200 ± 4239	8826 ± 1713	0.7763
Lymphocytes cells/mL mean ± SD	1300 ± 564	2473 ± 897	0.0001**
Fibrinogen mg/dL mean ± SD	289 ± 142	271 ± 127	0.4334
D-Dimer ng/mL mean ± SD	1389 ± 1106	622 ± 428	0.0172*
Urea mg/dL mean ± SD	31 ± 12	32± 9	0.6655
Ferritin ng/mL mean ± SD	730 ± 531	415 ± 284	0.0173*
LDH U/L mean ± SD	231 ± 139	202 ± 121	0.0963
CRP mg/mL mean ± SD	19.4 ± 19.4	2.4 ± 3.2	0.0040**
IL-6 pg/mL mean ± SD	51.8 ± 42.8	5.8 ± 6.5	0.0026**
RADIOLOGICAL			
Taylor median [IQR]	3.3 [0.82]	1.9[0.0]	0.0001**

*, p<0.05. **, p<0.01. Sat O_2, Saturation of Oxygen. LDH, lactate dehydrogenase. CRP, C-reactive protein. IL-6, interleukin 6. . IQR, Interquartile range. SD, standard deviation.

Table IV: Main Variables in patients treated in Spain and Slovakia, after rectal Ozone insufflation (n=32).

VARIABLES	PRE-O3	POST-O3	P
CLINICAL			
Saturation O_2 mean ± SD	88.89 ± 4.39	93.92 ± 2.21	0.0001**
BIOCHEMICAL			
Leucocytes cells/mL mean ± SD	88904 ± 3890	83067 ± 2210	0.4551
Lymphocytes cells/mL mean ± SD	11370 ± 538	18537 ± 955	0.0001**
Fibrinogen mg/dL mean ± SD	509 ± 250	427 ± 210	0.0089**
D-Dimer ng/mL mean ± SD	2349 ± 2130	996 ± 1044	0.0011**
Urea mg/dL mean ± SD	50 ± 35	44 ± 22	0.1463
Ferritin ng/mL mean ± SD	864 ± 683	635 ± 804	0.1478
LDH U/L mean ± SD	282,0356	222,3537	0.0052**
CRP mg/mL mean ± SD	14.01 ± 14.88	2.43 ± 3.46	0.0002**
IL-6 pg/mL mean ± SD	69.04 ± 49.09	18.58 ± 29.57	0.0001**
RADIOLOGICAL			
Taylor median [IQR]	4.07[2.0]	2.48[1.0]	0.0001**

*, p<0.05. **, p<0.01. Sat O_2, Saturation of Oxygen. LDH, lactate dehydrogenase. CRP, C-reactive protein. IL-6, interleukin 6. . IQR, Interquartile range. SD, standard deviation.

Figure 2: Biochemical variables in both Spanish and Slovakian Cohort (n=32). *, p<0.05.

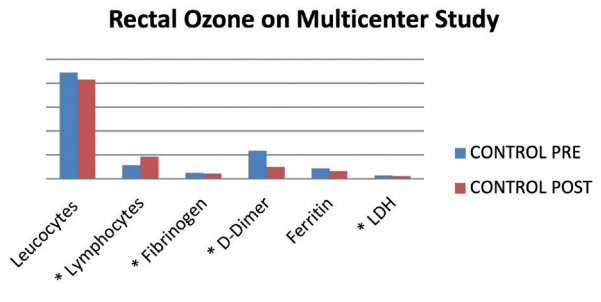
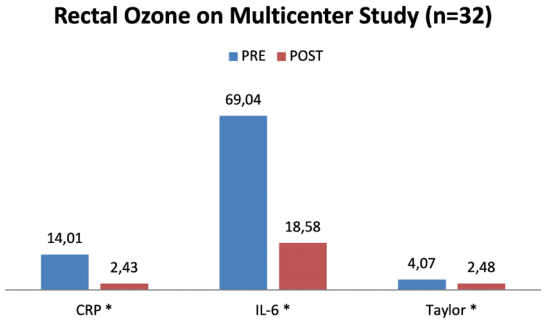
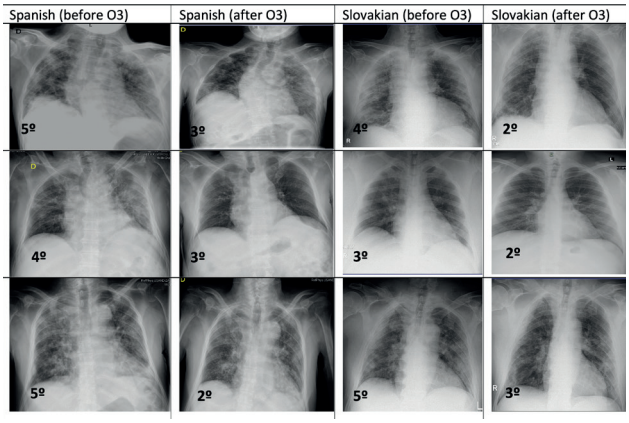


Figure 3: CRP, IL-6 and Radiological Taylor Scale in Spanish and Slovakian cohort. *, p<0.05 (n=32).



We present six cases of radiological improvement based on Taylor Scale, three patients from the Spanish cohort and three patients from the Slovakian cohort (**Figure 4**).

Figure 4: Three cases from Spanish and three cases from Slovakian cohorts are presented before/after Ozone (O_3).



Discussion

To the best of our knowledge, this is the first multicenter study on the effectiveness of Rectal Ozone insufflation protocol in severe COVID-19 pneumonic patients in the light of SARS-CoV-2 pandemic. After Standard of care protocol was prescribed and no further improvement was observed, Rectal ozone improved clinical, biochemical and radiological variables in a significant manner ($p<0.05$) in both Spanish and Slovakian cohorts.

Since no further improvement was observed after standard of care was administered, ozone was prescribed as complementary treatment in both cohorts. Slovakian cohort was younger and radiological pneumonia was not as severe as Spanish cohort, as evaluated by Taylor Scale. This would explain the shorter length of stay in Slovakian cohort.

To date, almost 1661 clinical trials are in course to determine the best treatment for COVID-19 infection, but most of the pharmacological therapies investigated have not demonstrated effectivity in the management of SARS-CoV-2 pandemic[4,16]. From the clinical trials evaluating ozone therapy, only 2 of them have published their results[7,13]. This study presents the use of a homogeneous rectal ozone protocol in two different cohorts of COVID-19 patients regarding location, ethnicity and age, and the effects from one population were reproducible in the other one.

Our study group identified previously four properties that could cope with the complications derived from this COVID-19 infection (anti-viral, anti-oxidant, anti-inflammatory and O_2 delivery enhancer)[12]. In the mentioned study, it is expected that those properties could cope with the complications derived from this COVID-19 infection[12]. Our results confirm that those properties are responsible for the clinical, biochemical and radiological improvement, as stated by some others authors[17-19]. Improvement of O_2 delivery to tissues included the lungs, will be the reason why O_2 saturation improved in such patients. This comes in line with what Menendez-Cepero observed; she mentioned that Ozone is capable of modulating interferons and cytokines, decreasing inflammation biomarkers[20].

Ayanian et al. have identified that high level of at least 5 variables such as D-dimer, CRP, IL-6, Ferritin and LDH which produce negative outcomes in COVID-19 patients (ICU [Intensive Care Unit] admission, intubation and death. Reversely, lower levels of such biomarkers are related with positive outcomes (survival)[21]. Moreover, Lorenz et al. have suggested that severe COVID-19 patients have some characteristics features: neutrophilia, lymphopenia, hypercoagulability (D Dimer elevation) and hyper ferritinemic syndrome[22]. Copaescu has stated that clinical biomarkers (Saturation of Oxygen and respiratory rate) and inflammatory biomarkers (IL-6 and CRP [CRP as a surrogate of IL-6]) may predict severity in COVID-19, and such biomarkers may evaluate response to therapy[23]. Therefore, we intended to demonstrate that ozone was capable of reducing such outcome biomarkers whether clinical (Saturation of Oxygen) or biochemical (D-dimer, CRP, IL-6, Ferritin and LDH).

In a recent review, Cattel has stated that ozone is antiviral and might inactivate the virus and inhibit its viral replication. Moreover, ozone could reduce inflammation and lung damage and ozone might favor immunity and oxygenation, and increase Oxygen saturation and decrease O_2 support. As a consequence, an increase in lymphocyte count, a decrease of inflammation biomarkers (CRP, IL-6, Ferritin, D-Dimer and LDH), an improvement in O_2 saturation and a decrease in O_2 supply; and finally a negativization of RT-PCR SARS-Cov-2 Test is expected after ozone treatment[24]. We have evaluated similar clinical and biochemical variables in both cohorts, the Spanish and the Slovakian, and we did observe such positive effects in both cohorts.

Chirumbolo et al. have stated that ozone produces improvement in COVID-19 patients whatever the method of ozone delivery was used. Major autohemotherapy, ozonized saline solution and even rectal ozone has reduced inflammation in COVID-19 patients[25]. In our study, ozone by rectal insufflation was chosen because the technique is very simple, economic and safe[12].

To date, there are 21 manuscripts that postulate the use of ozone against COVID-19[26]. There are also 21 articles that state the benefit of ozone in treating 682 patients with COVID-19 (patients recruited from China, Spain, Cuba, Italy, Iran, India and USA). Ozone reduces

inflammation; time of ventilatory support and time to normalize (negativize) RT-PCR for SARS-CoV-2[26].

In our study, an improvement in Saturation of Oxygen was observed (Oxygen Saturation from 88.89 to 93.92%). Similarly, in another study, Franzini observed an improvement of 85 to 95% in Oxygen saturation ($p<0.001$)[27]. Araimo observed that ozone reduced the need for ventilatory support in COVID-19 disease[5]. Ozone improves saturation of Oxygen, as observed by Franzini, Araimo and our study[5,27].

In our multicentric study, an improvement in leucocyte count, in biomarkers of inflammation and in biomarkers of coagulation was observed (Fibrinogen, D-Dimer, LDH, CRP and IL-6). Similar results have been observed by Araimo[5], Franzini[27], Tascini[28], Schwartz[29] and Hernández[30], in different cohorts, in Italy and in Spain.

Finally, and improvement in radiological severity based on Taylor scale was observed in our multicentric study, (change in Taylor scale from 4.07 to 2.48 points). This comes in line Schwartz et al., who observed an improvement in lung affection from 60% to 24%; and the improvement, occurred at 3-5 days from ozone treatment[29].

Mortality of an external control cohort regarding similar age and sex in Spain using Standard of care was 21%[14]. The overall mortality in first and second wave in the Community of Madrid was 23% in hospitalized COVID-19 patients[29]. However, when mortality was compared to hospitalized patients treated by ozone, mortality decreased to 12.5% in both Spanish and Slovakian cohorts. These observations would suggest that ozone could decrease mortality in severe COVID-19 pneumonic patients.

Shah et al. and Hendawy et al. have published a case-control study and a case report, respectively; using rectal ozone insufflation. Shah et al. used a protocol of rectal ozone insufflation, 150 ml at a 40 µg/ml concentration, 2 times/day, for up to 10 days[7]. They observed clinical (oxygen saturation and clinical NEWS Score) and biochemical improvement (LDH, CRP, Ferritin), although the improvement was not statistically significant. Moreover, on 10th day of treatment, 100% of patients showed RT-PCR negativity vs 70% in control group ($p=0.01$)[7]. Ozone was superior to negativize SARS-Cov-2 infection[7].

Hendawy et al. reported the use of rectal ozone, one single insufflation, and a total dose of 25.2 mg (2000 ml at a 12.6 µg/ml concentration) in two cases, and an immediate improvement of oxygen saturation from 84% to 94-97% was observed[31]. The observations form both authors (Shah and Hendawy) are similar to ours[7,31]. Rectal ozone insufflation improved oxygen saturation, and decreased both biomarkers of inflammation and coagulation.

Peña-Lora and Fernandez-Cuadros have published another case in which, after 5 session of rectal ozone (100ml, once a day at a 35 µg/ml), oxygen saturation improved from 90% to 94%, biochemical variables ameliorated (IL-6, PCR, D dimer, Fibrinogen and ferritin) and radiological improvement was observed (from 5 to 3 on Taylor Scale)[32].

In the present study, we have used a dose of 35 µg/mL. The dose is similar to the one used in a Cuban protocol directed by Leon-Fernandez et al, which has been lately published[33].

A limitation of this multicentric study is the small sample size analyzed. Moreover, with such a small sample size (32 patients, 16 in each cohort), we cannot speculate why mortality was similar in both cohorts (12.5%). We expected to see some differences since Slovakian cohort was younger than the Spanish cohort. Maybe in a greater sample, these differences would be statistical, and could favor the younger cohort, because there is a linear correlation between age and mortality in COVID-19 patients[12]. We did not take into account comorbidities in these cohorts, and comorbidities might be related to age of population. In any case, the mortality was lower if compared to an external control group (23%). However, despite the number of patients evaluated, the fact that ozone improved all variables analyzed once standard of care was already finished; a larger sample in a new study is needed in order to confirm the effect of rectal ozone insufflation in the management of COVID-19 patients, as it was observed in this manuscript.

Conclusions

In patients with severe COVID-19 pneumonia, after Standard of care protocol was prescribed and no further improvement was observed, rectal Ozone improved O_2 saturation, decreased inflammation biomarkers and improved Taylor's radiological scale with statistical significant difference in both Spanish and Slovakian cohorts. Although age, grade of severity and days of hospitalization were inferior in the Slovakian cohort, mortality was similar between both cohorts, but inferior if compared to an external control group. It is necessary to develop a Randomized Control Trial to confirm these promising observations.

Author contributions

Conceptualization; drafting; investigation, project administration, supervision, writing, review, editing and translation: MEFC. Biochemical Analysis, data-curation and validation: JRDC and JV. Patients' treatment: MEFC, OSPM, MJAF, JV. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement
All patients signed informed consent for treatment and publication.

Ethics approval
This study was approved by Ethics Committee of Hospital Universitario Santa Cristina (15-04-2020), by Hospital Universitario la Princesa (25-06-20, acta CElm 14/20, Registry number 4146), Madrid-Spain; and by Zilina´s Ethic Comission (17/1/2021).

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Conflicts of interest
The authors declare no conflicts of interest.

References

1. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). Crit Care Med. 2020 Jun;48(6):e440-e469. doi: 10.1097/CCM.0000000000004363.

2. Uthman AT, Al-Rawi NN, Othman B, Al-Rawi NH. COVID-19: Unraveling 10 most significant answers about the current pandemic. Journal of International Dental and Medical Research 2021;14(1):394-403.

3. https://www.eldiario.es/sociedad/coronavirus-sobrecarga-sanidad-Comunidad-Madrid_0_1004050083.html. Accessed on 15th Dec 2022.

4. WHO. Coronavirus disease (COVID-2019) situation reports. 2020.

5. Araimo F, Imperiale C, Tordiglione P, Ceccarelli G, Borrazzo C, Alessandri F, et al. Ozone as adjuvant support in the treatment of COVID-19: A preliminary report of probiozovid trial. J Med Virol. 2021 Apr;93(4):2210-2220. doi: 10.1002/jmv.26636.

6. https://rpcec.sld.cu/ensayos/RPCEC00000320-Sp. Accessed on 4th December 2022.

7. Shah M, Captain J, Vaidya V, Kulkarni A, Valsangkar K, Nair PMK, et al. Safety and efficacy of ozone therapy in mild to moderate COVID-19 patients: A phase 1/11 randomized control trial (SEOT study). Int Immunopharmacol. 2021 Feb;91:107301. doi: 10.1016/j.intimp.2020.107301.

8. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, Stemmler HJ, Schlößer HA, Schlaak M, et al. Cytokine release syndrome. J Immunother Cancer. 2018 Jun 15;6(1):56. doi: 10.1186/s40425-018-0343-9.

9. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020 Mar 28;395(10229):1033-1034. doi: 10.1016/S0140-6736(20)30628-0

10. Fernández-Cuadros ME, Pérez-Moro OS, Albaladejo-Florín MJ. Ozone fundamentals and effectiveness in knee pain: Chondromalacia and knee osteoarthritis. Germany: Lambert Academic Publishing; 2016.

11. Fernández-Cuadros ME, Pérez-Moro OS, Albaladejo-Florín MJ, Álava-Rabasa S. El ozono intraarticular modula la inflamación, mejora el dolor, la rigidez, la función y tiene un efecto anabólico sobre la artrosis de rodilla: estudio cuasi-experimental prospectivo tipo antes-después, 115 pacientes. Rev Soc Esp Dolor 2020; 27(2):78-88, https://doi.org/10.20986/resed.2020.3775/2019.

12. Fernández-Cuadros ME, Albaladejo-Florín MJ, Peña-Lora D, Álava-Rabasa S, Pérez-Moro OS. Ozone (O3) and SARS-CoV-2: Physiological Bases and Their Therapeutic Possibilities According to COVID-19 Evolutionary Stage. SN Compr Clin Med. 2020;2(8):1094-1102. doi: 10.1007/s42399-020-00328-7.

13. Fernández-Cuadros ME, Albaladejo-Florín MJ, Álava-Rabasa S, Usandizaga-Elio I, Martinez-Quintanilla Jimenez D, Peña-Lora D, et al. Effect of Rectal Ozone (O3) in Severe COVID-19 Pneumonia: Preliminary Results. SN Compr Clin Med. 2020;2(9):1328-1336. doi: 10.1007/s42399-020-00374-1.

14. Fernández-Cuadros ME, Albaladejo-Florín MJ, Álava-Rabasa S, Gallego-Galiana J, Pérez-Cruz GF, Usandizaga-Elio I, et al. Compassionate Use of Rectal Ozone (O3) in Severe COVID-19 Pneumonia: a Case-Control Study. SN Compr Clin Med. 2021;3(5):1185-1199. doi: 10.1007/s42399-021-00849-9.

15. Taylor E, Haven K, Reed P, Bissielo A, Harvey D, McArthur C, et al. A chest radiograph scoring system in patients with severe acute respiratory infection: a validation study. BMC Med Imaging. 2015 Dec 29;15:61. doi: 10.1186/s12880-015-0103-y.

16. Di Franco S, Alfieri A, Petrou S, Damiani G, Passavanti MB, Pace MC, et al. Current status of COVID-19 treatment: An opinion review. World J Virol. 2020 Sep 25;9(3):27-37. doi: 10.5501/wjv.v9.i3.27.

17. Martínez-Sánchez G, Schwartz A, Donna VD. Potential Cytoprotective Activity of Ozone Therapy in SARS-CoV-2/COVID-19. Antioxidants (Basel). 2020 May 6;9(5):389. doi: 10.3390/antiox9050389.

18. Conti P, Gallenga CE, Tetè G, Caraffa A, Ronconi G, Younes A, et al. How to reduce the likelihood of coronavirus-19 (CoV-19 or SARS-CoV-2) infection and lung inflammation mediated by IL-1. J Biol Regul Homeost Agents. 2020 March-April,;34(2):333-338. doi: 10.23812/Editorial-Conti-2.

19. Marini S, Maggiorotti M, Dardes N, Bonetti M, Martinelli M, Re L, et al. Oxygen-ozone therapy as adjuvant in the current emergency in SARS-COV-2 infection: a clinical study. J Biol Regul Homeost Agents. 2020 May-Jun;34(3):757-766. doi: 10.23812/20-250-E-56.

20. Menendez-Cepero S, Marques-Magallanes-Regojo JA, Hernandez-Martinez A, Tallón FJ H, Baeza-Noci J. Therapeutic effects of Ozone therapy that justifies its use for the treatment of COVID-19. Research Open J Neurol 2020; 3(1):1-6, https://doi.org/10.31038/JNNC.2020314.

21. Ayanian S, Reyes J, Lynn L, Teufel K. The association between biomarkers and clinical outcomes in novel coronavirus pneumonia in a US cohort. Biomark Med. 2020 Aug;14(12):1091-1097. doi: 10.2217/bmm-2020-0309.

22. Lorenz G, Moog P, Bachmann Q, La Rosée P, Schneider H, Schlegl M, et al. Cytokine release syndrome is not usually caused by secondary hemophagocytic lymphohistiocytosis in a cohort of 19 critically ill COVID-19 patients. Sci Rep. 2020 Oct 26;10(1):18277. doi: 10.1038/s41598-020-75260-w.

23. Copaescu A, James F, Mouhtouris E, Vogrin S, Smibert OC, Gordon CL, et al. The Role of Immunological and Clinical Biomarkers to Predict Clinical COVID-19 Severity and Response to Therapy-A Prospective Longitudinal Study. Front Immunol. 2021 Mar 17;12:646095. doi: 10.3389/fimmu.2021.646095.

24. Cattel F, Giordano S, Bertiond C, Lupia T, Corcione S, Scaldaferri M, et al. Ozone therapy in COVID-19: A narrative review. Virus Res. 2021 Jan 2;291:198207. doi: 10.1016/j.virusres.2020.198207.

25. Chirumbolo S, Valdenassi L, Simonetti V, Bertossi D, Ricevuti G, Franzini M, et al. Insights on the mechanisms of action of ozone in the medical therapy against COVID-19. Int Immunopharmacol. 2021 Jul;96:107777. doi: 10.1016/j.intimp.2021.107777.

26. Martinez-Sanchez G. La ozonoterapia como terapia complementaria en el enfrentamiento a la COVID-19. Revista Cubana de Farmacia 2021; 54(1).

27. Franzini M, Valdenassi L, Ricevuti G, Chirumbolo S, Depfenhart M, Bertossi D, et al. Oxygen-ozone (O2-O3) immunoceutical therapy for patients with COVID-19. Preliminary evidence reported. Int Immunopharmacol. 2020 Nov;88:106879. doi: 10.1016/j.intimp.2020.106879.

28. Tascini C, Sermann G, Pagotto A, Sozio E, De Carlo C, Giacinta A, et al. Blood ozonization in patients with mild to moderate COVID-19 pneumonia: a single centre experience. Intern Emerg Med. 2021 Apr;16(3):669-675. doi: 10.1007/s11739-020-02542-6.

29. Schwartz A, Martínez-Sánchez G, de Lucía AM, Viana SM, Mita CA. Complementary application of the ozonized saline solution in mild and severe patients with pneumonia COVID-19: A non-randomized pilot study. Journal of Pharmacy and Pharmacognosy Research 2021;9(2):126-42, https://jppres.com/jppres.

30. Hernández A, Viñals M, Pablos A, Vilás F, Papadakos PJ, Wijeysundera DN, et al. Ozone therapy for patients with COVID-19 pneumonia: Preliminary report of a prospective case-control study. Int Immunopharmacol. 2021 Jan;90:107261. doi: 10.1016/j.intimp.2020.107261.

31. Hendawy HA, Mosallam W, Abuelnaga ME, Sabry AM. Old Treatment for a New Disease: Can Rectal Ozone Insufflation Be Used for COVID-19 Management? A Case Report. SN Compr Clin Med. 2021;3(6):1424-1427. doi: 10.1007/s42399-021-00895-3.

32. Peña-Lora D, Albaladejo-Florín MJ, Fernández-Cuadros ME. Uso de ozonoterapia en paciente anciana con neumonía grave por COVID-19. Revista Espanola de Geriatria y Gerontologia 2020; 55(6):362-4, https://doi.org/10.1016/j.regg.2020.07.005.

33. León Fernández OS, Oru GT, Hansler RV. Medical Ozone: The Pharmacological Mechanisms Accounting for its Effectiveness against COVID-19. J Med-Clin Res & Rev 2021;5(3):1-10

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ORIGINAL

Concordancia entre pruebas no invasivas para la implementación de algoritmos de cribado de fibrosis hepática en pacientes de alto riesgo

Concordance between non-invasive tests for the implementation of liver fibrosis screening algorithms in high-risk patients

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Resumen

Introducción y objetivo: La evaluación de la fibrosis hepática es de vital importancia para la valoración de pacientes con cualquier enfermedad hepática crónica para la toma de decisiones terapéuticas, el pronóstico y la evaluación de la respuesta al tratamiento. La biopsia hepática es actualmente el estándar de referencia para su identificación y estadificación, pero presenta varias limitaciones. Los enfoques con métodos no invasivos basados en biomarcadores séricos o la valoración de la rigidez hepática mediante elastografía, se están incorporando cada vez más en la práctica clínica reemplazando a la biopsia. Nuestro objetivo es evaluar la concordancia entre algunas de estas pruebas no invasivas: índice FIB-4, test Enhanced Liver Fibrosis (ELF) y elastografía transitoria, en pacientes con hepatitis crónica de etiología diversa con alta prevalencia de fibrosis, para determinar su utilidad simultánea o secuencial en la práctica clínica.
Métodos: Estudio retrospecivo en el que se incluyeron 179 pacientes y se comprobó la concordancia bivariante entre FIB-4, ELF score y Fibroscan con los puntos de corte considerados.
Resultados: La concordancia entre el valor de FIB-4 y ELF score se encontró del 29.94%, cuando se comparó la concordancia entre el valor de FIB-4 y Fibroscan se encontró del 50.46% y la concordancia entre el valor de ELF score y Fibroscan fue del 29.38%.
Conclusiones: la concordancia para detectar los puntos de corte considerados entre las pruebas no invasivas estudiadas es pobre, lo que sugiere la necesidad de utilizar varios marcadores no invasivos con diferentes puntos de corte para varios umbrales clínicamente relevantes según la mejor tasa de detección para cada patología.

Palabras clave: cirrosis, fibrosis hepática, marcadores no invasivos, elastografía transitoria, FIB-4, ELF, cribado.

Abstract

Introduction and objective: The evaluation of liver fibrosis is of vital importance in the assessment of patients with any chronic liver disease for therapeutic decision making, prognosis and evaluation of response to treatment. Liver biopsy is currently the gold standard for identification and staging, but has several limitations. Non-invasive approaches based on serum biomarkers or assessment of liver stiffness by elastography are increasingly being incorporated in clinical practice replacing biopsy. Our objective is to evaluate the concordance between some of these non-invasive tests: FIB-4 index, Enhanced Liver Fibrosis (ELF) test and transient elastography, in patients with chronic hepatitis of diverse etiology with high prevalence of fibrosis, to determine their simultaneous or sequential usefulness in clinical practice.
Methods: Retrospective study in which 179 patients were included and the bivariate concordance between FIB-4, ELF score and Fibroscan with the cut-off points considered was tested.
Results: The concordance between FIB-4 value and ELF score was found to be 29.94%, when the concordance between FIB-4 value and Fibroscan was compared it was found to be 50.46% and the concordance between ELF score and Fibroscan was 29.38%.
Conclusions: The concordance for detecting the cut-off points considered between the non-invasive tests studied is poor, suggesting the need to use several non-invasive markers with different cut-off points for various clinically relevant thresholds according to the best detection rate for each pathology.

Key words: cirrhosis, liver fibrosis, non-invasive markers, transient elastography, FIB-4, Enhanced Liver Fibrosis test, screening.

Introducción

La enfermedad hepática crónica y la cirrosis suponen 2 millones de muertes en todo el mundo cada año, además de una alta carga de discapacidad y una mayor utilización de la atención médica. La cirrosis es la undécima causa más común de muerte a nivel mundial y las muertes por cirrosis han aumentado de 899.000 a más de 1,32 millones de 1990 a 2017, aunque es probable, que las estimaciones de mortalidad sean conservadoras y subestimen su verdadera carga. Las etiologías más comunes de enfermedad hepática crónica y cirrosis son, el virus de la hepatitis B (VHB), el virus de la hepatitis C (VHC), la enfermedad hepática relacionada con el alcohol (ALD) y la enfermedad del hígado graso no alcohólico (NAFLD). Las tasas de mortalidad están aumentado, lo que es atribuible a la hepatitis viral, pero también impulsadas por la creciente prevalencia de ALD y NAFLD que ahora son las causas más comunes de enfermedad hepática crónica en el mundo occidental[1].

En España pueden existir más de un millón de personas (prevalencia 3.6%) con fibrosis hepática significativa, estimándose que 1 de cada 6 de estos pacientes presentan cirrosis. Esta población, comparada con la población general ajustada por género y edad, tiene más comorbilidad y utiliza más frecuentemente los recursos sanitarios[2].

Fibrosis

Las diferentes causas capaces de generar daño hepático conducen a hepatocitos dañados e infiltración de células inmunitarias que activan la transdiferenciación de células estrelladas hepáticas (HSC) en miofibroblastos productores de colágeno. En las enfermedades hepáticas crónicas, un desequilibrio de los mecanismos profibrogénicos y antifibrogénicos, provoca una activación persistente de miofibroblastos proliferantes, contráctiles y migratorios que conducen a una producción excesiva de matriz extracelular, cuya acumulación progresiva es la fibrosis, que favorece la destrucción de la arquitectura fisiológica del hígado[3].

Se trata de un proceso con un importante período de latencia durante el cual las personas afectadas pueden carecer de signos o síntomas evidentes de enfermedad. Eventualmente, la fibrosis puede progresar a cirrosis clínicamente evidente e insuficiencia hepática[4] que, pueden desembocar en el desarrollo de hipertensión portal y complicaciones relacionadas. Además, los pacientes que experimentan una progresión fibrogénica también tienen un riesgo significativo de desarrollar carcinoma hepatocelular (CHC)[5]. El diagnóstico precoz permite iniciar tratamientos específicos o medidas para prevenir la progresión de la enfermedad y mejorar la supervivencia.

Los grados de fibrosis (F) en personas con enfermedad hepática se dividen en 4 según el sistema METAVIR[6]:

- F0 (no fibrosis)
- F1 (fibrosis portal sin septos: fibrosis mínima)
- F2 (fibrosis portal con unos pocos septos: fibrosis moderada o fibrosis clínicamente significativa)
- F3 (fibrosis septal con muchos septos, pero no cirrosis: fibrosis severa)
- F4 (cirrosis)

Diferenciar entre estos grados de fibrosis es complicado con pruebas clínicas, de laboratorio y de imagen completas, porque los hallazgos son a menudo inespecíficos o insensibles. La biopsia hepática sigue siendo el estándar de referencia para evaluar la fibrosis hepática; sin embargo, el uso de métodos no invasivos es cada vez más común en la práctica clínica. Las pruebas no invasivas, la biopsia hepática/métodos de diagnóstico invasivos y la evaluación clínica tienen que ser integradas para lograr diagnósticos correctos y la estratificación de riesgo en enfermedades hepáticas crónicas[7].

Biopsia hepática

A pesar de ser el "estándar de oro" para la evaluación de la fibrosis hepática, tiene varias limitaciones, incluida la invasividad, el alto costo, el error de muestreo y la variabilidad entre observadores en la interpretación patológica[8]. Además, conlleva un pequeño pero significativo riesgo de complicaciones y de contraindicaciones[9].

Pruebas no invasivas para evaluar la fibrosis hepática

Durante la última década ha surgido una variedad de metodologías no invasivas que incluyen, entre otras, la elastografía transitoria (ET) y biomarcadores séricos (FIB-4, Enhanced Liver Fibrosis…) para la evaluación de la fibrosis[10]. En condiciones estandarizadas, la precisión de estos métodos suele ser sólida para la fibrosis/cirrosis avanzada; sin embargo, las características de diagnóstico varían significativamente según el valor de corte y la etiología subyacente de la enfermedad hepática crónica[11]. Sus ventajas incluyen una mejor aceptación por parte de los pacientes, una mayor disponibilidad para la detección de cohortes o basada en la población y grados relativamente altos de concordancia con los resultados obtenidos mediante la evaluación de la histología hepática para resultados clínicamente relevantes (p. ej., fibrosis/cirrosis avanzada)[4]. Permiten identificar y estratificar el nivel de fibrosis hepática al hacer referencia a puntuaciones histológicas, como la puntuación METAVIR[7].

El uso de la prueba ELF y otras pruebas no invasivas, se recomienda en las pautas de la European Association for the Study of the Liver (EASL)[12] para la estratificación del riesgo de pacientes con enfermedad hepática crónica, la guía de la British Society for Gastroenterology (BSG)

sobre la investigación de la función hepática anormal[13] y la guía del National Institute for Health and Care Excellence (NICE)[14] sobre la enfermedad del hígado graso no alcohólico (NAFLD).

Elastografía transitoria

Técnica en la que se evalúa la elasticidad o rigidez hepática, es decir, el grado de dureza del tejido hepático o fibrosis. La ET mide ondas vibratorias, las cuales, según su velocidad de propagación indican el grado de rigidez o fibrosis ya que se propagan más rápido en el tejido hepático duro que en el tejido hepático blando[15]. Entre estas técnicas, la ET con FibroScan® (Echosens, París, Francia) se usa ampliamente para clasificarla en la práctica clínica habitual[8] y ha demostrado una gran utilidad diagnóstica para la predicción de fibrosis avanzada/cirrosis hepática. Cuando se utiliza la biopsia hepática como estándar de referencia, la ET proporciona alta sensibilidad y valores predictivos negativos para la detección de cirrosis superiores al 95%, para un amplio rango de prevalencias y etiologías de enfermedad hepática subyacente, por lo que resulta más útil para descartar cirrosis que para confirmarla[2]. En cuanto a los puntos de corte empleados para los diferentes grados de fibrosis, en la literatura hay una gran variedad: Castera et al[16]: ≥7,1 kPa para F ≥ 2 y ≥12,5 kPa para F4, Ziol et al.[17] ≥ 8,8 kPa para F≥ 2 y ≥14.6 kPa para F4 o los publicados en un metaánalisis en el que había varias causas de enfermedad hepática crónica[18]: ≥7,7 kPa para F≥ 2 y 13,1≥ kPa para F4, entre otros.

Enhanced Liver Fibrosis (ELF)

La prueba Enhanced Liver Fibrosis (ELF) es una de las pruebas que emplea biomarcadores séricos directos. Es el resultado de un algoritmo logarítmico que combina mediciones séricas cuantitativas de tres marcadores del metabolismo de la matriz extracelular hepática: ácido hialurónico (HA), inhibidor tisular de metaloproteinasa-1 (TIMP-1) y péptido N-terminal de procolágeno III (PIIINP)[19].

La prueba ELF ha sido validada para la evaluación de la fibrosis hepática en una amplia variedad de enfermedades hepáticas crónicas y se ha demostrado que es un marcador pronóstico preciso para la mortalidad por todas las causas y las complicaciones de la cirrosis y puede ser más preciso que la histología hepática para determinar el pronóstico[20].

Según los datos del fabricante el ELF debe interpretarse de la siguiente manera[21]:

- <7.7 : sin fibrosis a leve (F0 a F1)
- ≥7.7 a <9.8: fibrosis moderada (≥F2)
- ≥ 9.8 a <11.3 fibrosis clínicamente significativa (≥F3).
- ≥ 11.3 : cirrosis (≥F4)

Índice FIB-4

Es una puntuación basada en parámetros séricos fácilmente disponibles que se miden de forma rutinaria (edad, AST, ALT y recuento de plaquetas) y se calcula de la siguiente manera (edad en años, ALT y AST en UI/L, y recuento de plaquetas en 10^9/L):

$$\text{Índice FIB4} = \frac{(\text{edad} \times \text{AST})}{\text{recuento de plaquetas} \times \sqrt{\text{ALT}}}$$

Numerosos estudios han evaluado la fibrosis hepática de forma no invasiva siguiendo dos pasos: el índice FIB-4 y modalidades de imagen para descartar y confirmar fibrosis avanzada, respectivamente, dando lugar a una estrategia eficaz en la práctica clínica para la detección de fibrosis avanzada. FIB-4 tiene un alto valor predictivo negativo y podría usarse como prueba de cribado de primera línea para identificar pacientes con bajo riesgo de fibrosis hepática avanzada que no requieren evaluación adicional (se evitarían biopsias o derivaciones innecesarias)[22]. El punto de corte FIB4 ≥ 3,25, es el que originalmente fue validado para indicar una posible fibrosis avanzada para la infección por VHC, también ha sido validado para otras patologías, como hepatitis B y NAFLD[23]. Las puntuaciones FIB-4 tienen zonas intermedias considerables (~30%), lo que, añadido a su bajo valor predictivo positivo, ha originado que se hayan propuesto varios algoritmos secuenciales basados en este índice, especialmente para evaluar a pacientes con NASH[24].

Metodología

Diseño del estudio

Este estudio fue diseñado como un estudio de un solo centro observacional retrospectivo realizado en pacientes que acuden a una consulta especializada de hepatología de un hospital de tercer nivel, para evaluar la concordancia entre las pruebas no invasivas de cribado (FIB-4, ELF y ET) de de fibrosis hepática en pacientes de alto riesgo e identificar qué algoritmo o aplicación secuencial de pruebas no invasivas podría traducirse en una mejor estrategia diagnóstica en estas patologías Se ha solicitado la aprobación del estudio a la Comisión de Investigación de nuestro Hospital y al Comité Etico de les Illes Balears.

Población de estudio

Registramos 195 pacientes consecutivos que se derivaron a una consulta de hepatología del Hospital Universitario Son Espases entre 2016 y 2020 a los que se les solicitó ELF y a los que se les calculó el índice FIB4. De ellos fueron excluídos 18 pacientes cuya edad era inferior a 18 años, ausencia de datos en las variables a estudiar o errores de cuantificación y registro que impidan la obtención de un resultado de FIB-4 y/o ELF score. A 179 pacientes se le pudo calcular el FIB-4, siendo la etiología de su hepatitis, VHC en 77, VHB en 12, ALD en 14, NAFLD en 49 y otras causas en 27. Dos de ellos no tenían la determinación de ELF, mientras que a 114

pacientes se les había realizado la elastografía. El 59% eran hombres, con una edad media de 56 +/- 12 años).

Recolección de datos

Obtuvimos la siguiente información de la historia clínica del paciente: edad, sexo etiología de la hepatopatía y resultados de la ET.

Pruebas bioquímicas/hematologicas

Los participantes ayunaron durante la noche antes de la recolección de la muestra de sangre. Examinamos las siguientes pruebas bioquímicas: recuento de plaquetas en un contador hematológico Alinity HQ de Abbott y AST y ALT en un autoanalizador Architect ci series de Abbott. HA , TIMP-1 y PIIINP se determinaron mediante inmunoensayo en un autoanalizador ADVIACentaur® (ADVIA CentaurTM, SiemensHealthcare Diagnostics, Tarrytown, NY, EE. UU.).

FIB-4

El índice FIB-4 se calculó como describimos anteriormente:

$$\frac{\text{edad (años)} \times \text{AST (U/L)}}{\text{recuento de plaquetas } (10^9/\text{L})) \times \text{ALT (U/L)}^{1/2}}$$

Se utilizó el índice FIB-4 para identificar pacientes de: bajo riesgo de fibrosis <1.3; riesgo intermedio de fibrosis (≥1.3 a 3.25); riesgo alto de fibrosis ≥ 3.25.

ELF

La prueba ELF se genera como una puntuación única que combina las mediciones séricas cuantitativas de TIMP-1, PIIINP y HA. El instrumento calculó automáticamente la puntuación ELF empleando la ecuación recomendada [ELF = 2.278 + 0.851 ln(HA) + 0.751 ln(PIIINP) + 0.394 ln(TIMP-1)] y se expresó como un valor numérico sin unidades. Se emplearon los valores de corte recomendados por el fabricante para indentificar el grado de fibrosis: <7.7 – sin fibrosis a leve (F0 a F1); ≥7.7 a <9.8: fibrosis moderada (≥F2); ≥ 9.8: fibrosis clínicamente significativa (≥F3).

Elastografía transitoria

Las medidas de rigidez hepática se obtuvieron con Fibroscan (Echosense) M. Los valores de corte que empleamos fueron los del metaanálisis citado en la introducción que incluía varias causas de enfermedad hepática crónica como en nuestro caso: ≥7.7 kPa para F≥ 2 y 13.1≥ kPa para F4.

Análisis Estadístico

Se comprobó la concordancia bivariante entre FIB-4 (considerando los puntos de corte para tres estratos de gravedad <1.3, ≥1.3-3.25 y ≥3.25), ELF score (considerando los puntos de corte para tres estratos de gravedad <7.7, ≥7.7-9.8, ≥ 9.8) y Fibroscan (considerando los puntos de corte para tres estratos de gravedad <7.7 kPa, ≥ 7.7-13 y >13 kPa). Se utilizó el grado de concordancia por el índice de Kappa de Cohen ajustado con corrección de Fleiss.

Se determinó la correlación de los valores mediante cálculo del coeficiente de correlación de Pearson. Se consideró una significación estadística del 5%. Se consideró un índice de Kappa superior a 0.4 una fuerza de concordancia moderada y un coeficiente de correlación r> 0.5 como moderado.

Se compararon los porcentajes de pacientes clasificados con grado de fibrosis F≥2 mediante ELF versus ET, en el grupo con FIB-4<1.3 mediante la prueba de Chi-cuadrado.

Resultados

Las concordancias que encontramos entre las diferentes pruebas no invasivas para los tres estratos de gravedad considerados fueron las siguientes:

Al comparar la concordancia entre el valor de FIB-4 y ELF score se encontró del 29.94%, con un índice Kappa de 0.0252 (error standard de 0.0161). El coeficiente de correlación de Pearson fue de r=0.4107 (r2= 0.1687; p<0.00001). Se consideró una concordancia pobre, con una correlación positiva débil significativa.

Cuando se comparó la concordancia entre el valor de FIB-4 y Fibroscan se encontró del 50.46%, con un índice Kappa de 0.029 (error standard de 0.096). El coeficiente de correlación de Pearson fue de r=0.3076 (r2= 0.0946; p=0.0011). Se consideró una concordancia pobre, con una correlación positiva muy débil significativa.

La concordancia entre el valor de ELF score y Fibroscan se encontró del 29.38%, con un índice Kappa de 0.0585 (error standard de 0.0303). El coeficiente de correlación de Pearson fue de r=0.4535 (r2= 0.2057; p<0.00001). Se consideró una concordancia pobre, con una correlación positiva débil significativa.

Finalmente se evaluó el subgrupo de pacientes con un cribado por FIB-4 inferior al grupo de clasificación de ELF score a los que tambien se habia realizado Fibroscan (n=57). Se obtuvo una concordancia para resultado positivo de Fibroscan del 29.82% (70.18% para resultado negativo), con una concordancia combinada para cualquier resultado del 36.30%, p<0.00001. El índice de Kappa fue de 0.29. En este subgrupo: FIB-4 correlaciona con Fibroscan con una Rho de 0.327 (p=0.012), y ELF score con Fibroscan con Rho 0.357 (p=0.0064). Se consideró una concordancia pobre, con una correlación positiva débil significativa.

Los porcentajes de pacientes clasificados con grado de fibrosis F≥2 mediante ELF versus ET, en el grupo con FIB-4 <1.3 fueron de 97.8% y 40.98 % respectivamente y las diferencias eran estadísticamente significativas (p<0.00001).

Si analizamos la concordancia para FIB-4 en un valor umbral de < 1.3, con el número de pacientes con ELF < 9.8, es decir en los que se descartaría grado de fibrosis clínicamente significativa (F≥3), encontramos 61 (de 91; 67.03 %). Mientras que con FIB-4 ≥ 1.3, el número de pacientes con presencia de fibrosis significativa con ELF sería de 43 (de 91; 47.25 %). El índice de kappa fue de 0.17 (error standard de 0.07), que sería una concordancia pobre.

En las siguientes tablas se expone la evidencia de fibrosis (F≥2) según ELF o ET y la etiología de la enfermedad hepática según lo valores de FIB-4:

Tabla I: Con FIB4 <1.3, **tabla II**: Con FIB4 ≥ 1.3-<3.5 y **tabla III**: Con FIB4 ≥3.25

Tabla I: FIB-4 <1.3

	N	ELF pedidos	ET realizada
NUMERO TOTAL DE CASOS CON FIB4 <1,3	92	91	61
EVIDENCIA DE FIBROSIS F≥2		89 (97,8%)	25 (40,98%)
ETIOLOGIA			
VHC	38	37	13
VHB	6	6	2
NALFD	30	29	7
ALCOHOL	6	6	1
OTROS DIAGNÓSTICOS	12	11	2
SIN EVIDENCIA DE FIBROSIS			
ETIOLOGIA		2 (2,19%)	35 (57,33 %)
VHC		1	12
VHB			1
NALFD			12
ALCOHOL			3
OTROS DIAGNÓSTICOS		1	7

Tabla II: FIB-4 ≥1.3-<3.25

	N	ELF pedidos	ET realizada
NUMERO TOTAL DE CASOS CON FIB4 ≥1,3-<3,25	73	72	41
EVIDENCIA DE FIBROSIS F≥2		72 (100%)	20 (48,78%)
ETIOLOGIA			
VHC	30	30	10
VHB	3	2	2
NALFD	18	18	4
ALCOHOL	7	7	1
OTROS DIAGNÓSTICOS	15	15	3
SIN EVIDENCIA DE FIBROSIS		-	21 (51,21%)
ETIOLOGIA			
VHC			10
VHB			1
NALFD			6
ALCOHOL			3
OTROS DIAGNÓSTICOS			1

Tabla III: FIB-4 ≥3.25

	N	ELF pedidos	ET realizada
NUMERO TOTAL DE CASOS CON FIB4 ≥3,25	14	14	8
EVIDENCIA DE FIBROSIS F≥2		14 (100%)	4 (50%)
ETIOLOGIA			
VHC	9	9	2
VHB	3	3	1
NALFD	1	1	
ALCOHOL	1	1	
OTROS DIAGNÓSTICOS			1
SIN EVIDENCIA DE FIBROSIS			4 (50%)
ETIOLOGIA			
VHC			4
VHB			
NALFD			
ALCOHOL			
OTROS DIAGNÓSTICOS			

Discusión

En nuestro estudio hemos encontrado concordancias pobres entre las pruebas no invasivas de cribado de fibrosis hepática, en el contexto de etiologías de enfermedad hepática crónica con alta prevalencia de fibrosis/cirrosis. Este hallazgo pone de manifiesto, la dificultad con la que nos encontramos a la hora de identificar qué algoritmo o aplicación secuencial de pruebas no invasivas podría traducirse en una mejor estrategia diagnóstica en estas patologías. Las guías respaldan un proceso de estratificación del riesgo de al menos dos niveles, proporcionando como ejemplo FIB-4 como la primera prueba de elección dado su aceptable valor predictivo negativo en entornos de baja prevalencia, seguida de una ET y/o ELF para identificar a los pacientes con mayor probabilidad de tener una lesión significativa (≥F2) o fibrosis avanzada (F3/4) que requieren evaluación adicional.

En la actualidad no existen directrices sólidas en las guías de práctica clínica con respecto a selección de pacientes para la evaluación del riesgo de fibrosis significativo en la enfermedad hepática. NICE recomienda el uso del ELF en pacientes con evidencia de NAFLD, pero no describe qué tipo de estrategia utilizar. La guía actual de la British Society of Gastroenterology recomienda la evaluación de la fibrosis usando uno de los parámetros basados en sangre en la comunidad (FIB4 o NAFLD Fibrosis Score) en pacientes con sospecha de NAFLD, pero solo en el contexto de enzimas hepáticas elevadas. Estas directrices en guías previas, sugerían que estas pruebas se han de realizar en el ámbito de la atención especializada, sin embargo, dada la creciente carga de hepatopatía, se está defendiendo su uso en atención primaria.

No obstante, un punto clave para evaluar el rendimiento de una prueba es partir de la base de que este depende de la prevalencia de la enfermedad, lo que significa que en poblaciones de baja prevalencia la sensibilidad y el valor predictivo positivo son menores. Además, cualquier prueba, dependiendo de su naturaleza y el punto de corte elegido, se asocia con resultados de prueba falsos positivos y falsos negativos, una limitación de la toma de decisiones binaria. Un algoritmo paso a paso que combine pruebas no invasivas podría reducir la tasa de pruebas falsas positivas, pero existe un número limitado de estudios con resultados sobre el cribado de la fibrosis hepática usando diferentes métodos no invasivos y puntos de corte. En ellos las tasas de detección para fibrosis variaron desde 0,7% y 7,5% en cohortes de población general, frente a 18%-27% en poblaciones de alto riesgo[25].

En nuestro estudio hemos empleado los puntos de corte más descritos en la literatura, pero los enfoques basados en algoritmos requieren de una validación de puntos de corte basados en la etiología de la enfermedad, etnicidad y prevalencia, así como la consideración de

limitaciones socioeconómicas regionales y acceso a la ET y atención especializada.

En cuanto a FIB-4, su principal limitación es una zona gris que no permite definir con precisión si el paciente tiene una fibrosis importante o puede necesitar una prueba complementaria para estratificar mejor al paciente en esta situación, sin embargo, actualmente, la estrategia principal con respecto a la estadificación de la fibrosis en la hepatopatía por VHC, es identificar a los pacientes con fibrosis/cirrosis avanzada. En general, el rendimiento diagnóstico de los marcadores séricos es mejor para la cirrosis que para la fibrosis significativa en estos pacientes, ya que esos datos son muy relevantes en la era del tratamiento con antivirales. La estadificación precisa de la fibrosis antes del tratamiento es menos crucial desde el punto de vista clínico que la identificación de fibrosis avanzada o cirrosis, que requiere una vigilancia continua posterior al tratamiento. Definir el diagnóstico de cirrosis antes del tratamiento es de suma importancia, así como estratificar a aquellos con cirrosis descompensada para iniciar el tratamiento antes o después del trasplante hepático. Como ya comentamos, el valor de corte para FIB-4 ≥3.25 del estudio original, ha sido corroborado en estudios adicionales, mostrando su utilidad para diagnosticar fibrosis avanzada. En nuestro estudio solo hemos detectado 14 pacientes con ese valor de FIB-4, por lo que no podemos valorar el rendimiento de las pruebas evaluadas a ese punto de corte, dada la limitación de individuos en ese subgrupo.

Destacamos también el elevado porcentaje de pacientes con FIB-4 < 1.3, que tendrían un grado de fibrosis F≥2 mediante ELF (97.8%) en comparación con el 40.98% que se obtuvo por ET, que nos lleva a plantear la hipótesis de que con el punto de corte del fabricante puede que ELF sobreestime el grado de fibrosis. De hecho, si seleccionamos como punto de corte para ELF ≥ 9.8 (≥F3), grado de fibrosis que como hemos comentado puede ser clínicamente más relevante, en el grupo de pacientes con FIB-4 < 1.3, el porcentaje de pacientes con fibrosis clínicamente significativa sería de 32.96%. Esta situación también se reproduce en los otros dos estratos de pacientes, donde considerando este punto de corte de 9.8 pasaríamos de: 100% a 44.4% en el grupo de pacientes con FIB-4 en zona intermedia y de 100% a 78.5% en el grupo con FIB-4 ≥3.25. Aunque hemos de señalar que a esos puntos de corte, la concordancia seguiría siendo pobre.

Las principales limitaciones de nuestro estudio es su carácter retrospectivo, el número relativamente pequeño de pacientes y el hecho de que no hemos podido comparar ninguna de estas pruebas con el método de referencia que es la biopsia hepática.

Creemos que son necesarios más estudios en los se deberían seleccionar diferentes puntos de corte para las diferentes pruebas no invasivas en función de la etiología, posiblemente la edad y el grado de fibrosis que se pretenda descartar/confirmar. Para ello necesitamos estudios con muestras de gran tamaño que aborden las lagunas de conocimiento más importantes, en particular comparando las pruebas no invasivas existentes de fibrosis en términos de precisión y aplicabilidad en entornos específicos, evaluando la rentabilidad de la detección e investigando posibles efectos beneficiosos a largo plazo.

Bibliografía

1. Moon AM, Singal AG, Tapper EB. Contemporary Epidemiology of Chronic Liver Disease and Cirrhosis. Vol. 18, Clinical Gastroenterology and Hepatology. W.B. Saunders; 2020. p. 2650–66.

2. Romero-Gómez M, Aller R, Ampuero J, Fernández Rodríguez C, Augustín S, Latorre R, et al. AEEH «Consensus about detection and referral of hidden prevalent liver diseases». Gastroenterologia y Hepatologia. Ediciones Doyma, S.L.; 2022.

3. Roehlen N, Crouchet E, Baumert TF. Liver Fibrosis: Mechanistic Concepts and Therapeutic Perspectives. Vol. 9, Cells. NLM (Medline); 2020.

4. Friedman SL, Pinzani M. Hepatic fibrosis 2022: Unmet needs and a blueprint for the future. Vol. 75, Hepatology. John Wiley and Sons Inc; 2022. p. 473-88.

5. Parola M, Pinzani M. Liver fibrosis: Pathophysiology, pathogenetic targets and clinical issues. Vol. 65, Molecular Aspects of Medicine. Elsevier Ltd; 2019. p. 37-55.

6. Gheorghe G, Bungău S, Ceobanu G, Ilie M, Bacalbaşa N, Bratu OG, et al. The non-invasive assessment of hepatic fibrosis. Vol. 120, Journal of the Formosan Medical Association. Elsevier B.V.; 2021. p. 794-803.

7. Berzigotti A, Tsochatzis E, Boursier J, Castera L, Cazzagon N, Friedrich-Rust M, et al. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis – 2021 update. J Hepatol. 2021 Sep 1;75(3):659-89.

8. Hur M, Park M, Moon HW, Choe WH, Lee CH. Comparison of non-invasive clinical algorithms for liver fibrosis in patients with chronic hepatitis B to reduce the need for liver biopsy: Application of enhanced liver fibrosis and Mac-2 binding protein glycosylation isomer. Ann Lab Med. 2021;42(2):249-57.

9. Lai M, Afdhal NH. Liver Fibrosis Determination. Vol. 48, Gastroenterology Clinics of North America. W.B. Saunders; 2019. p. 281-9.

10. Sherman KE, Abdel-Hameed EA, Ehman RL, Rouster SD, Campa A, Martinez SS, et al. Validation and Refinement of Noninvasive Methods to Assess Hepatic Fibrosis: Magnetic Resonance Elastography Versus Enhanced Liver Fibrosis Index. Dig Dis Sci. 2020 Apr 1;65(4):1252-7.

11. Loomba R, Adams LA. Advances in non-invasive assessment of hepatic fibrosis. Vol. 69, Gut. BMJ Publishing Group; 2020. p. 1343-52.

12. Archer AJ, Belfield KJ, Orr JG, Gordon FH, Abeysekera KW. EASL clinical practice guidelines: non-invasive liver tests for evaluation of liver disease severity and prognosis. Frontline Gastroenterol. 2022 Sep;13(5):436-9.

13. Newsome PN, Cramb R, Davison SM, Dllon JF, Foulerton M, Godfrey EM, et al. Guidelines on the management of abnormal liver blood tests. Gut. 2018 Jan 1;67(1):6-19.

14. Non-alcoholic fatty liver disease (NAFLD): assessment and management NICE guideline [Internet]. 2016. Available from: www.nice.org.uk/guidance/ng49

15. Oeda S, Tanaka K, Oshima A, Matsumoto Y, Sueoka E, Takahashi H. Diagnostic accuracy of fibroscan and factors affecting measurements. Vol. 10, Diagnostics. MDPI AG; 2020.

16. Castéra L, Vergniol J, Foucher J, le Bail B, Chanteloup E, Haaser M, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology. 2005;128(2):343-50.

17. Ziol M, Handra-Luca A, Kettaneh A, Christidis C, Mal F, Kazemi F, et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. Hepatology. 2005 Jan;41(1):48-54.

18. Friedrich-Rust M, Ong MF, Martens S, Sarrazin C, Bojunga J, Zeuzem S, et al. Performance of Transient Elastography for the Staging of Liver Fibrosis: A Meta-Analysis. Gastroenterology. 2008;134(4).

19. Patel PJ, Connoley D, Rhodes F, Srivastava A, Rosenberg W. A review of the clinical utility of the Enhanced Liver Fibrosis test in multiple aetiologies of chronic liver disease. Vol. 57, Annals of Clinical Biochemistry. SAGE Publications Ltd; 2020. p. 36–43.

20. Day J, Patel P, Parkes J, Rosenberg W. Derivation and Performance of Standardized Enhanced Liver Fibrosis (ELF) Test Thresholds for the Detection and Prognosis of Liver Fibrosis. J Appl Lab Med. 2019 Mar 1;3(5):815-26.

21. Day J, Patel P, Parkes J, Rosenberg W. Derivation and Performance of Standardized Enhanced Liver Fibrosis (ELF) Test Thresholds for the Detection and Prognosis of Liver Fibrosis. J Appl Lab Med. 2019 Mar 1;3(5):815-26.

22. Yamamura S, Kawaguchi T, Nakano D, Tomiyasu Y, Yoshinaga S, Doi Y, et al. Profiles of advanced hepatic fibrosis evaluated by FIB-4 index and shear wave elastography in health checkup examinees. Hepatology Research. 2020 Feb 1;50(2):199-213.

23. Blanco-Grau A, Gabriel-Medina P, Rodriguez-Algarra F, Villena Y, Lopez-Martínez R, Augustín S, et al. Assessing liver fibrosis using the fib4 index in the community setting. Diagnostics. 2021 Dec 1;11(12).

24. Kim M, Jun DW, Park H, Kang BK, Sumida Y. Sequential combination of FIB-4 followed by m2bpgi enhanced diagnostic performance for advanced hepatic fibrosis in an average risk population. J Clin Med. 2020 Apr 1;9(4).

25. Ginès P, Castera L, Lammert F, Graupera I, Serra-Burriel M, Allen AM, et al. Population screening for liver fibrosis: Toward early diagnosis and intervention for chronic liver diseases. Vol. 75, Hepatology. John Wiley and Sons Inc; 2022. p. 219-28.

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ORIGINAL

Relationship between nonalcoholic fatty liver disease and liver fibrosis risk scales with overweight and obesity scales in 219,477 spanish workers

Relación entre escalas de riesgo de higado graso no alcohólico y fibrosis hepática con escalas de sobrepeso y obesidad en 219.477 Trabajadores españoles

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Abstract

Introduction: Non-alcoholic fatty liver disease (NAFLD) is a highly prevalent pathology of multifactorial etiology that can lead to liver fibrosis. The aim of this study is to assess the association between NASFLD and liver fibrosis risk scales and overweight-obesity scales.
Material and methods: Descriptive and cross-sectional study in 219477 Spanish workers in which the relationship between the values of different NASH risk scales such as Fatty liver index (FLI), Hepatic steatosis index (HSI), Zhejiang University index (ZJU), Fatty liver disease index (FLD), Framingham steatosis index (Framingham steatosis index), Zhejiang University index (ZJU) and Fatty liver disease index (FLD) was determined, Framingham steatosis index (FSI), Lipid accumulation Product (LAP) and liver fibrosis (BARD score) with values of overweight-obesity scales (waist/height index, body mass index, Clínica Universitaria de Navarra Body Fat Estimator (CUN BAE) and Metabolic Score for Visceral Fat (METS-VF).
Results: Both the mean values and the prevalence of high-risk values for NASH and liver fibrosis are higher in people with obesity determined with all the scales. The highest prevalences are obtained when applying the BMI and CUN BAE scales.
Conclusion: The close relationship between the values of different NASH and liver fibrosis risk scales and the values of overweight-obesity scales is confirmed.

Keywords: Non-alcoholic fatty liver disease (NAFLD). Liver fibrosis, overweight, obesity.

Resumen

Introducción: La Enfermage del hígado graso no alcohólico (EHGNA) es una patología altamente prevalente y de etiología multifactorial que puede terminar en fibrosis hepática. El objetivo de este estudio es valorar la asociación entre escalas de riesgo de EHGNA y fibrosis hepática y escalas de sobrepeso-obesidad.
Material y métodos: Estudio descriptivo y transversal en 219477 trabajadores españoles en los que se determina la relación entre los valores de diferentes escalas de riesgo de EHGNA como Fatty liver index (FLI), Hepatic steatosis index (HSI), Zhejian University index (ZJU), Fatty liver disease index (FLD), Framingham steatosis index (FSI), Lipid accumulation Product (LAP) y fibrosis hepática (BARD score) con valores de escalas de sobrepeso-obesidad (índice cintura/altura, índice de masa corporal, Clínica Universitaria de Navarra Estimador de grasa corporal (CUN BAE) y Metabolic Score for Visceral Fat (METS-VF).
Resultados: Tanto los valores medios como la prevalencia de valores de alto riesgo de presentar EHGNA y fibrosis hepática son más elevados en las personas con obesidad determinados con todas las escalas. Las prevalencias más elevadas se obtienen al aplicar las escalas de BMI y CUN BAE.
Conclusión: Se confirma la estrecha relación entre los valores de diferentes escalas de riesgo de EHGNA y fibrosis hepática con los valores de escalas de sobrepeso-obesidad.

Palabras clave: Enfermedad del hígado graso no alcohólico (EHGNA). Fibrosis hepática, sobrepeso, obesidad.

Introduction

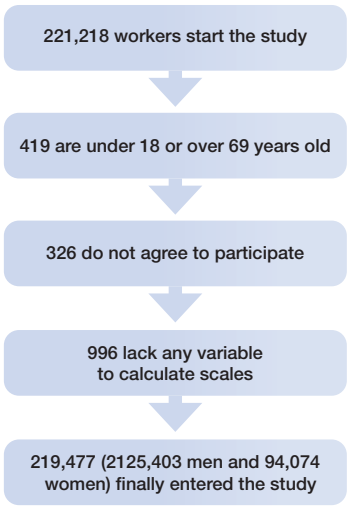
Non-alcoholic fatty liver disease (NAFLD) is a clinical entity that brings together various liver conditions in people who do not consume or consume small amounts of alcohol[1]. The most characteristic histological lesion of NAFLD is the excessive accumulation of fat at the level of liver cells[2]. We know that NASH is increasing in prevalence in all countries of the world, but these figures are especially worrying in the most developed countries[3], in some cases, such as the United States, where it affects one in four people[4]. NAFLD can progress to non-alcoholic steatohepatitis, which is considered one of the most aggressive forms of the disease. This condition presents high levels of liver inflammation that can lead to significant scarring (cirrhosis) and even liver failure. Many risk factors have been associated with NAFLD, the most significant being dyslipidemia[5], obesity[6], mainly abdominal obesity[7], polycystic ovary syndrome[8], diabetes mellitus[9], hypothyroidism[10], hypopituitarism[11] and advanced age[12].

The aim of our study was to determine the relationship between the values of different scales that assess the risk of NAFLD and liver fibrosis with scales that assess overweight and obesity in a group of Spanish workers.

Material and methods

Descriptive and cross-sectional study conducted in 219,477 Spanish workers from different regions and labor sectors (public administration, health, hospitality, construction and commerce mainly). The workers included in the study were selected from those who attended occupational medical examinations performed between January 2017 and December 2019. See Flow chart in **Figure 1**.

Figure 1: Flow chart of participants in the study.



Inclusion criteria:

- Ages between 18 and 69 years.
- Acceptance to participate in the study.
- Authorize the use of the data obtained for epidemiological purposes.
- Belonging to one of the companies included in the study and not being on temporary disability at the time of the study.

All measurements, whether anthropometric (height, weight and waist circumference), analytical or clinical, were performed by the occupational health professionals of the participating companies after standardization of the processes to avoid interobserver bias.

Weight (in kg) and height (in cm) were obtained with a SECA 700 scale-measuring device. Waist circumference was determined with a tape measure placed parallel to the floor at the level of the last floating rib while the person was standing upright, with feet together and abdomen relaxed.

Blood pressure is determined after 10 minutes of rest and with the person in a seated position. Three measurements are taken at one-minute intervals and the average of the three is obtained.

The blood test is obtained after at least 12 hours of fasting and processed within 48-72 hours. Automated enzymatic techniques are used for blood glucose, total cholesterol and triglycerides. For HDL-cholesterol the Cl2Mg dextran sulfate precipitation technique is used. LDL-cholesterol is determined indirectly by applying the Friedewald formula which is only valid when triglycerides do not exceed 400. All analytical parameters are expressed in mg/dL.

LDL= Total colesterol total -HDL-c- triglycerides/5

As scales of overweight and obesity were used:

- Waist/height index. It is obtained by dividing waist circumference by height, both in cm. The cut-off point was 0.50[13].
- Body mass index. It is obtained by dividing weight (in kg) by height^2 (in m). Underweight < 18.5, normal weight between 18.5 and 24.9, overweight between 25 and 29.9 and obesity over 30 kg/m^2 are considered.
- Clínica Universitaria de Navarra-Body Fat Estimator (CUN BAE)[14].

CUN BAE = -44.988 + (0.503 x age) + (10.689 x sex) + (3.172 x age) - (0.026 x BMI2) + (0.181 x BMI x sex) - (0.02 x BMI x age) - (0.005 x BMI2 x sex) + (0.00021 x BMI2 x age).

Man = 0 woman = 1.

The cut-off points are: normal weight (< 30 in women and < 20 in men), overweight (30-35 in women and 20-25 in men) and obesity (> 35 in women and > 25 in men).

- Metabolic score for visceral fat (METS-VF)[15]

METS-VF = 4.466 + 0.011*(Ln(METS-IR))^3 + 3.239*(Ln(WtHR))3 + 0.319*(Sex) + 0.594*(Ln(age)). Man = 1 woman = 0

METS-IR = Ln [(2*glycaemia) + Triglycerides]*BMI)/ (Ln[HDLc])[16]
High risk is considered as from 7,18.

The following risk scales for nonalcoholic fatty liver disease and liver fibrosis were used:

- Fatty liver index (FLI)[17]

$FLI = (e^{0.953*\log_e (triglycerides) + 0.139*BMI + 0.718*\log_e (GGT) + 0.053*waist\ circumference - 15.745}) / (1 + e^{0.953*\log_e (triglycerides) + 0.139*BMI + 0.718*\log_e (GGT) + 0.053*waist\ circumference - 15.745}) \times 100$

High risk is considered as from 60

- Hepatic steatosis index (HSI)[18]
HSI = 8 × AST/ALT + BMI + 2 if diabetes, + 2 if woman.
High risk is considered as from 36.

- Zhejian University index (ZJU index)[19]
ZJU = BMI + Glycaemia (mmol L) + Triglycerides (mmol L) +3 AST/ALT +2 if woman.
High risk is considered as from 38.

- Fatty liver disease index (FLD)[20]
FLD = BMI+Triglycerides+3 × (AST/ALT) +2 × Hyperglycaemia (present=1; absent=0).
High risk is considered as from 37.

- Framingham esteatosis index (FSI)[21]
FSI = -7,981 + 0,011 x age – 0,146 x sex (woman =1, man = 0) + 0,173 x BMI + 0,007 x triglycerides + 0,593 x hypertension (yes = 1, no =0) + 0,789 x diabetes (yes = 1, no =0) + 1,1 x AST/ALT ratio ≥1,33 (yes = 1, no =0)

- Lipid accumulation product (LAP)[22]

- Men: (waist (cm) - 65) x (triglycerides (mMol)).

- Women: (waist (cm) - 58) x (triglycerides (mMol)).
High risk is considered as from 42,7.

- BARD score[23]

It is a risk scale for liver fibrosis.
BMI from 28 (1 point), AST/ALT from 0.8 (2 points), diabetes mellitus (2 points). Values between 2-4 points indicate high risk.

We considered a smoker to be a person who has smoked at least one cigarette (or its equivalent in other types of consumption) in the last month or who has quit smoking less than a year ago.

The social class is obtained using the proposal of the Spanish Society of Epidemiology based on the 2011 National Classification of Occupations[24]. Three groups are considered: class I (directors, managers and university professionals), class II (intermediate occupations and self-employed workers) and class III (manual workers).

Statistical analysis

A descriptive analysis of the categorical variables was performed, calculating the frequency and distribution of the responses for each of them. For quantitative variables, the mean and standard deviation were calculated following a normal distribution.

Bivariate association analysis was performed using the chi2 test (with correction for Fisher's exact statistic when conditions required it) and Student's t test for independent samples (for comparison of means). Multivariate techniques were used to establish the variables associated with the most significant risk factors. Logistic regression was used for multivariate analysis, with calculation of the odds ratio and the Hosmer-Lemeshow goodness-of-fit test. Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) version 28.0 (IBM Company, New York, NY, USA) for Windows, with an accepted statistical significance level of 0.05.

Ethical considerations and/or aspects

The research team undertook at all times to follow the ethical principles of health sciences research established nationally and internationally (Declaration of Helsinki), paying special attention to the anonymity of the participants and the confidentiality of the data collected. Approval was requested from the Ethics and Research Committee of the Balearic Islands (CEI-IB), which was obtained with indicator IB 4383/20. Participation in the study was voluntary, so the participants gave their written and oral consent to participate in the study after receiving sufficient information about the nature of the study. To this end, they were given an informed consent form, as well as an information sheet explaining the objective of the study.

The data collected for the study were identified by a code and only the person responsible for the study can relate these data to the participants. The identity of the participants will not be disclosed in any report of this study. The investigators will not disseminate any information that could identify them. In any case, the research team undertakes to strictly comply with the Organic Law 3/2018, of December 5, on the protection of personal data and guarantee of digital rights, guaranteeing the participant in this study that he/she may exercise his/her rights of access, rectification, cancellation and opposition of the data collected

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Ethical considerations and/or aspects

The research team undertook at all times to follow the ethical principles of health sciences research established nationally and internationally (Declaration of Helsinki), paying special attention to the anonymity of the participants and the confidentiality of the data collected. Approval was requested from the Ethics and Research Committee of the Balearic Islands (CEI-IB), which was obtained with indicator IB 4383/20. Participation in the study was voluntary, so the participants gave their written and oral consent to participate in the study after receiving sufficient information about the nature of the study. To this end, they were given an informed consent form, as well as an information sheet explaining the objective of the study.

The data collected for the study were identified by a code and only the person responsible for the study can relate these data to the participants. The identity of the participants will not be disclosed in any report of this study. The investigators will not disseminate any information that could identify them. In any case, the research team undertakes to strictly comply with the Organic Law 3/2018, of December 5, on the protection of personal data and guarantee of digital rights, guaranteeing the participant in this study that he/she may exercise his/her rights of access, rectification, cancellation and opposition of the data collected

Results

The mean age of the sample is slightly older than 40 years, the majority being between 30 and 49 years of age. Anthropometric, clinical and analytical variables show more unfavorable values in men. The majority social class is III. Approximately one third of the patients were smokers. The complete data are presented in **table I**.

Table II shows the mean values of different scales of non-alcoholic fatty liver disease and liver fibrosis according to the values of the overweight and obesity scales. The mean values of all the aforementioned risk scales increase as the value of the overweight-obesity scales increases. The mean values in all cases are higher in men. In all cases the differences observed are statistically significant.

Table I: Characteristics of the population.

	Men n=125,403 Mean (SD)	Women n=94,074 Mean (SD)	p
Age	41.8 (10.5)	39.9 (10.5)	<0.0001
Height	175.2 (6.8)	162.3 (6.3)	<0.0001
Weight	82.6 (15.0)	68.0 (14.7)	<0.0001
SBP	126.1 (15.6)	115.4 (15.5)	<0.0001
DBP	77.3 (11.1)	72.3 (10.5)	<0.0001
Cholesterol	195.6 (37.9)	192.1 (35.5)	<0.001
HDL-c	52.1 (9.8)	57.2 (10.3)	<0.0001
LDL-c	118.4 (35.1)	116.3 (33.5)	<0.001
Tryglicerides	125.7 (76.0)	93.1 (45.6)	<0.0001
Glycaemia	93.4 (21.5)	88.3 (16.0)	<0.0001
AST	29.0 (17.5)	18.7 (11.6)	<0.0001
ALT	24.4 (13.3)	18.2 (7.9)	<0.0001
GGT	32.7 (31.8)	18.8 (16.3)	<0.0001
Creatinine	0.86 (0.17)	0.68 (0.14)	<0.0001
	%	**%**	**p**
18-29 years	14.4	19.4	<0.0001
30-39 years	26.6	28.9	
40-49 years	33.6	32.0	
50-59 years	21.5	16.8	
60-69 years	3.9	2.9	
Social class I	6.1	7.5	<0.0001
Social class II	14.5	20.5	
Social class III	79.4	72.0	
Non smokers	67.5	66.7	<0.001
Smokers	32.5	33.3	

SBP systolic blood pressure. DBP diastolic blood pressure. HDL High density lipoprotein. LDL Low density lipoprotein. AST aspartate transaminase. ALT alanine transaminase. GGT gamma-glutamyl transferase.

Table II: Mean values of the different risk scales for fatty liver and liver fibrosis according to the values of the overweight and obesity scales by sex.

		FLI	HSI	ZJU	FLD	FSI	LAP	BARD
Men	**n**	**Media (dt)**	**Media (dt)**	**Media (dt)**	**Media (dt)**	**Media (dt)**	**Media (dt)**	**Media (dt)**
WtHR <0.50	68703	23.3 (16.3)	33.7 (5.1)	34.1 (3.7)	29.1 (3.5)	0.12 (0.11)	20.3 (14.7)	0.72 (0.85)
WtHR ≥0.50	56700	59.6 (23.3)	40.6 (6.5)	40.8 (5.5)	35.6 (5.1)	0.30 (0.21)	49.9 (33.5)	1.64 (1.06)
Underweight	936	5.4 (4.6)	25.7 (3.0)	26.6 (2.0)	21.7 (1.4)	0.03 (0.03)	8.1 (8.0)	0.33 (0.54)
Normalweight BMI	44979	16.8 (11.5)	31.8 (4.2)	32.3 (2.6)	27.4 (2.4)	0.09 (0.08)	17.4 (12.6)	0.50 (0.69)
Overweight BMI	53751	41.9 (18.5)	37.3 (4.6)	37.6 (2.8)	32.5 (2.5)	0.19 (0.13)	34.6 (23.0)	1.17 (0.98)
Obesity BMI	25737	76.2 (15.7)	44.8 (5.9)	45.0 (4.6)	39.6 (4.3)	0.44 (0.20)	61.2 (38.5)	2.18 (0.86)
Normalweight CUN BAE	21081	11.6 (7.9)	30.0 (3.9)	30.5 (2.4)	25.7 (2.1)	0.06 (0.05)	14.4 (10.3)	0.30 (0.54)
Overweight CUNBAE	35814	23.7 (13.8)	33.9 (4.3)	34.2 (2.3)	29.3 (2.2)	0.11 (0.09)	22.0 (15.4)	0.58 (0.71)
Obesity CUN BAE	68508	56.7 (23.0)	40.4 (6.1)	40.7 (4.9)	35.4 (4.6)	0.30 (0.20)	45.7 (32.5)	1.68 (1.00)
METS-VF normal	116616	34.1 (22.8)	35.6 (5.9)	35.9 (4.5)	30.9 (4.3)	0.16 (0.14)	28.6 (22.2)	0.97 (0.97)
METS-VF high	14787	81.5 (14.1)	45.6 (6.3)	46.2 (5.3)	40.6 (5.0)	0.50 (0.21)	71.4 (43.1)	2.35 (0.87)
Women	**n**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Cintura/altura<0.50	72132	9.9 (9.6)	33.9 (5.0)	34.5 (3.9)	27.7 (3.7)	0.09 (0.08)	12.9 (9.8)	0.42 (0.68)
Cintura/altura≥0.50	21942	50.8 (24.2)	44.2 (6.3)	44.8 (5.6)	37.7 (5.3)	0.33 (0.21)	40.3 (23.2)	1.37 (0.83)
Underweight BMI	2844	2.2 (1.3)	27.1 (3.0)	27.9 (1.5)	21.2 (1.4)	0.03 (0.02)	4.7 (4.2)	0.13 (0.38)
Normalweight BMI	46083	6.0 (4.5)	32.2 (3.9)	32.8 (2.4)	26.1 (2.3)	0.06 (0.05)	10.2 (7.2)	0.24 (0.49)
Overweight BMI	27090	19.1 (11.3)	37.9 (3.9)	38.5 (2.4)	31.5 (2.1)	0.14 (0.10)	20.7 (12.5)	0.74 (0.82)
Obesity BMI	18057	57.1 (21.6)	45.9 (5.7)	46.4 (4.8)	39.3 (4.5)	0.37 (0.20)	42.6 (23.9)	1.56 (0.75)
Normalweight CUN BAE	20523	3.8 (2.6)	29.8 (3.4)	30.5 (2.0)	23.9 (1.9)	0.04 (0.03)	8.4 (6.3)	0.09 (0.31)
Overweight CUNBAE	24492	6.8 (4.7)	33.2 (3.5)	33.8 (1.9)	27.0 (1.8)	0.07 (0.05)	11.0 (7.6)	0.24 (0.48)
Obesity CUN BAE	49059	32.3 (24.7)	40.6 (6.3)	41.1 (5.4)	34.1 (5.2)	0.23 (0.18)	28.0 (20.8)	1.06 (0.87)
METS-VF normal	92934	18.6 (21.1)	36.1 (6.6)	36.7 (5.8)	29.8 (5.5)	0.14 (0.15)	18.6 (17.0)	0.62 (0.81)
METS-VF high	1140	91.6 (7.9)	55.5 (5.5)	56.2 (5.0)	48.7 (4.7)	0.73 (0.16)	72.5 (34.5)	1.76 (0.85)

FLI Fatty liver index. HSI Hepatic steatosis index. ZJU Zhejiang University index. FLD Fatty liver disease. FSI Framingham Steatosis index. LAP Lipid accumulation product. BMI Índice de masa corporal. CUN BAE Clínica Universitaria de Navarra Body Adiposity Estimator. METS-VF Metabolic Score for Visceral Fat. WtHR Waist to height ratio. Statistically significant differences (p<0.001) in all cases.

Table III shows the prevalence of elevated values of different nonalcoholic fatty liver disease and liver fibrosis risk scales according to the overweight-obesity scales. The same trend that we have seen with the mean values is observed, i.e. an increase in the prevalences as the values of the overweight-obesity scales increase. Prevalences are lower in women. In all cases the differences found are statistically significant.

Table IV shows the results of the multivariate analysis using multinomial logistic regression. The risk of presenting elevated values of all the nonalcoholic fatty liver disease and liver fibrosis scales is greater in those who present higher values of the overweight-obesity scales, with the greatest differences being observed when considering BMI and CUN BAE.

Table III: Prevalence of high values of the different risk scales for fatty liver and liver fibrosis according to values of the overweight and obesity scales by sex.

		FLI high	HSI high	ZJU high	FLD high	LAP high	BARD high
Men	**n**	**%**	**%**	**%**	**%**	**%**	**%**
WtHR <0.50	68703	3.9	27.0	13.5	60.7	16.3	17.0
WtHR ≥0.50	56700	51.3	76.7	68.3	62.0	71.6	54.0
Underweight BMI	936	0.0	0.3	0.3	0.0	1.0	3.5
Normalweight BMI	44979	0.9	11.7	1.9	30.8	10.5	9.3
Overweight BMI	53751	18.4	58.5	39.9	39.5	46.6	34.3
Obesity BMI	25737	83.3	98.6	99.7	95.2	85.6	76.4
Normalweight CUN BAE	21081	0.1	5.8	0.5	11.7	5.4	3.5
Overweight CUNBAE	35814	2.4	22.4	4.9	72.6	19.8	11.0
Obesity CUN BAE	68508	45.1	77.1	67.3	70.6	63.6	55.0
METS-VF normal	116616	15.6	41.0	28.9	24.5	32.5	25.8
METS-VF high	14787	91.4	96.8	97.0	62.8	93.9	83.1
Women	**n**	**%**	**%**	**%**	**%**	**%**	**%**
WtHR <0.50	72132	0.3	30.1	18.9	43.1	12.1	7.9
WtHR ≥0.50	21942	35.9	92.9	90.2	49.2	81.2	35.6
Underweight BMI	2844	0.0	0.8	0.0	0.2	0.1	1.3
Normalweight BMI	46083	0.01	12.6	1.5	18.9	4.4	2.6
Overweight BMI	27090	0.7	67.3	54.1	37.4	34.3	17.0
Obesity BMI	18057	43.6	99.7	100.0	97.4	84.3	42.6
Normalweight CUN BAE	20523	0.0	3.8	0.2	1.7	2.3	0.5
Overweight CUNBAE	24492	0.02	16.4	1.7	26.5	5.9	2.3
Obesity CUN BAE	49059	16.4	76.0	67.1	71.4	50.2	26.2
METS-VF normal	92934	7.5	44.0	34.7	2.1	27.4	13.9
METS-VF high	1140	99.2	100.0	100.0	45.3	99.2	53.4

FLI Fatty liver index. HSI Hepatic steatosis index. ZJU Zhejiang University index. FLD Fatty liver disease. FSI Framingham Steatosis index. LAP Lipid accumulation product. BMI Índice de masa corporal. CUN BAE Clínica Universitaria de Navarra Body Adiposity Estimator. METS-VF Metabolic Score for Visceral Fat. WtHR Waist to height ratio. Statistically significant differences (p<0.001) in all cases.

Table IV: Multinomial logistic regression.

	FLI high OR (95% CI)	HSI high OR (95% CI)	ZJU high OR (95% CI)	FLD high OR (95% CI)	LAP high OR (95% CI)	BARD high OR (95% CI)
Cintura/altura<0.50	1	1	1	1	1	1
Cintura/altura≥0.50	5.68 (5.43-5.95)	1.39 (1.35-1.43)	1.42 (1.38-1.47)	0.82 (0.78-0.85)	4.63 (4.51-4.76)	1.57 (1.53-1.62)
Bajo-Normalweight BMI	1	1	1	1	1	1
Overweight BMI	4.30 (4.16-4.45)	3.98 (3.81-4.15)	8.72 (8.51-8.93)	1.45 (1.28-1.63)	2.51 (2.43-2.60)	1.97 (1.91-2.03)
Obesity BMI	16.04 (14.16-18.17)	8.38 (8.22-8.55)	23.11 (22.89-23.33)	3.18 (2.94-3.40)	7.25 (6.86-7.67)	2.53 (2.39-2.68)
Normalweight CUN BAE	1	1	1	1	1	1
Overweight CUNBAE	2.88 (2.65-3.13)	3.06 (2.96-3.16)	8.17 (7.77-8.59)	1.92 (1.84-2.01)	1.56 (1.51-1.62)	4.09 (3.91-4.28)
Obesity CUN BAE	26.63 (17.93-39.54)	10.54 (9.96-11.15)	32.42 (27.44-38.32)	19.62 (18.52-20.78)	3.94 (3.69-4.21)	14.62 (13.47-15.87)
METS-VF normal	1	1	1	1	1	1
METS-VF high	11.19 (10.53-11.90)	1.48 (1.34-1.65)	2.17 (1.95-2.43)	4.02 (3.88-4.17)	4.04 (3.76-4.34)	3.99 (3.82-4.17)

FLI Fatty liver index. HSI Hepatic steatosis index. ZJU Zhejiang University index. FLD Fatty liver disease. FSI Framingham Steatosis index. LAP Lipid accumulation product.
BMI Índice de masa corporal. CUN BAE Clínica Universitaria de Navarra Body Adiposity Estimator. METS-VF Metabolic Score for Visceral Fat. Statistically significant differences (p<0.001) in all cases.

Figure 2 and **table V** show the areas under the curve with their 95% confidence intervals of the cardiovascular risk scales for predicting the presence of high values of the NASH and liver fibrosis risk scales. The largest areas under the curve were found with high FLI and high ZJU while the lowest values were found with high FLD.

Figure 1: ROC curve.

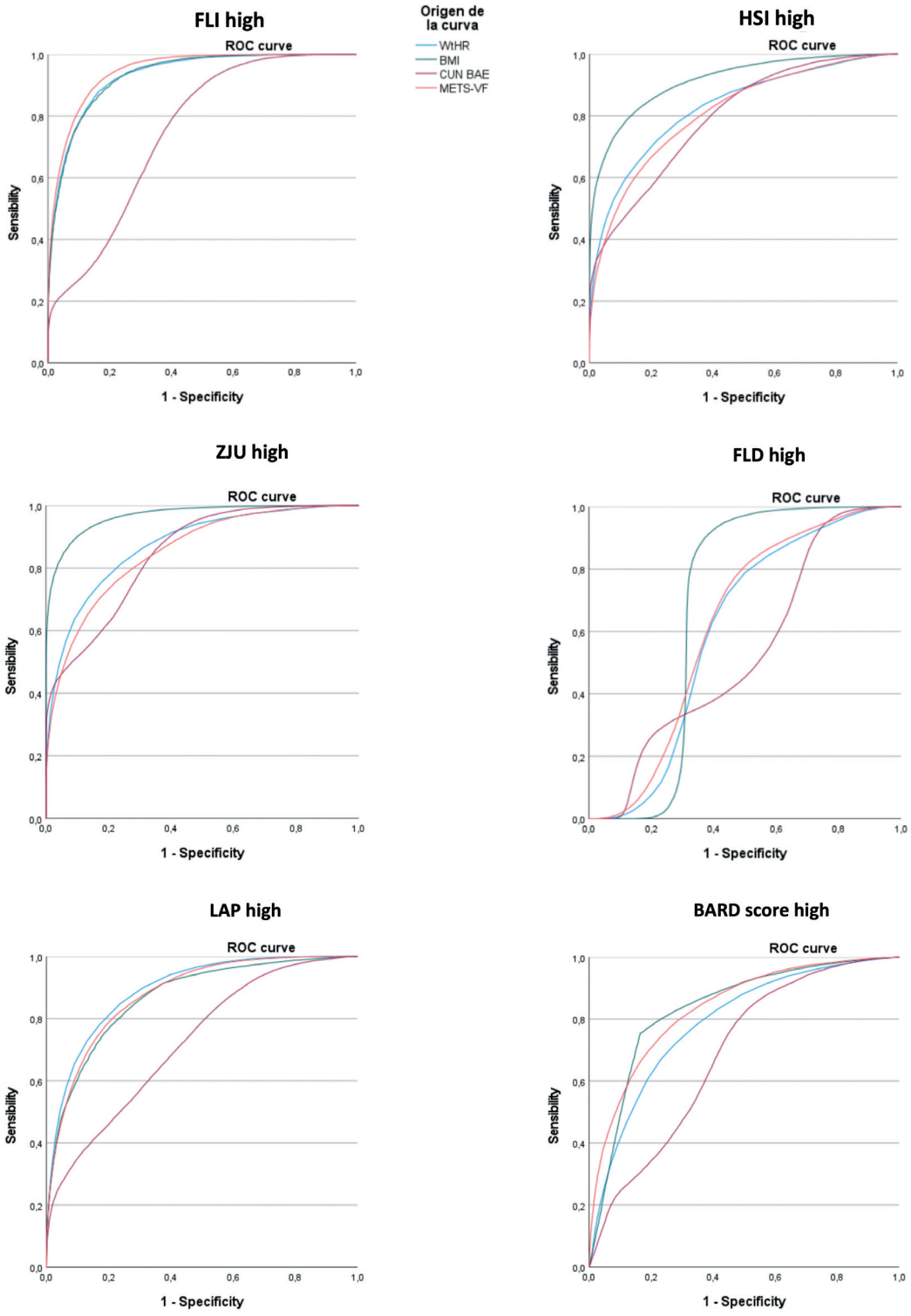

Table V: ROC curve (Area under the curve).

	FLI high AUC (95% CI)	HSI high AUC (95% CI)	ZJU high AUC (95% CI)	FLD high AUC (95% CI)	LAP high AUC (95% CI)	BARD high AUC (95% CI)
WtHR	0.933 (0.931-0.935)	0.828 (0.826-0.829)	0.875 (0.873-0.876)	0.603 (0.600-0.605)	0.893 (0.891-0.894)	0.788 (0.785-0.790)
IMC	0.932 (0.931-0.933)	0.914 (0.913-0.916)	0.968 (0.967-0.968)	0.677 (0.674-0.679)	0.868 (0.867-0.870)	0.834 (0.832-0.835)
CUN BAE	0.749 (0.747-0.751)	0.795 (0.794-0.797)	0.847 (0.845-0.848)	0.535 (0.532-0.537)	0.723 (0.720-0.725)	0.685 (0.682-0.687)
METS-VF	0.946 (0.945-0.947)	0.811 (0.809-0.813)	0.854 (0.863-0.856)	0.623 (0.620-0.625)	0.879 (0.878-0.880)	0.835 (0.833-0.837)

FLI Fatty liver index. HSI Hepatic steatosis index. ZJU Zhejiang University index. FLD Fatty liver disease. FSI Framingham Steatosis index. LAP Lipid accumulation product. WtHR Waist to height ratio. BMI Body mass index. CUN BAE Clínica Universitaria de Navarra Body Adiposity Estimator. METS-VF Metabolic Score for Visceral Fat.

Discussion

In our study, the mean values and the prevalence of high values for all the nonalcoholic fatty liver disease and liver fibrosis risk scales analyzed were higher in those individuals with higher values for the overweight-obesity scales.

When we performed the analysis using multinomial logistic regression we found that in all cases the level of risk with the scales that assess NAFLD and liver fibrosis is higher in the overweight-obese group, with the highest values in the case of obesity assessed with BMI and CUN BAE.

The multivariate analysis showed that the variable that most increased the risk of presenting high values of the different non-alcoholic fatty liver disease and liver fibrosis risk scales was age, followed by sex and social class, without finding any influence of tobacco consumption.
We have not found any article that simultaneously assesses the influence that exists between different scales of NAFLD and liver fibrosis risk and scales of overweight-obesity, so we will focus our discussion on the relationship between NAFLD and obesity.

The relationship between obesity and NAFLD is well established. Obesity is related not only to the initial stages of the disease, the so-called simple steatosis (SS), but also to its progression. Epidemiologically, both pathologies have an increasing prevalence worldwide. Pathogenically, obesity and its associated insulin resistance favor the initial accumulation of fat in hepatocytes (ES) and also the progression of ES to non-alcoholic steatohepatitis (NAFLD), cirrhosis and even hepatocellular carcinoma.

A study performed in transgenic mice showed that NASH and obesity are epidemiologically correlated with each other[25]. In the same vein, a study by Milić et al[26] expressed that up to 80% of NASH patients are obese, defined as a body mass index (BMI) > 30 kg/m^2, although it was especially relevant in those with morbid obesity in whom visceral adipose tissue is very abundant.

Strengths and limitations

As strengths of the study, we can especially highlight the large sample size, which exceeds 200,000 individuals, and the large number of NASH and liver fibrosis risk scales and overweight and obesity scales used. The main limitation is that no objective diagnostic techniques for NAFLD or liver fibrosis other than the risk scales were used.

Conclusions

Taking into account the results obtained in our study, we can conclude that in this Spanish working population there is a direct relationship between the values of the different NASH risk scales and liver fibrosis and the values of the overweight-obesity scales. We found high predictive values for the different overweight-obesity scales to predict the occurrence of high risk values for NAFLD and liver fibrosis except for FLD.

Conflict of Interest

The authors declare that no competing interests exist.

References

1. Younossi ZM, Paik JM, Al Shabeeb R, Golabi P, Younossi I, Henry L. Are there outcome differences between NAFLD and metabolic-associated fatty liver disease? Hepatology. 2022 Nov;76(5):1423-1437. doi: 10.1002/hep.32499.

2. Nassir F. NAFLD: Mechanisms, Treatments, and Biomarkers. Biomolecules. 2022 Jun 13;12(6):824. doi: 10.3390/biom12060824.

3. Lazarus JV, Mark HE, Anstee QM, Arab JP, Batterham RL, Castera L, et al. Advancing the global public health agenda for NAFLD: a consensus statement. Nat Rev Gastroenterol Hepatol. 2022 Jan;19(1):60-78. doi: 10.1038/s41575-021-00523-4.

4. Estes C, Anstee QM, Arias-Loste MT, Bantel H, Bellentani S, Caballeria J, et al. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016-2030. J Hepatol. 2018 Oct;69(4):896-904. doi: 10.1016/j.jhep.2018.05.036.

5. Morrow MR, Batchuluun B, Wu J, Ahmadi E, Leroux JM, Mohammadi-Shemirani P, et al. Inhibition of ATP-citrate lyase improves NASH, liver fibrosis, and dyslipidemia. Cell Metab. 2022 Jun 7;34(6):919-936.e8. doi: 10.1016/j.cmet.2022.05.004.

6. Pouwels S, Sakran N, Graham Y, Leal A, Pintar T, Yang W, et al. Non-alcoholic fatty liver disease (NAFLD): a review of pathophysiology, clinical management and effects of weight loss. BMC Endocr Disord. 2022 Mar 14;22(1):63. doi: 10.1186/s12902-022-00980-1.

7. Vilalta A, Gutiérrez JA, Chaves S, Hernández M, Urbina S, Hompesch M. Adipose tissue measurement in clinical research for obesity, type 2 diabetes and NAFLD/NASH. Endocrinol Diabetes Metab. 2022 May;5(3):e00335. doi: 10.1002/edm2.335.

8. Chen Y, Ma L, Ge Z, Pan Y, Xie L. Key Genes Associated With Non-Alcoholic Fatty Liver Disease and Polycystic Ovary Syndrome. Front Mol Biosci. 2022 May 25;9:888194. doi: 10.3389/fmolb.2022.888194.

9. Stefan N, Cusi K. A global view of the interplay between non-alcoholic fatty liver disease and diabetes. Lancet Diabetes Endocrinol. 2022 Apr;10(4):284-296. doi: 10.1016/S2213-8587(22)00003-1.

10. Hatziagelaki E, Paschou SA, Schön M, Pshighpoulou T, Roden M. NAFLD and thyroid function: pathophysiological and therapeutic considerations. Trends Endocrinol Metab. 2022 Nov;33(11):755-768. doi: 10.1016/j.tem.2022.08.001.

11. Huang Q, Xu H, Wang X, Mao J, Yu B, Zhu Y, et al. Relationship between growth hormone deficiency and nonalcoholic fatty liver disease in patients with pituitary stalk interruption syndrome. Clin Endocrinol (Oxf). 2022 Nov;97(5):612-621. doi: 10.1111/cen.14732.

12. Riazi K, Azhari H, Charette JH, Underwood FE, King JA, Afshar EE, et al. The prevalence and incidence of NAFLD worldwide: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2022 Sep;7(9):851-861. doi: 10.1016/S2468-1253(22)00165-0.

13. Siwarom S, Pirojsakul K, Aekplakorn W, Paksi W, Kessomboon P, Neelapaichit N, et al. Waist-to-Height Ratio Is a Good Predictor of Metabolic Syndrome in Adolescents: A Report From the Thai National Health Examination Survey V, 2014. Asia Pac J Public Health. 2022 Jan;34(1):36-43. doi: 10.1177/10105395211046474.

14. López-González AA, Jover AM, Martínez CS, Artal PM, Bote SA, Jané BA, et al. The CUN-BAE, Deurenberg Fat Mass, and visceral adiposity index as confident anthropometric indices for early detection of metabolic syndrome components in adults. Sci Rep. 2022 Sep 15;12(1):15486. doi: 10.1038/s41598-022-19343-w.

15. Bello-Chavolla OY, Antonio-Villa NE, Vargas-Vázquez A, Viveros-Ruiz TL, Almeda-Valdes P, Gomez-Velasco D, et al. Metabolic Score for Visceral Fat (METS-VF), a novel estimator of intra-abdominal fat content and cardio-metabolic health. Clin Nutr. 2020 May;39(5):1613-1621. doi: 10.1016/j.clnu.2019.07.012.

16. Bello-Chavolla OY, Almeda-Valdes P, Gomez-Velasco D, Viveros-Ruiz T, Cruz-Bautista I, Romo-Romo A, et al. METS-IR, a novel score to evaluate insulin sensitivity, is predictive of visceral adiposity and incident type 2 diabetes. Eur J Endocrinol. 2018 May;178(5):533-544. doi: 10.1530/EJE-17-0883.

17. Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol. 2006 Nov 2;6:33. doi: 10.1186/1471-230X-6-33.

18. Wang C, Cai Z, Deng X, Li H, Zhao Z, Guo C, et al. Association of Hepatic Steatosis Index and Fatty Liver Index with Carotid Atherosclerosis in Type 2 Diabetes. Int J Med Sci. 2021 Jul 23;18(14):3280-3289. doi: 10.7150/ijms.62010.

19. Li L, You W, Ren W. The ZJU index is a powerful index for identifying NAFLD in the general Chinese population. Acta Diabetol. 2017 Oct;54(10):905-911. doi: 10.1007/s00592-017-1024-8.

20. Lee I, Cho J, Park J, Kang H. Association of hand-grip strength and non-alcoholic fatty liver disease index in older adults. J Exerc Nutrition Biochem. 2018 Dec 31;22(4):62-68. doi: 10.20463/jenb.2018.0031.

21. Long MT, Pedley A, Colantonio LD, Massaro JM, Hoffmann U, Muntner P, et al. Development and Validation of the Framingham Steatosis Index to Identify Persons With Hepatic Steatosis. Clin Gastroenterol Hepatol. 2016 Aug;14(8):1172-1180.e2. doi: 10.1016/j.cgh.2016.03.034.

22. Sheng G, Lu S, Xie Q, Peng N, Kuang M, Zou Y. The usefulness of obesity and lipid-related indices to predict the presence of Non-alcoholic fatty liver disease. Lipids Health Dis. 2021 Oct 10;20(1):134. doi: 10.1186/s12944-021-01561-2.

23. Xiao G, Zhu S, Xiao X, Yan L, Yang J, Wu G. Comparison of laboratory tests, ultrasound, or magnetic resonance elastography to detect fibrosis in patients with nonalcoholic fatty liver disease: A meta-analysis. Hepatology. 2017 Nov;66(5):1486-1501. doi: 10.1002/hep.29302.

24. Domingo-Salvany A, Bacigalupe A, Carrasco JM, Espelt A, Ferrando J, Borrell C; del Grupo de Determinantes Sociales de Sociage Española de Epidemiología. Propuestas de clase social neoweberiana y neomarxista a partir de la Clasificación Nacional de Ocupaciones 2011. Gac Sanit. 2013 May-Jun;27(3):263-72. doi: 10.1016/j.gaceta.2012.12.009.

25. Liu Z, Zhang Y, Graham S, Wang X, Cai D, Huang M, et al. Causal relationships between NAFLD, T2D and obesity have implications for disease subphenotyping. J Hepatol. 2020 Aug;73(2):263-276. doi: 10.1016/j.jhep.2020.03.006.

26. Milić S, Lulić D, Štimac D. Non-alcoholic fatty liver disease and obesity: biochemical, metabolic and clinical presentations. World J Gastroenterol. 2014 Jul 28;20(28):9330-7. doi: 10.3748/wjg.v20.i28.9330.

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ORIGINAL

Comparing the effect of three trigger methods (human HCG, combination of recombinant HCG with GnRH agonist, and double recombinant HCG) on the fertility outcome of patients with poor ovarian response in ovulation stimulation cycle (IVF/ICSI)

Comparación del efecto de tres métodos desencadenantes (HCG humana, combinación de HCG recombinante con agonista de GnRH y HCG recombinante doble) en el resultado de la fertilidad de pacientes con respuesta ovárica deficiente en el ciclo de estimulación de la ovulación (FIV/ICSI)

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Abstract

Aim: The aim of this study is comparing the effect of three trigger methods (human HCG, combination of recombinant HCG with GnRH agonist, and double recombinant HCG) on the fertility outcome of patients with in poor ovarian response in ovulation stimulation cycle (IVF/ICSI).

Methods: In this double-blind randomized clinical trial study, 158 patients with low ovarian reserve were divided to three groups: Group 1: Two doses of recombinant HCG (Ovitrelle) at a dose of 250 µg at 12 hour intervals, Group 2: HCG trigger (KARMA) alone at a dose of 10,000 units, and Group 3: 250 µg of recombinant HCG+ GNRH agonist. Collected data includes age, BMI, AMH, type of transferred embryo (Fresh or Freez), number of embryos, and results of pregnancy (clinical pregnancy rate/ongoing pregnancy rate/ implantation rate). Three groups is statistically similar in terms of age and BMI, AMH, and AFC.

Results: In groups 1 and 3, the number of oocytes, the number of M2 oocytes and the number of 2PN embryos was higher than group 2 after ovulation. The percentage of empty follicle syndrome was low in the two groups 1 and 3. Three groups had no significant difference in term of fertilization rate, the number of embryos A, B, and C, chemical pregnancy, clinical pregnancy, ongoing pregnancy, and implantation rate.

Conclusion: Dual trigger treatment with recombinant hCG and GNRH agonist and double recombinant hCG can improve fertility outcome patients with poor response in ovulation stimulation cycle. However, there were no significant differences among three groups regarding pregnancy results.

Keywords: recombinant HCG, GnRH agonist, Fertility, Pregnancy, Ovulation.

Resumen

Objetivo: El objetivo de este estudio es comparar el efecto de tres métodos desencadenantes (HCG humana, combinación de HCG recombinante con agonista de GnRH y HCG recombinante doble) sobre el resultado de fertilidad de pacientes con respuesta ovárica deficiente en el ciclo de estimulación de la ovulación (FIV/ ICSI).

Metodología: En este ensayo clínico aleatorio doble ciego, 158 pacientes con baja reserva ovárica se dividieron en tres grupos: Grupo 1: Dos dosis de HCG recombinante (Ovitrelle) a una dosis de 250 µg a intervalos de 12 horas, Grupo 2: HCG desencadenante (KARMA) solo a una dosis de 10.000 unidades, y Grupo 3: 250 µg de agonista de HCG+ GNRH recombinante. Los datos recopilados incluyen edad, IMC, AMH, tipo de embrión transferido (fresco o congelado), número de embriones y resultados del embarazo (tasa de embarazo clínico/tasa de embarazo en curso/tasa de implantación). Los tres grupos son estadísticamente similares en términos de edad e IMC, AMH y AFC.

Resultados: En los grupos 1 y 3, el número de ovocitos, el número de ovocitos M2 y el número de embriones 2PN fue mayor que el grupo 2 después de la ovulación. El porcentaje de síndrome de folículo vacío fue bajo en los dos grupos 1 y 3. Los tres grupos no tuvieron diferencias significativas en términos de tasa de fertilización, número de embriones A, B y C, embarazo químico, embarazo clínico, embarazo en curso y tasa de implantación.

Conclusiones: El tratamiento de activación dual con hCG recombinante y agonista de GNRH y hCG recombinante doble puede mejorar los resultados de fertilidad en pacientes con una respuesta deficiente en el ciclo de estimulación de la ovulación. Sin embargo, no hubo diferencias significativas entre los tres grupos con respecto a los resultados del embarazo.

Palabras clave: HCG recombinante, agonista de GnRH, Fertilidad, Embarazo, Ovulación.

Introduction

People with poor ovarian response in ovulation stimulation cycle are identified according to the Blogna criteria[1]. According to these criteria, individuals who meet two of the following three criteria may be considered poor responders to ovarian stimulation:

1. Age over 40 years or risk factors for reducing ovarian reserve, such as a history of surgery on the ovary, etc.
2. History of previous poor response to IVF (less than 3 oocytes in the previous cycle)
3. Abnormal ovarian reserve test AFC (antral follicle count) (less than 5 to 7) or AMH (anti-Müllerian hormone) less than 1.1[1]

During various studies, different treatment strategies (such as stimulating ovulation, vitamin supplements, various trigger methods, and etc.) have been stated to increase the response of infertile patients in the IVF cycle with poor response[2-6]. None of these strategies has been stated as the main protocol yet, due to the sensitivity of these patients and the small amount of ovarian reserve[6]. So, more research is still needed in this field. In the IVF cycle, when the size of the follicle reaches the appropriate amount, the HCG hormone is used to resume meiosis and enter the oocyte into meiosis II due to its structural similarity with the LH hormone. Ovulation is carried out under ultrasound guidance after 36 hours. In studies in patients with poor ovulation response in the IVF cycle, changes in this hormone have been applied. In a number of studies, the combination of HCG with GNRH agonist has been used in patients with low reserve, and the rate of pregnancy results is higher than HCG alone for triggering in the IVF cycle. According to a hypothesis, in a study, two injections of newly synthesized HCG have been used in the IVF cycle of patients with low reserve, with the mechanism that the second dose of HCG at an interval of 12 hours can release the cumulus mass and attached oocyte to the follicle wall, and prevent from the empty follicle syndrome. Zhang et al. comprised HCG trigger method with or without GNRH in IVF patients with poor response. This group showed that there was a higher number of oocytes in the combined treatment group, but there was no difference between the two groups in terms of fertility results[7]. In similar study, Eftekhar et al. showed no difference in the number of oocytes and fertility results in HCG trigger method with or without GNRH in IVF patients with poor response[8]. Lin et al.[9] and Maged et al.[10] indicated that HCG trigger method along with GNRH can enhance both number of oocytes and fertility results. Tesarik et al. used recombinant HCG in IVF patients with poor response. This groups showed that the follicles had oocytes in the new cycle after treatment[11]. So, based on limited studies with various results, in our study, we comprised three trigger methods (human HCG, combination of recombinant HCG with GNRH agonist, and double recombinant HCG) on the fertility outcome of patients with poor response in ovulation stimulation cycle (IVF/ICSI).

Materials and methods

This is a double-blind randomized clinical trial study. Patients under the age of 43 with two bologna criteria were included in study:

1. Age over 40 years or risk factors for reducing ovarian reserve, such as a history of surgery on the ovary, etc.
2. History of previous poor response to IVF (less than 3 oocytes in the previous cycle)
3. Abnormal ovarian reserve test: Antral Follicle Count (AFC) less than 5 to 7 or anti-Müllerian hormone (AMH) less than 1.1.

Patients with azoospermia, history of surgery on the uterus, endocrine disorders such as diabetes, history of repeated abortions, repeated failure of implantation more than equal to 3 times in the history, and BMI>30 were not entered to study.

Patients who get infected with corona virus during the cycle, patients who did not respond properly to the ovulation stimulation cycle, and patients who have taken drugs incorrectly during the cycle were excluded from study. In the third day of menstruation cycle day, selected patients were administrated with combined 150IU units recombinant FSH (CINALF brand Iran) and 150 UI hMG (KARMA brand Iran). When a follicle was seen on TVS above 14 mm, 0.25 mg of GnRH antagonist (Cetrorelix) was given daily up to oocyte triggering. Then, after observing at least two or three follicles, patients were divided to three groups:

Group 1: Two doses of recombinant HCG (Ovitrelle) at a dose of 250 µg at 12 hour intervals.
Group 2: HCG trigger (KARMA) alone at a dose of 10,000 units.
Group 3: 250 µg of recombinant HCG+ GNRH agonist

COVID-19 polymerase chain reaction (PCR) test were checked for all patients before oocyte reteieval. Oocytes were retrieved under anesthesia and with vaginal ultrasound guidance (voluson E6 brand) 36 hours after triggering. On the same day, a sperm sample was taken from the wife and prepared by a laboratory process, and microinjection was performed by an embryologist. Three days after the preparation of embryos, their quality was determined by the embryologist based on the degree of fragmentation, and embryos with quality a, b were candidates for transfer Then in morula or blastocyst stage under sonographic guidance (voluson E6 brand) maximum two embryos was transferred with LABOTEK catheter. After embryo transfer, luteal phase support with progesterone (50 mg) twice a day intramuscularly from the day of ovulation and continues until 12 weeks of IM pregnancy. βhCG test was requested two weeks after embryo transfer and vaginal sonography was performed one week later to prove the presence of

pregnancy. Collected data includes age, BMI, AMH, type of transferred embryo (Fresh or Freeze), number of embryos, and results of pregnancy (clinical pregnancy rate/ongoing pregnancy rate/ implantation rate).

Data analysis was done by SPSS version 24. ANOVA test was used to compare the average number of M2 oocytes and the number of 2PN, A, B, C obtained embryos after ovulation in the three studied groups. Chi-square test was used to compare the frequency of chemical pregnancy, the frequency of implantation rate (the gestational sac in ultrasound number of embryo transferred), the frequency of clinical pregnancy (fetal heart activity in ultrasound per transfer), and the frequency of ongoing pregnancy (pregnancy continuing until the 12th week of pregnancy per transfer) in the three study groups. P<0.05 was considered significant. In the statistical analysis, v1 is the ratio of the number of oocytes to the number of follicles above 14. v2 is the number of gestational sacs, and its number divided by the number of transferred embryos represents the implantation rate. W12 is the number of gestational sacs with a heart at 12 weeks of pregnancy divided by the number of transferred cycles and is used to obtain the ongoing pregnancy rate.

Results

In this study, 158 patients with low ovarian reserve according to Blogna criteria were included. Eight patients were excluded from the study: Two patients due to a positive corona test, three patients due to non-acceptance of medication, and three patients due to the wrong use of medication. Three groups is statistically similar in terms of age and BMI, AMH, and AFC. There was no significant difference in term of progesterone and estradiol levels before the trigger among three groups. Three groups did not differ in terms of the total dose of gonadotropin and the duration of gonadotropin treatment and the number of follicles above 14 mm. In groups 1 and 3, the number of oocytes, the number of M2 oocytes and the number of 2PN embryos was higher than group 2 after ovulation. The percentage of empty follicle syndrome was low in the two groups 1 and 3 (**Table I**). Three groups had no significant difference in term of fertilization rate, the number of embryos A, B, and C, chemical pregnancy, clinical pregnancy, ongoing pregnancy, and implantation rate. In the statistical analysis, there is no significant difference among three groups in term of v1, v2, and v3 variables (**Table II**).

Discussion

In this study, we compared and evaluated the IVF/ICSI results of three methods, human HCG, combination of recombinant HCG with GNRH agonist, and double recombinant HCG. Acquired results showed that in groups with combination of recombinant HCG with GNRH agonist, and double recombinant HCG had higher number of oocytes, the number of M2 oocytes and the number of 2PN embryos than human HCG. The percentage of empty follicle syndrome was also lower in in groups with combination of recombinant HCG with GNRH agonist, and double recombinant HCG alone. In previous studies, similar results was reported. In these studies, dual-trigger using GnRH agonist and hCG was introduced as the best strategy. However, we used recombinant hCG in this dual-trigger method. More studies showed no significant differences between dual-trigger and hCG alone. In dual triggering, we used recombinant HCG. Eftekhar et al showed that recombinant HCG is as effective as urine HCG. This group indicated that the numbers of retrieved oocyte,

Table I: Comparison of demographic data among three groups.

	Trigger with 12 hour		Trigger with 2 hCG		Trigger with 2 deka and oitrel		p-value
	mean	SD	mean	SD	mean	SD	
Age	35.74	3.95	34.74	3.53	35.86	4.05	0.283
BMI	24.60	1.22	24.54	0.64	24.56	1.24	0.961
Amn	0.77	0.34	0.80	0.29	0.79	0.28	0.887
AFC	3.76	1.04	3.68	1.11	3.48	1.01	0.397
Basal fsh	7.39	1.38	7.15	1.46	7.34	1.23	0.654
Fertilizat rat	78.40	27.01	75.30	34.54	79.80	26.47	0.739
No_2PN	2.34	1.20	1.86*	1.21	2.56	1.16	0.31
Duration of stimulate day	10.06	1.83	10.22	1.56	10.16	1.60	0.890
Total_Dose_of_gonadotrop	1832.40	278.83	1808.50	240.77	1777.40	242.18	0.557
Serum_E2	931.90	385.20	883.40	388.28	880.34	427.01	0.771
Serum_pr	0.88	0.43	0.73	0.37	0.79	0.38	0.187
No_Follicle	4.04	1.41	4.00	1.17	4.26	1.44	0.585
No_Total_oocyte	3.40	1.47	2.54*	1.72	3.50	1.63	0.006
No_Muture_oocyte	2.52	1.35	1.46*	1.31	2.62	1.41	0.001
Empty follicle syndrome	17.56	3.08	40.66*	4.82	21.33	3.18	0.001
Total embryo	1.86	1.38	1.82	1.56	1.96	1.21	0.875
Embryo grade A	0.64	0.13	0.46	0.10	0.56	0.11	0.559
Embryo grade B	1.14	0.13	1.14	0.16	1.24	0.14	0.859
Embryo grade C	0.42	0.11	0.20	0.08	0.52	0.11	0.085
Total No embryo_transfer	1.26	1.02	0.94	0.99	1.36	0.87	0.08

Table II: Comparison of pregnancy-related data among three groups.

	Trigger with 12 hour		Trigger with 2 hCG		Trigger with 2 deka and oitrel		p-value
	number	%	number	%	number	%	
Previus_IVF_attempt							
0	35	70	27	54	40	80	0.066
1	13	26	18	36	9	18	
2	2	4	5	10	1	2	
IVF_indicator							
T	18	36	15	30	14	28	0.066
U	27	54	27	54	23	46	
M	5	19	8	16	8	16	
C	0	0	0	0	5	10	
Cancelation_rate							
BAD ANDOMETER	6	12	7	14	7	14	0.403
ABSENCE EMBRYO	9	18	11	22	6	12	
ABSENCE OVUM	2	4	6	12	2	4	
NO CANCEL	33	66	26	52	35	70	
No_embryo_grade_A							
0	32	64	34	68	32	64	0.499
1	6	12	9	18	8	16	
2	10	20	7	14	10	20	
3	2	4	0	0	0	0	
No_embryo_grade_B							
0	17	34	22	44	17	34	0.165
1	10	20	7	14	7	14	
2	22	44	14	28	24	48	
3	1	2	6	12	1	2	
4	0	0	1	2	1	2	
No_embryo_grade_C							
0	47	94	44	88	44	88	0.783
1	2	4	3	6	4	8	
2	1	2	2	4	2	4	
4	0	0	1	2	0	0	
No_transfer_grade_A							
0	38	76	44	88	33	66	0.148
1	4	8	2	4	8	16	
2	7	14	4	8	9	18	
3	1	2	0	0	0	0	
No_transfer_grade_B							
0	25	50	31	62	27	54	0.794
1	9	18	7	14	5	10	
2	15	30	11	22	17	34	
3	1	2	1	2	1	2	
No_transfer_grade_C							
0	50	100	47	94	50	100	0.190
1	0	0	1	2	0	0	
2	0	0	2	4	0	0	
Result_pregnancy							
NO	38	76	39	78	39	78	0.963
YES	12	24	11	22	11	22	
V1	0.82	0.21	0.59*	0.34	0.78	0.22	0.001
V2							
0	42	84	43	86	42	84	0.950
1	8	16	7	14	8	16	
V3							
0	44	88	45	90	44	88	0.936
1	6	12	5	10	6	12	
W12							
0	45	90	45	90	46	92	0.924
1	5	10	5	10	4	8	
Implementation rate							
	8/63	12.6	7/47	14.89	8/68	11.76	0.884

maturation rates, and fertilization and clinical pregnancy rates are similar in both recombinant and urine HCG[12]. Based on similar studies, increases of the number of oocyte, mature oocytes and the number of zygotes can improve the IVF outcome[9,13,14]. In current study, these increases is more in dual triggering than HCG alone. On the other hand, these increases is more in triggering with recombinant than urine HCG. Beck-Fruchter et al[15] and Castillo et al[16] mentioned that combination of HCG with GNRH agonist can used for treatment of recurrent empty follicle syndrome. Based on our results, the percentage of empty follicle syndrome was lower in dual triggering than HCG alone. Based on Humaidan et al study, administration of hCG either 12 or 35 hours after GnRH agonist trigger can lead to rescue of corpus luteum function[17]. This condition reduce the pregnancy loss rate. Lin et al also showed that dual triggering can increase ongoing pregnancy rates and clinical pregnancy rate[9]. In our study, number of oocyte is also better values in dual triggering than urine HCG alone group. However, these difference but result of pregnancy is not statistically significant in our study. Based on a Meta-analysis study (2021), seven studies data showed that dual trigger treatment by HCG and GNRH agonist had significant effects on clinical pregnancy rate compared with HCG trigger alone[18]. This data is not compatible with our study. We showed that there is no significant difference among three groups in term of clinical pregnancy rate. Our data is compatible with Eftekhar et al. study[8]. Similar to our study, Hu el in Meta-analysis study showed that dual trigger treatment was associated with a significant increase in the number of oocytes, maturate oocytes, and empty follicle syndrome[18]. There are conflicting results regarding the effect of dual trigger treatment and hCG alone treatment on implantation and clinical pregnancy rates[19-22]. These conflicting results can be because most of the reported studies are retrospective. In these studies, potential confounding factors can limit data. Our study showed that in some variable (total oocyte, mature oocyte, and empty follicle syndrome), dual trigger and double trigger treatment has more significant effect than hCG alone treatment. In another variables, especially implementation rate, clinical pregnancy rate, and ongoing pregnancy rate, there was no significant difference. In a pilot study, Tesarik et al. also used double HCG trigger (HCG ovulation trigger 36.5 hours before ovarian puncture and second HCG trigger 12.5 hours later) in women with a paucifollicular response to ovarian stimulation. This group showed that a double HCG trigger appears to improve the rate of oocyte recovery[11]. Similar to Tesarik et al., we showed similar data by application of same double HCG trigger procedure. Our data also showed that dual trigger treatment can improve the number of oocytes, maturate oocytes, and empty follicle syndrome. Similar to Tesarik et al. suggestion, the addition of a second injection of HCG at 12 hour intervals can improve pregnancy in patients with poor ovarian response. Moreover, we showed that application of combination method (recombinant HCG+ GnRH agonist) also improve pregnancy rates.

Conclusion

In conclusion, our study showed that dual trigger treatment with recombinant hCG and GNRH agonist and double recombinant hCG can improve fertility outcome patients with poor response in ovulation stimulation cycle. However, there were no significant differences among three groups regarding pregnancy results. It's recommended that a study with larger populations design and comprise the live birth rates. It is necessary to study the pregnancy results of frozen embryos in these patients. Further studies are also required to identify the specific characteristics of women to help the fertility specialist's counseling based on patient's characteristics.

Conflict of Interest

The authors declare that no competing interests exist.

References

1. Younis JS, Ben-Ami M, Ben-Shlomo I. The Bologna criteria for poor ovarian response: a contemporary critical appraisal. Journal of ovarian research. 2015;8:76.

2. Ubaldi F, Vaiarelli A, D'Anna R, Rienzi L. Management of poor responders in IVF: is there anything new? BioMed research international. 2014;2014:352098.

3. Drakopoulos P, Bardhi E, Boudry L, Vaiarelli A, Makrigiannakis A, Esteves SC. Update on the management of poor ovarian response in IVF: the shift from Bologna criteria to the Poseidon concept. 2020;14:2633494120941480.

4. Oehninger S. Poor responders in in vitro fertilization (IVF) therapy: the challenge continues. Facts, views & vision in ObGyn. 2011;3(2):101-8.

5. Ubaldi FM, Rienzi L, Ferrero S, Baroni E, Sapienza F, Cobellis L, et al. Management of poor responders in IVF. Reproductive biomedicine online. 2005;10(2):235-46.

6. Jeve YB, Bhandari HM. Effective treatment protocol for poor ovarian response: A systematic review and meta-analysis. Journal of human reproductive sciences. 2016;9(2):70-81.

7. Zhang J, Wang Y, Mao X, Chen Q, Hong Q, Cai R, et al. Dual trigger of final oocyte maturation in poor ovarian responders undergoing IVF/ICSI cycles. Reproductive biomedicine online. 2017;35(6):701-7.

8. Eftekhar M, Naghshineh E, Neghab N, Hosseinisadat R. A comparison of dual triggering (by administration of GnRH agonist plus HCG) versus HCG alone in poor ovarian responders in ART outcomes. Middle East Fertility Society Journal. 2018;23(4):350-3.

9. Lin MH, Wu FSY, Lee RKK, Li SH, Lin S Hwu YM. Dual trigger with combination of gonadotropin-releasing hormone agonist and human chorionic gonadotropin significantly improves the live-birth rate for normal responders in GnRH-antagonist cycles. Fertility and sterility. 2013;100(5):1296-302.

10. Maged AM, Ragab MA, Shohayeb A, Saber W, Ekladious S, Hussein EA, et al. Comparative study between single versus dual trigger for poor responders in GnRH-antagonist ICSI cycles: A randomized controlled study. International Journal of Gynecology & Obstetrics. 2021;152(3):395-400.

11. Tesarik J, Galán-Lázaro M, Mendoza N, Mendoza-Tesarik R. Double HCG trigger improves recovery of oocytes in women with a paucifollicular response to ovarian stimulation: A pilot study. International Journal of Gynecology & Obstetrics. 2022;157(1):149-53.

12. Eftekhar M, Khalili MA, Rahmani E. The efficacy of recombinant versus urinary HCG in ART outcome. Iranian journal of reproductive medicine. 2012;10(6):543-8.

13. Orvieto R. Triggering final follicular maturation-hCG, GnRH-agonist or both, when and to whom? Journal of ovarian research. 2015;8(1):1-6.

14. Haas J, Bassil R, Cadesky K, Casper R. Dual trigger vs. HCG for final oocyte maturation. A prospective randomized controlled, double blinded study: preliminary results. Fertility and Sterility. 2017;108(3):e229.

15. Beck-Fruchter R, Weiss A, Lavee M, Geslevich Y, Shalev E. Empty follicle syndrome: successful treatment in a recurrent case and review of the literature. Human Reproduction. 2012;27(5):1357-67.

16. Castillo JC, Moreno J, Dolz M, Bonilla-Musoles F. Successful pregnancy following dual triggering concept (rhCG+ GnRH agonist) in a patient showing repetitive inmature oocytes and empty follicle syndrome: case report. Journal of Medical Cases. 2013;4(4):221-6.

17. Humaidan P, Bungum L, Bungum M, Andersen CY. Rescue of corpus luteum function with peri-ovulatory HCG supplementation in IVF/ICSI GnRH antagonist cycles in which ovulation was triggered with a GnRH agonist: a pilot study. Reproductive biomedicine online. 2006;13(2):173-8.

18. Hu KL, Wang S, Ye X, Zhang D, Hunt S. GnRH agonist and hCG (dual trigger) versus hCG trigger for follicular maturation: a systematic review and meta-analysis of randomized trials. Reproductive biology and endocrinology : RB&E. 2021;19(1):78.

19. Lin M-H, Wu FS-Y, Hwu Y-M, Lee RK-K, Li R-S, Li S-H. Dual trigger with gonadotropin releasing hormone agonist and human chorionic gonadotropin significantly improves live birth rate for women with diminished ovarian reserve. Reproductive biology and endocrinology. 2019;17(1):1-7.

20. Griffin D, Benadiva C, Kummer N, Budinetz T, Nulsen J, Engmann L. Dual trigger of oocyte maturation with gonadotropin-releasing hormone agonist and low-dose human chorionic gonadotropin to optimize live birth rates in high responders. Fertility and sterility. 2012;97(6):1316-20.

21. Griffin D, Feinn R, Engmann L, Nulsen J, Budinetz T, Benadiva C. Dual trigger with gonadotropin-releasing hormone agonist and standard dose human chorionic gonadotropin to improve oocyte maturity rates. Fertility and sterility. 2014;102(2):405-9.

22. Chen C-H, Tzeng C-R, Wang P-H, Liu W-M, Chang H-Y, Chen H-H, et al. Dual triggering with GnRH agonist plus hCG versus triggering with hCG alone for IVF/ICSI outcome in GnRH antagonist cycles: a systematic review and meta-analysis. Archives of gynecology and obstetrics. 2018;298(1):17-26.

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ORIGINAL

Evaluation of the Antibacterial Effects of the Various Nanoparticles Coated Orthodontic Brackets: A Systematic Review and Meta-analysis

Evaluación de los efectos antibacterianos de los diversos brackets de ortodoncia recubiertos con nanopartículas: Una revisión sistemática y metanálisis

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Abstract

Objectives: The antibacterial activity of zinc oxide (ZnO) and silver (Ag) nanoparticles (NPs) has been investigated in this study to present achievements in this field with the consensus of outcomes. This systematic review and meta-analysis clarified the antibacterial potential of silver, zinc-oxide NPs-coated Orthodontic Brackets.

Methods: PRISMA 2020 Checklist was the basis for performing the current systematic review and meta-analysis. The search strategy was to screen the relevant databases on PubMed, Embase, Web of Science, Scopus, ISI Web of knowledge, and EBSCO from inception until 1 November 2022. We calculated a 95% confidence interval (95%CI) for the mean difference (MD) based on the fixed effect model and Inverse-variance method. Stata/MP version 17 software was applied to conduct the meta-analysis.

Results: In the initial search, duplicate studies were removed, and the abstracts of 209 separate relevant articles were presented. Two individual authors reviewed the full text of 32 articles, resulting in the final eight articles. The mean difference (MD) of the antibacterial effect of bracket coatings against L. acidophilus between AgNPs coating and the controls was estimated at 2.71 (MD, 2.71 95%CI 2.05-3.37; p=0.00). The mean difference (MD) of the antibacterial potential of bracket coatings against S. mutans between ZnONPs coating and the controls was estimated to be -275.54 (MD, -275.54 95%CI -281.23, -269.85; p=0.00).

Conclusions: The results of our meta-analysis revealed that Ag, ZnO, and Ag/ZnO NPs-coated brackets had antibacterial activity against L. acidophilus and S. mutans compared to uncoated brackets.

Keywords: Orthodontic, Orthodontic bracket, Nanoparticles.

Resumen

Objetivos: En este estudio se investigó la actividad antibacteriana de las nanopartículas (NP) de óxido de zinc (ZnO) y plata (Ag) para presentar los logros en este campo con el consenso de los resultados. Esta revisión sistemática y metanálisis aclararon el potencial antibacteriano de los brackets de ortodoncia recubiertos con NPs de óxido de zinc y plata.

Métodos: La lista de verificación PRISMA 2020 fue la base para realizar la revisión sistemática y el metanálisis actuales. La estrategia de búsqueda fue examinar las bases de datos relevantes en PubMed, Embase, Web of Science, Scopus, ISI Web of Knowledge y EBSCO desde el inicio hasta el 1 de noviembre de 2022. Calculamos un intervalo de confianza del 95% (IC del 95%) para la diferencia de medias (MD) basado en el modelo de efectos fijos y el método de la varianza inversa. Se aplicó el software Stata/MP versión 17 para realizar el metanálisis.

Resultados: en la búsqueda inicial, se eliminaron los estudios duplicados y se presentaron los resúmenes de 209 artículos relevantes separados. Dos autores individuales revisaron el texto completo de 32 artículos, lo que resultó en los ocho artículos finales. La diferencia media (DM) del efecto antibacteriano de los recubrimientos de brackets contra L. acidophilus entre el recubrimiento de AgNP y los controles se estimó en 2,71 (DM, 2,71; IC del 95%: 2,05-3,37; p=0,00). La diferencia media (DM) del potencial antibacteriano de los recubrimientos de brackets contra S. mutans entre el recubrimiento de ZnONP y los controles se estimó en -275,54 (DM, -275,54, IC del 95%: -281,23, -269,85; p = 0,00).

Conclusiones: Los resultados de nuestro metanálisis revelaron que los brackets recubiertos con Ag, ZnO y Ag/ZnO NPs tenían actividad antibacteriana contra L. acidophilus y S. mutans en comparación con los brackets sin recubrimiento.

Palabras clave: Ortodoncia, bracket de ortodoncia, nanopartículas.

Introduction

Orthodontic treatment is usually done for cosmetic purposes; using fixed appliances in orthodontic treatment is the most common method. However, it causes changes in the oral environment[1]. These changes cause a decrease in Ph and an increase in the microbial load in the tooth cavity, which can be the retention of food particles[2]. Studies have shown that *Lactobacillus acidophilus* (L. acidophilus) and *Streptococcus mutans* (S. mutans) are among the microorganisms that increase in the graft and/or band in the oral cavity[3,4]. Evidence shows that S. mutans has a critical role in the initiation of the decay process[5], and L. acidophilus plays a more significant role in the process of caries propagation[6]. Also, the decrease in pH results in the demineralization of tooth enamel as white spot lesions (WSLs), eventually developing more cavitation. Accordingly, one of the main concerns of the patient and the orthodontist is the appearance of WSLs during bonding[7].

Oral hygiene care is recommended and emphasized to all patients during orthodontic treatment. However, the increased microbial load is still noted. The use of resin materials containing antibacterial agents[8], varnish[9], and modified orthodontic elastomers[10] are among the methods that are used to control and prevent the development of WSLs. The addition of nanoparticles (NPs) to orthodontic adhesives[10,11] has recently been of great interest. NPs with a size smaller than 100 nm and insoluble materials have been introduced[12]; Therefore, due to their small size, NPs have a greater surface-to-volume ratio and strongly interact with microbial membranes of microorganisms; which can have antimicrobial activity[13]. Since the introduction of NPs, multiple metals such as silver (Ag), gold (Au), copper (Cu), titanium (Ti), and zinc (Zn) have shown antimicrobial activity. Studies have shown that each activity has different properties and scope[3,14]. Ag, Ag ions, and Ag compounds are the most common antibacterial agents[15]. Studies have shown that AgNPs have antimicrobial properties by augmenting dental resin composites and being coated on orthodontics brackets and wires[16-18]. Using zinc oxide (ZnO) NPs can also affect the activity of bacteria[19]. A study has shown that using ZnO on the coating of orthodontic wires can have antibacterial activity[20]. Studies have shown that AgNPs have greater antimicrobial potential than ZnONPs[21]. However, studies introduced AgNPs as genotoxic and cytotoxic agents for human cells[22]. Studies show that the cost of using AgNPs is also higher in addition to the cytotoxicity of AgNPs. Therefore, the current study investigated the antibacterial performance of ZnONPs and AgNPs to present achievements in this field with the consensus of outcomes. This systematic review and meta-analysis clarified the antibacterial potential of AgNPs and ZnONPs-coated Orthodontic Brackets.

Method

The process of searching for articles

PRISMA 2020 Checklist was the basis for performing the current systematic review and meta-analysis. [23]. The search strategy was to screen the relevant databases on PubMed, Embase, Web of Science, Scopus, ISI Web of knowledge, and EBSCO using keywords related to the objectives of the study until 1 November 2022 were reviewed. Google Scholar search engine was also used to find related articles. MeSH keywords:

(((((((“Orthodontic Brackets”[Mesh] OR “Orthodontic Wires”[Mesh] OR “Orthodontic Appliances”[Mesh] OR “Orthodontic Appliances, Fixed”[Mesh] OR “Dental Cements”[Mesh] OR “Dental Bonding”[Mesh]) AND “Nanoparticles”[Mesh]) OR (“Nanoparticles/microbiology”[Mesh] OR “Nanoparticles/standards”[Mesh] OR “Nanoparticles/statistics and numerical data”[Mesh] OR “Nanoparticles/toxicity”[Mesh])) AND “Silver”[Mesh]) AND “Zinc Oxide”[Mesh]) AND “Metal Nanoparticles”[Mesh]) AND (“Anti-Bacterial Agents”[Mesh] OR “Anti-Bacterial Agents” [Pharmacological Action])) AND “mutacin III, Streptococcus mutans” [Supplementary Concept]) AND “acidocin D20079, Lactobacillus acidophilus” [Supplementary Concept].

Data items, Data collection, and Selection process

Table II represents the used checklist, involving the name of the first author, year of publication, sample size, study design, control group, intervention group, and survival rate extracted and reported. Also, the data required for meta-analysis, including clinical outcome, Antibacterial effect of brackets coating, were extracted from the studies. All articles were selected based on the inclusion criteria, two reviewers independently screened each record, and each report was retrieved.

Eligibility criteria

Inclusion criteria: Inclusion criteria were a response to PICO, as reported in **table I**. Articles published in English, in-vitro studies, and studies that assessed the antibacterial effect of AgNPs and ZnONPs-coated Orthodontic Brackets.

Exclusion criteria: Case studies, case reports, and review papers. Studies without full-text access.

Table I: PICO search strategy.

PICO strategy	Description
P	Population: orthodontic brackets
I	Intervention: AgNPs and ZnONPs, Ag/ZnO NPs
C	Comparison: brackets as received without modifications
O	Outcome: clinical outcome, Antibacterial activity

Study risk of bias assessment

The quality assessment of searched articles was performed by the modified CONSORT (Guidelines for reporting pre-clinical in vitro studies on dental materials) criteria[24]; Each study was reviewed with 14 items, and the parameters were reported as yes or no. These items were:

Structured abstract of trial design, methods, findings and conclusion, introduction and causes, aims and hypotheses, the applied intervention like processes and duration, with sufficient detail to allow for replication, well-defined primary and secondary outcomes like when and how evaluated, the estimation process of sample size, the generation and implementation processes of randomized allocation, who created the randomized allocation, the blinded participants after assigning the intervention, statistical analysis for group comparison, post-intervention findings and estimated effect size and precision, limitations of the study, assessment of possible bias, lack of accuracy, and where the full trial protocol is available in case of multiplicity of analysis, funding and other support.

The modified Cochrane risk of bias tool was used, each item of which was given a score of 2, 1, or 0 with the sum of scores 0-3, 4-7, and 8-10, meaning low, moderate, and high risks of bias, respectively. In this tool, the lowest score was 0, and the highest score was 10[25].

Data analysis

Data were analyzed by STATA/MP. V17 software. We calculated a 95% confidence interval (95%CI) for the mean difference (MD) based on the fixed effect model and Inverse-variance method. Random effects were used. I2 showed possible heterogeneity, with a value of less than 50% as low and above 50% as moderate-to-high heterogeneity.

Results

The selection process of searched articles

In the initial search, 209 articles related to the keywords were found. Of these, 5 studies were Duplicate records, 8 articles were removed due to ineligibility based on automation tools, and 12 articles were deleted for other reasons. In the next step, abstracts of 184 articles were reviewed, and finally, 152 articles were omitted because of exclusion criteria. After reviewing the full text of 32 articles according to the inclusion criteria, 24 studies were excluded, and eight studies were selected (**Figure 1**).

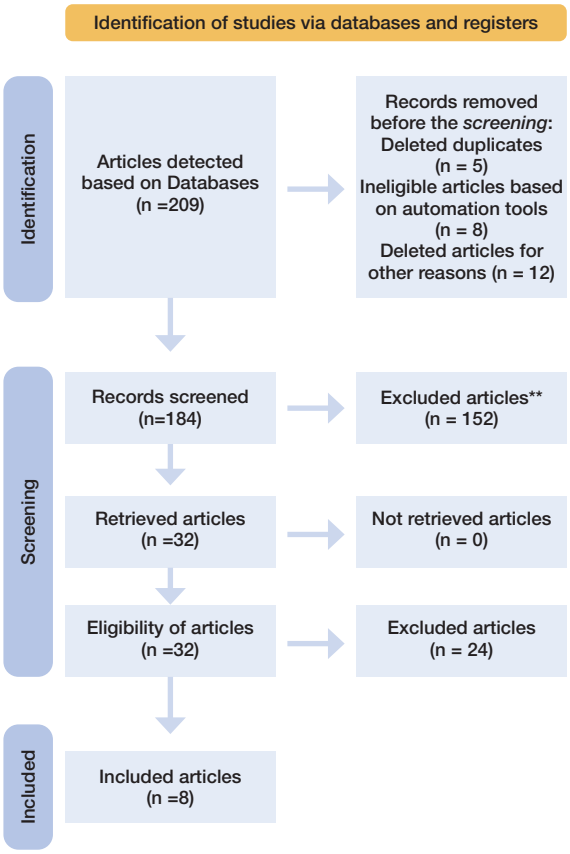
Study characteristics

A total of 566 Orthodontic Brackets were examined; the data from previous attempts are reported in **table II**.

Risk of bias in studies

According to the risk of the bias assessment tool, five studies possessed a moderate risk of bias, and three possessed a low risk of bias (**Tables III** and **IV**).

Figure 1: PRISMA 2020 Checklist.



Antibacterial testing

Antibacterial activity of brackets coating against L. acidophilus

The mean difference (MD) of the antibacterial potential of brackets coating against *L. acidophilus* between Ag NPs coating and the control group was 2.71 (MD, 2.71 95% CI = 2.05, 3.37; p=0.00) with high heterogeneity (I^2=99.84%; P =0.00). The statistical findings indicated a significantly reduced effect on the survival rate of *L. acidophilus* with Ag NPs than the control group (**Figure 2**).

The MD of the antibacterial potential of brackets coating against *L. acidophilus* between ZnO NPs coating and control group was -3.50 (MD, -3.50 95% CI = -4.38, -2.63; p=0.00) with high heterogeneity (I^2=99.81%; P =0.00). The statistical findings indicated a significantly reduced effect on the survival rate of *L. acidophilus* with ZnO NPs than the control group (**Figure 2**).

The MD of the antibacterial potential of brackets coating against *L. acidophilus* between Ag/ZnO NPs coating and controls was -58.12 (MD, -58.12 95% CI = -68.68, -47.56; p=0.00). The statistical findings indicated a significantly reduced effect on the survival rate of *L. acidophilus* with Ag/ZnO NPs than the control group (**Figure 3**).

Figures 2, 3, and **4** statistically significantly reduce the survival rate of L. acidophilus, using Ag/ZnO NPs with the highest impact and then using Ag NPs and ZnO NPs.

Table II: Summary of data.

n	Study. Years	Sample size	Nanoparticle type (n)	Number of the control group	preparation	Antibacterial activity assessment
1	Zeidan et al., 2022 [3]	48	Ag NPs [12], ZnO NPs [12], and Ag/ZnO NPs [12]	12	Before coating the brackets, any unwanted macroscopic contamination was removed; the brackets were cleaned and underwent autoclave sterilization, then stored in a sealed container.	*S. mutans* strain (ATCC 25,175), suspension of concentration 1.5× 106 CFU/mL. Lactobacillus acidophilus
2	Tanbakuchi et al., 2021[26]	30	Ag [10], ZnO [10]	10	The ZnO suspension was prepared by dissolving ZnO powder (0.1 g) in acetone (3 mL); the same way was followed to prepare Ag suspension, followed by pumping at 10-mL/hr flow rate via a syringe pump at 3 cm from the bands.	*S. mutans* ATCC 35668, *L. acidophilus* ATCC 314 and C. albicans ATCC 14053
3	Kachoei et al., 2021 [27]	120	Ag NPs [30], ZnO NPs [30], and Ag/ZnO NPs [30]	30	After dissolving zinc acetylacetonate (0.4 g) with absolute ethanol (20 mL), 30% starch solution (20 mL) was poured drop by drop while stirring within 4 h. The $AgNO_3$ aqueous solution was added dropwise inside the solution while stirring within half an hour and then heating in a water bath.	*S. mutans* ATCC 35668, Staphylococcus aureus ATCC 25923, Lactobacillus gasseri ATCC 33323, Escherichia coli ATCC 25922, and Candida albicans ATCC 10231
4	Yassaei et al., 2020 [28]	130	Hydroxyapatite [26], titanium oxides [26], zinc oxide [26], copper oxide [26], and silver oxide [26] NPs	6	The preparation of hydroxyapatite, zinc, titanium oxides, silver, and copper NPs was performed at the concentrations of 0.5 and 1 wt%, followed by blending with light cure orthodontics.	*S. mutans*
5	Eslamian et al., 2020 [29]	34	Ag NPs [17]	17	The groups individually underwent 0.022-inch bond stainless steel twin brackets, Transbond XT, and nano-adhesive, followed by etching with 37% phosphoric acid for 30 seconds and washing with water for 15 seconds.	*S. mutans*
6	Kambalya et al., 2018 [19]	60	Ag [15], TiO2 [15], and ZnO [15] NPs	15	Equal amounts of TiO2, Ag, and ZnO NPs (160 mg) were added to different sterile test tubes containing BHI broth (4mL), meaning 4% concentration (10mg of the test compound in 1mL BHI broth is equal to 1% of the test compound.	*S. mutans* (ATCC 25175)
7	Ramazanzadeh et al., 2015 [30]	72	nano copper oxide (CuO) [20], ZnO NPs [20], and CuO-ZnO [20]	12	Add the sodium hydroxide solution to zinc sulfate aqueous solution (at the ratio of 1:2) drop by drop while vigorously stirring for 12 hours, then filtering the resultant precipitate and washing it several times with de-ionized water.	*S. mutans*
8	Mirhashemi et al., 2013 [31]	72	ZnO NPs [36]	36	Mixing nano-powder (64 mg) with Transbond XT composite (576 mg) to prepare a dental composite bearing 10% NPs, and reaching a uniform consistency with the aid of a mixing spatula on a glass slab under a semi-dark condition	*S. mutans* ATCC 25175, S. sanguis ATCC 10556 and *L. acidophilus* ATCC 4356

Table III: Quality of the included studies.

Study. Years	Item													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Zeidan et al., 2022[3]	√	√	×	×	×	×	×	×	×	√	×	×	×	×
Tanbakuchi et al., 2021[26]	√	√	√	√	√	√	×	×	×	√	√	√	×	×
Kachoei et al., 2021[27]	√	√	√	√	√	√	×	×	×	√	√	√	×	×
Yassaei et al., 2020[28]	√	√	√	√	√	√	×	×	×	√	√	√	×	×
Eslamian et al., 2020[29]	×	×	×	×	×	×	×	×	×	√	√	√	×	×
Kambalya et al., 2018[19]	×	×	×	×	×	×	×	×	×	√	√	√	×	×
Ramazanzadeh et al., 2015[30]	√	√	√	√	×	√	×	×	×	√	√	√	×	×
Mirhashemi et al., 2013[31]	√	√	×	×	×	×	×	×	×	√	×	×	×	×

Table IV: Risk assessment.

Study. Years	Allocation concealment	Sample size	Blinding	Assessment methods	Selective outcome reporting	Risk of bias
Zeidan et al., 2022[3]	1	1	2	0	0	Moderate
Tanbakuchi et al., 2021[26]	1	0	2	0	0	Low
Kachoei et al., 2021[27]	1	0	2	0	0	Low
Yassaei et al., 2020[28]	1	0	2	0	0	Low
Eslamian et al., 2020[29]	1	1	2	0	0	Moderate
Kambalya et al., 2018[19]	1	1	2	0	0	Moderate
Ramazanzadeh et al., 2015[30]	1	1	2	0	0	Moderate
Mirhashemi et al., 2013[31]	1	1	2	0	0	Moderate

Figure 2: Forest plot showed the Antibacterial potential of Ag NPs-coated Orthodontic Brackets against *L. acidophilus*.

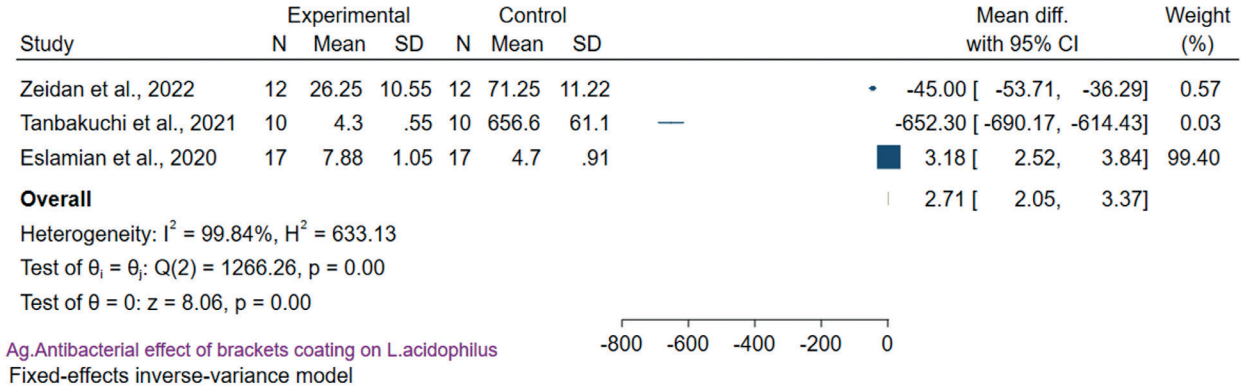


Figure 3: Forest plot showed the Antibacterial potential of ZnO NPs-coated Orthodontic Brackets against *L. acidophilus*.

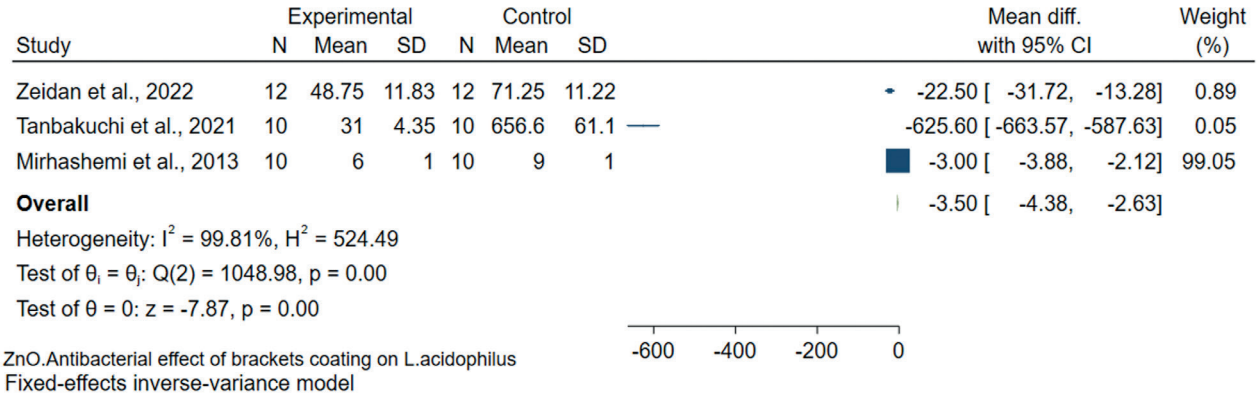
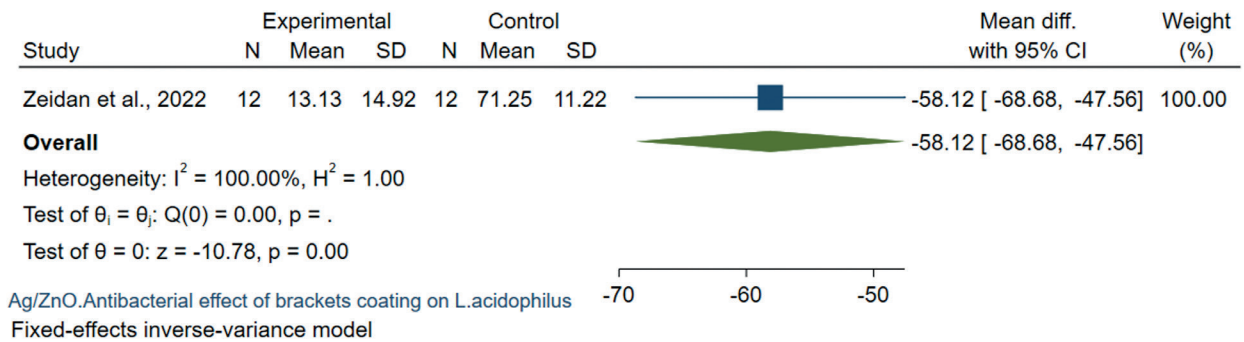


Figure 4: Forest plot showed the antibacterial potential of Ag/ZnO NPs-coated Orthodontic Brackets against *L. acidophilus*.



The MD of the antibacterial performance of brackets coating against *S. mutans* between Ag NPs coating and the controls was -2.87 (MD, -2.87 95% CI = -3.59, -2.15; p=0.00) with high heterogeneity (I^2=100%; P =0.00). The statistical findings indicated a significantly reduced effect on the survival rate of *S. mutans* with Ag NPs than control (**Figure 5**).

The MD of the antibacterial performance of brackets coating against *S. mutans* between ZnO NPs coating and controls was -275.54 (MD, -275.54 95% CI = -281.23, -269.85; p=0.00) with high heterogeneity (I^2=99.99%; P =0.00). The statistical findings indicated a significantly reduced effect on survival rate of *S. mutans* with ZnO NPs than controls (**Figure 6**).

The MD in the antibacterial performance of brackets coating against *S. mutans* between Ag/ZnO NPs coating and the controls was -574 (MD, -574 95% CI = -580.03, -567.97; p=0.00). The statistical findings indicated a significantly reduced effect on the survival rate of S. mutans with Ag/ZnO NPs than controls (**Figure 7**).

Figure 5: Forest plot showed the antibacterial potential of Ag NPs-coated Orthodontic Brackets against *S. mutans*.

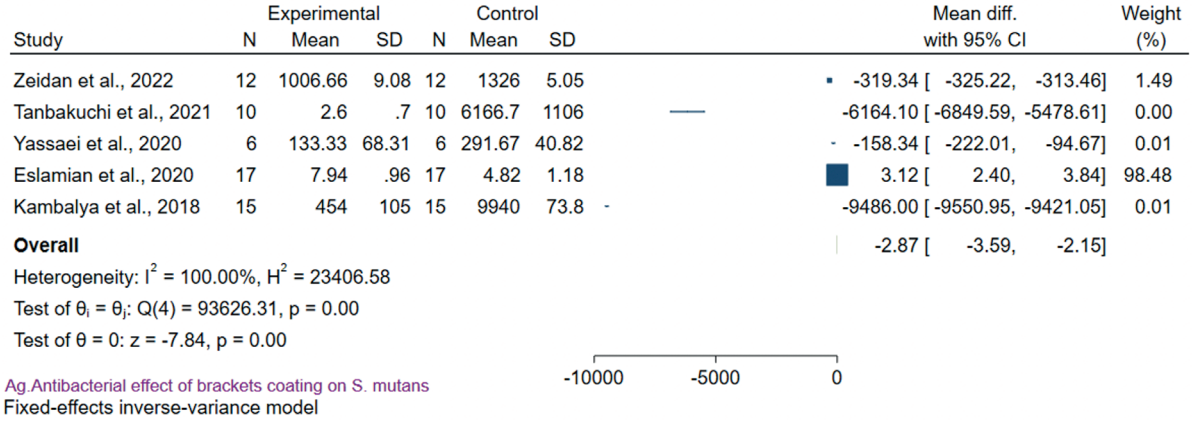


Figure 6: Forest plot showed the antibacterial potential of ZnO NPs-coated Orthodontic Brackets against *S. mutans*.

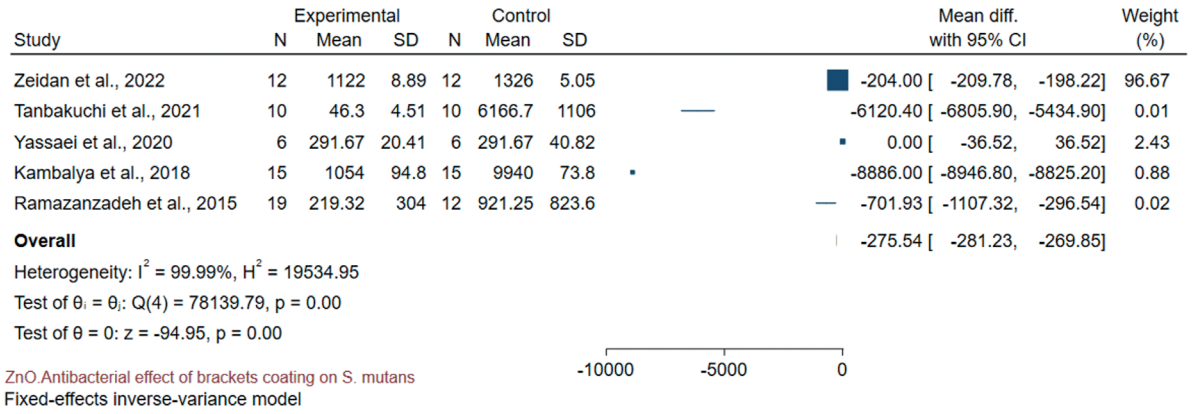
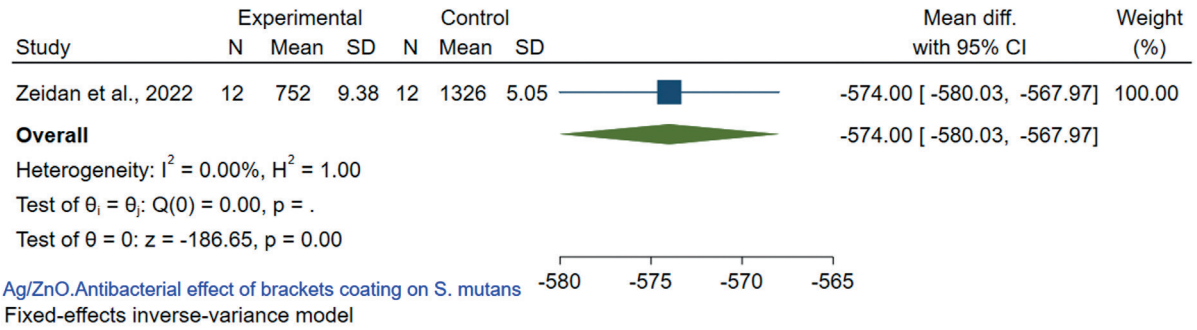


Figure 7: Forest plot showed the antibacterial potential of Ag/ZnO NPs-coated Orthodontic Brackets against *S. mutans*.



Discussion

We aimed to investigate the antibacterial potential of Ag, ZnO, and Ag/ZnO NPs-coated orthodontic brackets. One of the problems of orthodontic patients is tooth decay; Therefore, it is very important to use materials that have antibacterial activity during the orthodontic treatment process, especially in patients who do not brush their teeth[32]. Studies have shown that plaque accumulation, tooth surface demineralization, and the formation of white spot lesions are very common in orthodontic patients[33]. Based on the present meta-analysis, brackets coated with AgNPs, ZnO NPs, and Ag/ZnO NPs revealed a significant difference in antibacterial performance versus the two study bacteria. Similarly, it was shown that brackets coated with silver had an antibacterial activity versus the two study bacteria[34]. Another study showed the greater antimicrobial potential of AgNPs compared to ZnO NPs. The mentioned study investigated the antimicrobial potential of AgNPs and ZnO NPs against *S. mutans*[35]. A study showed that Ag/ZnO had an enhanced antibacterial effect against S. mutans[36]. The Ag and ZnO combination was synthesized to reduce any possible risk for cytotoxic and genotoxic impacts of AgNPs in humans[37] and to obtain the merits of its increased antibacterial activity compared to ZnO[21]. The studies selected in the present study were of medium to high quality. However, the studies had very high heterogeneity, and the reason for this could be related to the cognitive methodology and the use of different concentrations of NPs; therefore, citing our findings should be interpreted with caution. Also, the duration of the evaluation of the results was different; in some studies, the length of time was not stated. A study investigating the prolonged antibacterial performance of coated brackets was not found based on the results of studies on the two study bacteria. And then, Ag and ZnO the insignificant difference in the antimicrobial potential of the three groups over time, which means the persistence of the antimicrobial effect of the bracket coatings over time. However, the duration of the study may affect the informed results. The cognitive methodology of the studies should be the same in future studies.

Conclusion

Based on the present meta-analysis, brackets coated with silver, ZnO, and Ag/ZnO NPs had an antibacterial performance against *L. acidophilus* and *S. mutans* compared to the uncoated bracket. Further studies should be conducted to evaluate cytotoxicity and other complications for nanoparticle-coated brackets and their efficacy in clinically reducing the incidence of WSLs during orthodontic treatment. Also, more studies should be conducted to investigate the role of abrasion and friction on the NPs coating.

Conflict of Interest

The authors declared that there is no conflict of interest.

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References

1. Pabari S, Moles DR, Cunningham SJ. Assessment of motivation and psychological characteristics of adult orthodontic patients. American Journal of Orthodontics and Dentofacial Orthopedics. 2011;140(6):e263-72. https://doi.org/10.1016/j.ajodo.2011.06.022.

2. Rosenbloom RG, Tinanoff N. Salivary Streptococcus mutans levels in patients before, during, and after orthodontic treatment. American Journal of Orthodontics and Dentofacial Orthopedics. 1991;100(1):35-7. https://doi.org/10.1016/0889-5406(91)70046-Y.

3. Zeidan NK, Enany NM, Mohamed GG, Marzouk ES. The antibacterial effect of silver, zinc-oxide and combination of silver/zinc oxide nanoparticles coating of orthodontic brackets (an in vitro study). BMC Oral Health. 2022;22(1):1-4. https://doi.org/10.1186/s12903-022-02263-6.

4. Ahn SJ, Lim BS, Lee SJ. Prevalence of cariogenic streptococci on incisor brackets detected by polymerase chain reaction. American Journal of Orthodontics and Dentofacial Orthopedics. 2007;131(6):736-41. https://doi.org/10.1016/j.ajodo.2005.06.036.

5. Prihastari L, Rizkia S. Streptococcus Mutans Colonies on Plaque of Fixed Orthodontic Users after Gargling with Black Tea (Camellia Sinensis). International Journal of Scientific Research in Dental and Medical Sciences. 2022;4(3):97-100. https://doi.org/10.30485/ijsrdms.2022.349306.1327.

6. Ikeda T, Sandham HJ, Bradley Jr EL. Changes in Streptococcus mutans and lactobacilli in plaque in relation to the initiation of dental caries in Negro children. Archives of Oral Biology. 1973;18(4):555-66. https://doi.org/10.1016/0003-9969(73)90076-9.

7. Gorelick L, Geiger AM, Gwinnett AJ. Incidence of white spot formation after bonding and banding. American journal of orthodontics. 1982;81(2):93-8. https://doi.org/10.1016/0002-9416(82)90032-X.

8. Caldeira EM, Osorio A, Oberosler EL, Vaitsman DS, Alviano DS, Nojima MD. Antimicrobial and fluoride release capacity of orthodontic bonding materials. Journal of Applied Oral Science. 2013;21:327-34. https://doi.org/10.1590/1678-775720130010.

9. Ahn SJ, Lee SJ, Baek SH, Kim TW, Chang YI, Nahm DS, et al. Direct detection of cariogenic streptococci in metal brackets in vivo using polymerase chain reaction.2005;35:312-9.

10. Jeon HS, Choi CH, Kang SM, Kwon HK, Kim BI. Chlorhexidine-releasing orthodontic elastomerics. Dental materials journal. 2015;34(3):321-6. https://doi.org/10.4012/dmj.2014-216.

11. Sodagar A, Akhoundi MS, Bahador A, Jalali YF, Behzadi Z, Elhaminejad F, et al. Effect of TiO 2 nanoparticles incorporation on antibacterial properties and shear bond strength of dental composite used in Orthodontics. Dental press journal of orthodontics. 2017;22:67-74. https://doi.org/10.1590/2177-6709.22.5.067-074.oar.

12. Cushing BL, Kolesnichenko VL, O'connor CJ. Recent advances in the liquid-phase syntheses of inorganic nanoparticles. Chemical reviews. 2004;104(9):3893-946. https://doi.org/10.1021/cr030027b.

13. Allaker RP. The use of nanoparticles to control oral biofilm formation. Journal of dental research. 2010;89(11):1175-86. https://doi.org/10.1177/0022034510377794.

14. Raeder J, Larson D, Li W, Kepko EL, Fuller-Rowell T. OpenGGCM simulations for the THEMIS mission. Space Science Reviews. 2008;141(1):535-55. https://doi.org/10.1007/s11214-008-9421-5.

15. Kumar VA, Augustine D, Panikar D, Nandakumar A, Dinesh KR, Karim S, et al. Nocardia farcinica brain abscess: epidemiology, pathophysiology, and literature review. Surgical infections. 2014;15(5):640-6. https://doi.org/10.1089/sur.2012.205.

16. Mhaske AR, Shetty PC, Bhat NS, Ramachandra CS, Laxmikanth SM, Nagarahalli K, et al. Antiadherent and antibacterial properties of stainless steel and NiTi orthodontic wires coated with silver against Lactobacillus acidophilus—an in vitro study. Progress in orthodontics. 2015;16(1):1-6. https://doi.org/10.1186/s40510-015-0110-0.

17. Müller LK, Jungbauer G, Jungbauer R, Wolf M, Deschner J. Biofilm and orthodontic therapy. Oral Biofilms. 2021;29:201-13. https://doi.org/10.1159/000510193.

18. Bącela J, Łabowska MB, Detyna J, Zięty A, Michalak I. Functional coatings for orthodontic archwires—A review. Materials. 2020;13(15):3257. https://doi.org/10.3390/ma13153257.

19. Kambalyal PB, Shanmugasundaram K, Rajesh V, Donthula S, Patil SR. Comparative Evaluation of Antimicrobial Efficacy of Silver, Titanium Dioxide and Zinc Oxide Nanoparticles against Streptococcus mutans. Pesquisa brasileira em odontopediatria e clinica integrada. 2018;18(1):4150.

20. Kachoei M, Nourian A, Divband B, Kachoei Z, Shirazi S. Zinc-oxide nanocoating for improvement of the antibacterial and frictional behavior of nickel-titanium alloy. Nanomedicine. 2016;11(19):2511-27. https://doi.org/10.2217/nnm-2016-0171.

21. Vargas-Reus MA, Memarzadeh K, Huang J, Ren GG, Allaker RP. Antimicrobial activity of nanoparticulate metal oxides against peri-implantitis pathogens. International journal of antimicrobial agents. 2012;40(2):135-9. https://doi.org/10.1016/j.ijantimicag.2012.04.012.

22. Melchels FP, Feijen J, Grijpma DW. A review on stereolithography and its applications in biomedical engineering. Biomaterials. 2010;31(24):6121-30. https://doi.org/10.1016/j.biomaterials.2010.04.050.

23. Mardany A, Pornamazeh T, Ahmadvand A, Vatandoust MT, Mirmalek SP, Soltanian M. The Comparison of the Bonding Performance between the new Flash-free Orthodontic Bracket Bonding System and the Traditional Bracket Bonding System: A Systematic Review and Meta-analysis. International Journal of Scientific Research in Dental and Medical Sciences. 2022;4(4):196-200. https://doi.org/10.30485/ijsrdms.2022.375721.1408.

24. Tu YK, Needleman I, Chambrone L, Lu HK, Faggion Jr CM. A Bayesian network meta-analysis on comparisons of enamel matrix derivatives, guided tissue regeneration and their combination therapies. Journal of clinical periodontology. 2012;39(3):303-14. https://doi.org/10.1111/j.1600-051X.2011.01844.x.

25. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj. 2011;343. https://doi.org/10.1136/bmj.d5928.

26. Tanbakuchi B, Pourhajibagher M, Badiei A, Masaeli R, Bahrami R. Evaluation of the cell viability and antimicrobial effects of orthodontic bands coated with silver and zinc oxide nanoparticles: an in vitro study. The Korean Journal of Orthodontics.

27. Kachoei M, Divband B, Rahbar M, Esmaeilzadeh M, Ghanizadeh M, Alam M. A novel developed bioactive composite resin containing silver/zinc oxide (Ag/ZnO) nanoparticles as an antimicrobial material against *Streptococcus mutans*, lactobacillus, and candida albicans. Evidence-Based Complementary and Alternative Medicine. 2021. https://doi.org/10.1155/2021/4743411.

28. Yassaei S, Nasr A, Zandi H, Motallaei MN. Comparison of antibacterial effects of orthodontic composites containing different nanoparticles on Streptococcus mutans at different times. Dental Press Journal of Orthodontics. 2020;25:52-60. https://doi.org/10.1590/2177-6709.25.2.052-060.oar.

29. Eslamian L, Borzabadi-Farahani A, Karimi S, Saadat S, Badiee MR. Evaluation of the shear bond strength and antibacterial activity of orthodontic adhesive containing silver nanoparticle, an in-vitro study. Nanomaterials. 2020;10(8):1466. https://doi.org/10.3390/nano10081466.

30. Ramazanzadeh B, Jahanbin A, Yaghoubi M, Shahtahmassbi N, Ghazvini K, Shakeri M, et al. Comparison of antibacterial effects of ZnO and CuO nanoparticles coated brackets against Streptococcus mutans. Journal of Dentistry. 2015;16(3):200-5.

31. Mirhashemi AH, Bahador A, Kassaee MZ, Daryakenari G, Ahmad-Akhoundi MS, Sodagar A. Antimicrobial effect of nano-zinc oxide and nano-chitosan particles in dental composite used in orthodontics. Journal of Medical Bacteriology. 2013;2(3-4):1-0.

32. Øgaard B, Rølla G, Arends J. Orthodontic appliances and enamel demineralization: Part 1. Lesion development. American Journal of Orthodontics and Dentofacial Orthopedics. 1988;94(1):68-73. https://doi.org/10.1016/0889-5406(88)90453-2.

33. Bishara SE, Ostby AW. White spot lesions: formation, prevention, and treatment. InSeminars in orthodontics 2008;14(3):174-182).

34. Nalini D. Assessment of Antibacterial Property of Silver Coated Stainless Steel Orthodontic Brackets against Streptococcus Mutans, Lactobacillus Acidophilus and Porphyromonas Gingivalis: An In Vitro study: Tamil Nadu Government Dental College and Hospital, Chennai; 2017.

35. Hernández-Sierra JF, Ruiz F, Pena DC, Martínez-Gutiérrez F, Martínez AE, Guillén AD, Tapia-Pérez H, Castañón GM. The antimicrobial sensitivity of Streptococcus mutans to nanoparticles of silver, zinc oxide, and gold. Nanomedicine: Nanotechnology, Biology and Medicine. 2008;4(3):237-40. https://doi.org/10.1016/j.nano.2008.04.005.

36. Wang S, Wu J, Yang H, Liu X, Huang Q, Lu Z. Antibacterial activity and mechanism of Ag/ZnO nanocomposite against anaerobic oral pathogen Streptococcus mutans. Journal of Materials Science: Materials in Medicine. 2017;28(1):1-8. https://doi.org/10.1007/s10856-016-5837-8.

37. AshaRani PV, Low Kah Mun G, Hande MP, Valiyaveettil S. Cytotoxicity and genotoxicity of silver nanoparticles in human cells. ACS nano. 2009;3(2):279-90. https://doi.org/10.1021/nn800596w.

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ORIGINAL

What happens with the health system: Medical mistrust

Lo que ocurre con el sistema sanitario: Desconfianza médica

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Abstract

Aim: This research aims to determine the moderator role of gender in the effect of medical mistrust on the intention to use violence against healthcare professionals. The data in the study were obtained by the survey method.
Methods: The obtained data were analyzed with the SPSS program and the process macro software added to the SPSS program.
Results: The sample of the study consists of 628 people in total. According to the results of the research, a positive and significant relationship was found between medical mistrust and the intention to use violence on healthcare professionals. Gender has been found to have a moderator role in the effect of medical mistrust on the intention to use violence on healthcare professionals. The effect of medical mistrust on the intention to use violence on healthcare professionals was β=2,9054; t=12.8935 in individuals whose physicians were female; while in males β=1.6301; t=12.2957.
Conclusion: Accordingly, when the doctor's gender is female, the effect of medical mistrust on the intention to use violence on healthcare professionals becomes more evident.
Keywords: Medical mistrust, healthcare professionals, violence, gender.

Resumen

Objetivo: Esta investigación pretende determinar el papel moderador del género en el efecto de la desconfianza médica sobre la intención de usar la violencia contra los profesionales sanitarios.
Metodología: Los datos del estudio se obtuvieron mediante el método de encuesta. Los datos obtenidos se analizaron con el programa SPSS y el software process macro añadido al programa SPSS.
Results: La muestra del estudio consta de 628 personas en total. Se encontró una relación positiva y significativa entre la desconfianza médica y la intención de ejercer violencia sobre los profesionales sanitarios. Se ha observado que el género tiene un papel moderador en el efecto de la desconfianza médica sobre la intención de ejercer violencia sobre los profesionales sanitarios. El efecto de la desconfianza médica sobre la intención de ejercer violencia sobre los profesionales sanitarios fue de β=2,9054; t=12,8935 en los individuos cuyos médicos eran mujeres; mientras que en los hombres fue de β=1,6301; t=12,2957.
Conclusión: En consecuencia, cuando el género del médico es femenino, el efecto de la desconfianza médica sobre la intención de ejercer violencia sobre los profesionales sanitarios se hace más evidente.

Palabras clave: Desconfianza médica, profesionales sanitarios, violencia, género.

Introduction

Despite the deep and pervasive importance of trust in medical settings, there is no widely shared understanding of what trust means, and little is known about what trust actually makes, what factors trust influences, and how trust relates to other similar attitudes and behaviors. The importance of trust in medical relationships has been known for a long time[1-3], but trust in the system and trust in physicians have not been measured or systematically analyzed until recently. However, the doctor-patient relationship has recently attracted more attention (1,4). It is seen as a global feature of patient-doctor-treatment relationships, each of which has important importance in its own right, including many ancillary features such as trust, satisfaction, communication, competence, and privacy[5,6].

In this context, it is important to determine how important medical mistrust is in the intention to use violence against healthcare professionals. When the national literature is examined, it is seen that there are limited studies examining the effect of medical mistrust on the intention to inflict violence on healthcare workers. However, no article was found that examined the role of gender in the effect of medical mistrust on the intention to commit violence against healthcare professionals.

Materials and methods

Research Model

This study's main purpose is to determine the moderator role of gender in the effect of medical mistrust on the intention to inflict violence on healthcare workers. In the research, the independent variable of medical mistrust; Intention to inflict violence on healthcare workers was considered the dependent variable, and gender was the moderator variable.

Data Collection Tools

In this study, the survey method was preferred at the point of data collection. The questionnaires were delivered to the participants online. In the questionnaire, there are statements that reveal the opinions of the participants about the intention to use violence against health workers and medical mistrust, as well as descriptive personal characteristics. The medical mistrust scale is a scale developed by Thomas et al. The scale, adapted into Turkish by Şengül and Bulut (2020), consists of 17 statements[7]. As a result of the reliability analysis of the scale, which was structured as a 4-point Likert scale, Cronbach's Alpha coefficient was determined as 0.85. In this study, the said value was determined as 0.85.

The other scale included in the questionnaire is the "Intention to Inflict Violence Scale on Health Care Workers" developed by Şanlıtürk and Boy (2020)[8]. Scale; individuals' intention to commit violence[1], past experiences[2], attitude towards behavior[3,4,5,6,7,8], subjective norm[9,10,11,12,13] and perceived behavioral control[14,15] consists of 5 sub-dimensions. The scale, which included a total of 15 statements, was structured as a 5-point Likert scale, ranging from 1: I strongly disagree to 5: I strongly agree. As a result of the reliability analysis performed in the study, Cronbach's Alpha coefficient was determined as 0.81. In this study, the said value was determined as 0.81.

Statistical Analysis

The analysis of the data was made with the SPSS 26.0 program and it was studied with a confidence level of 95%. Frequency (n) and percentage (%) statistics for categorical (qualitative) variables, mean (mean), standard deviation (ss), minimum (min.), and maximum (max.) statistics are given for numerical (quantitative) variables. In the study, Cronbach's Alpha coefficient was used to reveal the reliability of the scales. Skewness and kurtosis values were calculated to examine the conformity of the scores obtained from the scales to the normal distribution. The kurtosis and skewness values obtained from the scale scores between +3 and -3 are considered sufficient for a normal distribution[9]. Accordingly, it was determined that the scores of Medical mistrust and Intention to Violence against Health Care Professionals showed a normal distribution. Therefore, parametric methods were used in the analyses. Pearson correlation test was used in the relationship between medical mistrust and intention to use violence against healthcare professionals, and Process Regression analysis was used in the moderator effect model. In the regulatory impact model, the effect of the interaction term should be significant.

Results

It was seen that the average age of the participants was 31.06 and 61.9% of them were male. In the distribution of perceived income level, it was seen that 69.3% of them had medium income. Finally, it was seen that the gender of the doctor in the last health institution from which service was received was male in 40.9% and female in 59.1% (**Table I**).

Table I: Descriptive Characteristics of Research Participants.

	Mean	Std. Deviation
Age	31,06	7,27
Gender	**N**	**%**
Male	389	61,9
Female	239	38,1
Income rate	**N**	**%**
High	97	15,4
Middle	435	69,3
Low	96	15,3
Gender of the doctor in the last health institution from which service was received	**N**	**%**
Male	257	40,9
Female	371	59,1

The mean score of medical mistrust of the respondents is 3.1±0.46, the mean score of intention is 2.22±1.56, the mean score of past experience is 4.46±1.13, the mean score of attitude towards behavior is 1.69±0.73, the subjective norm means the score was 2.10±0.70, and mean perceived behavioral control score was 2.13±1.12 (**Table II**).

Table II: Descriptive Statistics.

	Min.	Max.	Mean	Std. Devi.	Skewness	Kurtosis
MM	1	4	3,11	0,46	-0,41	0,05
Intention	1	5	2,22	1,56	0,85	-0,91
PB	1	5	4,46	1,13	-2,13	2,31
ATB	1	4	1,69	0,73	1,02	0,17
SN	1	4	2,1	0,7	0,39	-0,23
PBC	1	5	2,13	1,12	0,67	-0,47

ATB: attitude toward behavior; PB: past behavior; PBC: perceived behavioral control; SN: subjective norm, MM: Medical Mistrust

It was observed that there was a positive relationship between medical mistrust and intention to use violence against health professionals (r=.551, p<.01), PB (r=.384, p<.01), ATB (r=.505, p<.01), SN (r=.546, p<.01) and PBC (r=.563, p<.01) (**Table III**).

Table III: Relationships Between Medical Mistrust and Intention to Violence Against Healthcare Professionals.

	Intention	PB	ATB	SN	PBC
MM (r)	,551**	,384**	,505**	,546**	,563**

**p<0.01

It is seen that the model created for the moderator effect of the doctor's gender on the intention to commit violence against healthcare professionals of medical mistrust is significant (F=106,293; p<0.05). While the variables of medical mistrust (B=4.181) and gender (B=4.383) have a positive effect on the intention to inflict violence on healthcare workers, the interaction term (B=-1.275) has a negative effect (R^2=33.8%; p<0.05). When the doctor's gender is male, the intention to commit violence increases positively in case of medical mistrust (B=1,630). This becomes more evident when the gender of the doctor is female (B=2.905).(**Table IV**).

Table IV: The Regulatory Role of Gender in the Effect of Medical Mistrust on Intention to Violence against Health Care Professionals.

	B	LLCI-ULCI	t	p	R2	F
MM >Intention	4,181	3,258/5,103	8,899	**0,000***	0,338	106,293*
Gender >Intention	4,383	2,736/6,030	5,225	**0,000***		
MM* Gender >Intention	-1,275	2,347769029	-4,878	**0,000***		
MM*Gender (Female)	2,905	2,463/3,348	12,894	**0,000***		
MM* Gender (Male)	1,63	1,370/1,891	12,296	**0,000***		

Discussion

Medical mistrust is a multifactorial social phenomenon, which significantly depends on the type of community, the psychosocial status of a population, and individual beliefs. The predominance of cases of MM happens in diverse minorities of the public sector and extremely impacts clinical practice. Therefore, the MM linked to gender could be one of the most common and at the same time the most difficult for identification of doctor-patient issues.

In different social groups over the world, the rate of MM varies from 20 to 80%[10,11]. The negative skewness of MM with a mean value of 3.11 demonstrates in current research that 77.5% of questioned experienced MM and 44% had an intention of violence toward doctors. According to some research outcomes[12,13] 8,3-12.3% of represented groups avouched in the use of violence against medical professionals, mostly in verbal form - 77,5%[12-15]. Negative kurtosis of intention shows that the numbers of patients in this study who wished to implicit violence are slightly lower than the mean.

Past behavior has high mean values (4.46) in this study, showing not only possible experience of previously dissatisfactory doctor-patient communication or unsuccessful treatment but also a predisposition to further mistrust, conflicts, and possible violence. Our study revealed a notable statistical relationship between MM and the intention to use violence, which may indicate mistrust as a background of violent behavior attempts. When the gender of the doctor is male, the intention to commit violence increases on the background of mistrust and is more pronounced when the gender of the doctor is female.

The statistically evident fact of the current investigation, that gender has an impact on the intention to inflict violence towards female doctors (B=2.905) requires further investigations to rule out or prove discrimination. According to some studies, discrimination is often related to MM[10,12]. Further populational studies are necessary to clarify the causes of MM in the aspect of physician gender and should be directed to many aspects - its frequency in private and state medical institutions, its distribution among different medical specialties (f.i. there are more gynecologists women over the world and they have a preference among patients[14]), educational attainment of patients, the possible discrepancies in different age groups of patients as well as doctors, who experience MM. The role of gender in MM should also be considered together with other possible factors, which can overlap each other and have distinguished meanings alone.

Thus, MM is a complex problem, the roots of which come from both the doctor and the patient. Meticulous analysis of the biased attitude to female doctors could improve outcomes of treatment eventually and create better work conditions for this group of medical professionals.

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References

1. Hall MA, Dugan E, Zheng B, Mishra AK. Trust in physicians and medical institutions: what is it, can it be measured, and does it matter? Milbank Q. 2001;79(4):613-39, v. doi: 10.1111/1468-0009.00223.

2. Hall MA. Researching medical trust in the United States. J Health Organ Manag. 2006;20(5):456-67. doi: 10.1108/14777260610701812.

3. Zheng B, Hall MA, Dugan E, Kidd KE, Levine D. Development of a scale to measure patients' trust in health insurers. Health Serv Res. 2002 Feb;37(1):187-202.

4. Hall MA, Zheng B, Dugan E, Camacho F, Kidd KE, Mishra A, et al. Measuring patients' trust in their primary care providers. Med Care Res Rev. 2002 Sep;59(3):293-318. doi: 10.1177/1077558702059003004. Erratum in: Med Care Res Rev. 2003 Mar;60(1):118.

5. Lewandowski R, Goncharuk AG, Cirella GT. Restoring patient trust in healthcare: medical information impact case study in Poland. BMC Health Serv Res. 2021 Aug 24;21(1):865. doi: 10.1186/s12913-021-06879-2. PMID: 34429101;

6. Vega-Hurtado C. Importancia de las estrategias de comunicación entre médico y paciente [Importance of doctor-patient communication strategies]. Rev Med Inst Mex Seguro Soc. 2020 Apr 13;58(2):197-201. Spanish. doi: 10.24875/RMIMSS.M20000017.

7. Şengül H. Bulut A. "Tıbbi Güvensizlik Ölçeği ve Doktora Güven Ölçeğinin Türkçe Geçerlik Güvenirlik Çalışması" International Social Sciences Studies Journal, 2020 (e-ISSN:2587-1587) Vol:6, Issue: 62; pp:1956-64.

8. Şanlıtürk D. Boy Y. Determination of the Society's Perceptions, Experiences, and Intentions to Use Violence Against Health Professionals. Safety and Health at Work 2020. https://doi.org/10.1016/j.shaw.2020.12.004.

9. Hopkins KD, Weeks DL. "Tests for Normality and Measures of Skewness and Kurtosis: Their Place in Research Reporting", Educational and Psychological Measurement 1990; 50: 717-29.

10. Williamson LD, Bigman CA. A systematic review of medical mistrust measures. Patient Educ Couns. 2018 Oct;101(10):1786-94. doi: 10.1016/j.pec.2018.05.007.

11. Armstrong K, Rose A, Peters N, Long JA, McMurphy S, Shea JA. Distrust of the health care system and self-reported health in the United States. J Gen Intern Med. 2006 Apr;21(4):292-7. doi: 10.1111/j.1525-1497.2006.00396.x.

12. Döndü Ş, Yasemin B. Determination of the Society's Perceptions, Experiences, and Intentions to Use Violence Against Health Professionals. Saf Health Work. 2021 Jun;12(2):141-6. doi: 10.1016/j.shaw.2020.12.004.

13. Takak SÖ, Artantaş AB. Evaluation of patients' and their relatives' opinions and attitudes about violence against health care workers. Ankara Medical J. 2018;18:103-16. doi: 10.17098/amj.409020.

14. Riaz B, Sherwani NZF, Inam SHA, Rafiq MY, Tanveer S, Arif A, et al. Physician Gender Preference Amongst Females Attending Obstetrics/Gynecology Clinics. Cureus. 2021 May 14;13(5):e15028. doi: 10.7759/cureus.15028.

15. Baber A. The effect of the COVID-19 pandemic on the psychological state of healthcare workers around the world: A review. The Injector. 2022;1(1):16-30.

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ORIGINAL

Revisión Sistemática de la relación entre el dolor por infección herpes zóster y la calidad de vida de los sujetos que viven en la comunidad

Systematic review of the relationship between pain due to herpes zoster infection and the quality of life of subjects living in the community

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Resumen

La prevalencia de la infección por herpes zóster se encuentra en aumento, en parte debido al envejecimiento de la población más vulnerable a la misma, ancianos.

Este hecho, sumado a las diversas modificaciones inmunológicas que determinan la manifestación de esta enfermedad, obligan a detectar y analizar los elementos que intervienen en la fisiopatología del dolor producido por herpes, así como la necesidad de encontrar alternativas terapéuticas necesarias para el control de este.

Así pues, esta revisión sistemática, cuyo objetivo principal es conocer la relación existente entre dolor producido tras la infección por herpes zóster y el empeoramiento en la calidad de vida de los sujetos que presentan este diagnóstico para poder establecer aquellos síntomas de alarma que perpetúan dicho dolor.

Palabras clave: Dolor, Neuralgia Postherpética, Calidad de Vida, Alodinia, Polifarmacia.

Summary

The prevalence of herpes zoster infection is increasing, in partly due to the aging of the population most vulnerable to it, the elderly.

This fact, added to the various immunological modifications that determine the manifestation of this disease, make it necessary to detect and analyze the elements that intervene in the pathophysiology of pain caused by herpes, as well as the need to find therapeutic alternatives necessary for its control.

Thus, this systematic review, whose main objective is to know the relationship between pain produced after infection by herpes zoster and the deterioration in the quality of life of subjects with this diagnosis in order to establish those alarm symptoms that perpetuate said pain.

Key words: Pain, Postherpetic Neuralgia, Quality of Life, Allodynia, Polypharmacy.

Introducción

Atención Primaria supone el ámbito asistencial destacado y predominante donde se detectarán casos de infección por herpes zóster (HZ). El primer contacto del ser humano con el virus varicela zóster, se produce habitualmente durante la infancia, manifestando las lesiones cutáneas generalizadas que se inician siendo máculas, posteriormente se convierten en pápulas y finalizan siendo vesículas con morfología costrosa, en progresiva resolución. La característica fundamental de esta primoinfección es que permite que el virus permanezca acantonado en el sistema nervioso, es decir, permanece en un ganglio espinal (dorsal en su mayoría) o en un ganglio de los nervios de los pares craneales, habitualmente en el ganglio de Gasser o ganglio geniculado, dotando de mayor virulencia o gravedad esta segunda reactivación[1]. No obstante, no son las lesiones cutáneas las principales manifestaciones de esta patología, si no el dolor su síntoma predominante y más incapacitante en muchos casos. La incidencia de HZ en la población española es de 2,1 a 5,5/1.000 habitantes año[2]. En Europa es difícil concretar su prevalencia por la creciente diversidad de estudios y su deficiencia, sin embargo, cabe esperar una incidencia comparable a la española, y lo que es más llamativo aún, su aumento con la edad y el envejecimiento poblacional, de forma que en sujetos con edades superiores a 50 años, represente 7-8/1.000 casos, incrementándose a 10/1.000 casos a partir de los 80 años[2]. Los síntomas de la infección por varicela zóster se dividen en 3 fases: **1. Fase prodrómica:** Pueden aparecer síntomas sistémicos como mal estar general, mialgias o fiebre, así como un dolor urente, alodinia o hiperalgesia del dermatoma afecto donde se producirá el posterior desarrollo de las lesiones cutáneas. Esta fase corresponde desde 2, 3 días hasta semanas previas a la aparición de las lesiones cutáneas. **2. Fase eruptiva:** Como su nombre indica, corresponde a la presencia de lesiones papulosas eritematosas agrupadas que evolucionan a vesículas sobre una base eritematosa, finalizando en su evolución a costra al cabo de 3-10 días desde su inicio. Dicha distribución corresponde a la región de neuronas sensitivas del nervio donde se ha replicado el virus. De forma habitual y en sujetos inmunocompetentes, se afecta un único dermatoma, siendo los más involucrados y en este orden descendente: torácicos (53%), cervical (20%) y trigémino (15%). Lo más habitual es que afecte a un único dermatoma y no cruce la línea media. **3. Fase crónica:** Es la fase caracterizada por la presencia de dolor persistente tras 4 semanas desde el inicio del cuadro, acompañando al dolor, las parestesias, disestesias y cualquier otra sintomatología que afecte a la calidad de vida del sujeto y sea la causante del síndrome denominado neuralgia postherpética (NPH, siglas en español) persistiendo dichos síntomas durante meses o años tras la desaparición de las lesiones[3]. La neuralgia postherpética es la complicación más frecuente del HZ y supone un daño neurológico secundario a una respuesta inflamatoria inducida por la replicación viral en el interior del nervio. Su prevalencia supone el 20% de los pacientes con HZ, especialmente aquellos con más de 50 años en el momento de la primoinfección o reactivación. La definición más pragmática es la de dolor tipo ardor o descarga eléctrica en una distribución dermatómica mantenida durante al menos 90 días desde la aparición de las lesiones cutáneas[4]. Los factores de riesgo descritos de estas neuralgias son diversos, entre los cuales se encuentran, edad avanzada, erupción cutánea grave, dolor agudo intenso durante la fase prodrómica o activa, compromiso oftálmico, inmunosupresión o enfermedades crónicas como diabetes mellitus y lupus. Debido a las características de esta neuralgia, supone una merma considerable en la calidad de vida, con consecuencias físicas y psicológicas para el sujeto que lo padece[5]. De esta forma, es considerada una enfermedad crónica relevante por la predilección de afectación por los pacientes con edades superiores de 50 años, por las características de cronicidad del síndrome, desde 6 meses hasta años después de la manifestación inicial y por la variedad de síntomas del dolor neuropático postherpético que dificulta el tratamiento con analgésicos disponibles y aumenta la morbilidad de los pacientes que se ven obligados incluso, a ser valorados en unidades del dolor para poder alcanzar un alivio sintomático[6]. El mecanismo a partir del cual, el virus es capaz de dañar el sistema nervioso, incluye su replicación en el ganglio dorsal que se localice inicialmente, y su posterior migración a través del sistema nervioso periférico, alcanzando así las raíces espinales dorsales que en su mayoría afecta. La participación de sustancias nociceptivas así como los mecanismos inflamatorios involucrados en esta patogenia son los causantes principales del daño neurológico, en algunos casos irreversible que produce el herpes zóster[7]. En el sistema nervioso periférico el virus se manifiesta produciendo el típico exantema y posteriores vesículas como muestra de la inflamación de los tejidos y las células epiteliales. En la región medular, a nivel de los cordones espinales, el virus afecta a las células gliales manifestando distintas respuestas, por un lado, la activación de Nociceptores tipo C como causantes de la neuralgia postherpética; por otro lado, las distintas respuestas somatosensoriales que producen cambios asociados al desarrollo de neuralgias postherpética[8]. Este complejo entramado de manifestaciones clínicas diversas, complicaciones fisiopatológicas que influyen en distintos niveles de la esfera psico-social del paciente y la dificultad en el control y tratamiento de las distintas presentaciones del dolor asociado a la infección por herpes zóster, nos acomete en la necesidad de aunar toda aquella literatura relacionado con estos elementos. El objetivo principal de este estudio es analizar la relación entre la

infección por herpes zóster y su principal manifestación el dolor, con la afectación en la calidad de vida de los pacientes, ya sea a través de manifestaciones psicológicas (ansiedad y depresión), como físicas (dolor persistente, alodinia, dolor urente prolongado) mediante la consideración de la literatura presente hasta la fecha actual (septiembre 2022). Con ello se pretende: 1. Examinar con exactitud la vinculación existente entre ambos conceptos , así como las características comunes y distintas que los definen. 2. Indagar en la relación e influencia que representa el conjunto de síntomas (objetivos y subjetivos), todos ellos relevantes que se incluyen en el término neuralgia postherpética, en los ámbitos físicos y psicológicos del paciente con infección por herpes zóster. 3. A partir de la integración de dichos términos, detectar las áreas necesarias de mayor investigación que permitan llevar a cabo futuras investigaciones relacionadas..

Material y Métodos

Criterios de Inclusión:

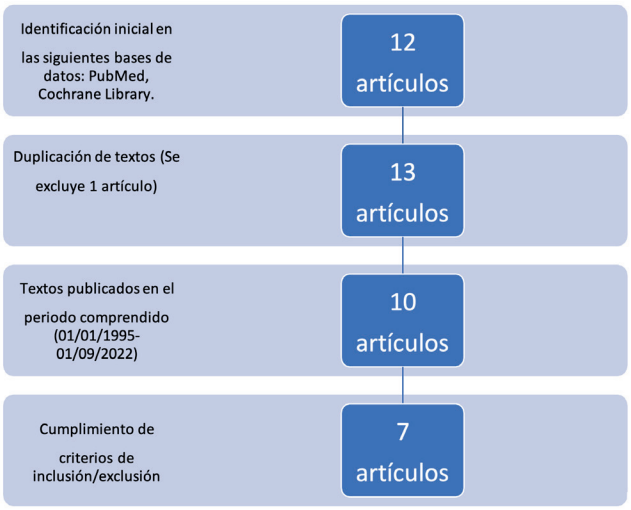
- Textos completos escritos en inglés y castellano.
- Localización revisión: Europa, Asia, América del Sur, Australia y Estados Unidos.
- Estudios incluidos entre 01/01/1995 y 01/09/2022.
- Esta revisión incluye estudios descriptivos transversales, estudios analíticos observacionales de casos y controles y cohortes (retrospectivos y prospectivos). También se incluyen revisiones bibliográficas que recopilan la información más relevante en este campo de la ciencia y cartas el editor que analizan aspectos de estudios publicados recientemente e incluidos en esta revisión.
- Estudios que incluyeron la asociación entre infección por herpes zóster y neuralgia, psicología y dolor, situación funcional y alodinia en sujetos que presentan o han presentado infección por herpes zóster.
- Se incluye solo aquellas búsquedas sobre las bases de datos a nivel de texto principal/completo.

Criterios de Exclusión:

- Estudios que incluyan sujetos inmunodeprimidos (neoplasias activas, uso crónico de glucocorticoides, enfermedades inmunes en estadios avanzados).
- Estudios que incluyan sujetos con patologías psiquiátricas o neurológicas, que influyan en el consumo de fármacos o drogas (antidepresivos, benzodiazepinas o abuso de analgésicos de forma crónica). Búsqueda en la literatura.

La presente revisión sistemática se ha llevado a cabo durante los meses de julio de 2022 a septiembre de 2022. Las principales bases de datos empleadas fueron PubMed y Cochrane Library. Las búsquedas bibliográficas se llevaron a cabo en PubMed utilizando la combinación de los siguientes términos MeSH: “Herpes Zoster/therapy” y “Neuralgia/psychology”. La búsqueda comenzó acotada a texto completo obteniendo 12 artículos. Se excluyeron aquellos que se encontraban duplicados[1].

A continuación se limitó la revisión a aquellos estudios que habían sido publicados en el periodo estipulado en los criterios de inclusión, incluyendo 10 artículos, eliminando 3 porque incluían sujetos en tratamiento glucocorticoide (uno de los criterios de exclusión) y otro incluía pacientes con enfermedades digestivas autoinmunes (enfermedad inflamatoria intestinal). Selección de estudios Con la aplicación de los criterios de inclusión/exclusión se obtienen 7 artículos en esta revisión bibliográfica sobre herpes zóster y neuralgia.



Resultados

En el global de los 7 estudios incluidos en esta revisión bibliográfica, 3 corresponden a estudio de cohortes observacionales, prospectivo en todos ellos, 2 cartas al editor, 1 estudio descriptivo transversal y 1 revisión bibliográfica (**Tabla I**).

Discusión

El principal objetivo de esta revisión sistemática, a pesar de su corta extensión, se observa en la relación bidireccional que presentan el dolor producido durante la infección por herpes-zóster, incluyendo en este término el dolor que persiste transcurrida la fase aguda o eruptiva, y el empeoramiento o repercusión en la calidad de vida de los sujetos de la muestra, de forma que a mayor intensidad del dolor, peores puntuaciones obtenidas en los distintos cuestionarios relacionados con la calidad de vida, los cuales incluyen, factores psicológicos, sociales y hábitos diarios, que sufren una merma considerable en estos pacientes.

Tabla I: Características principales de los estudios incluidos.

Primer Autor	Año publicación	Periodo de seguimiento	Características muestra	Material y Métodos	Resultados
Sybille	2018	6 meses	Edad: Grupo Control: 55.6±13.0 DE Grupo Casos: 55.1±16.0 DE Sexo (Φ/σ): Grupo Control: 13/7 Grupo Casos 46/28	Las pruebas sensoriales cuantitativas se el protocolo desarrollado por el German Research Red de Dolor Neuropático (DFNS) Inventario de Dolor y Síntomas Neuropáticos (NPSI) Índice de Discapacidad del Dolor (PDI), Encuesta de Salud de Forma Corta (SF-36), y la escala de estado de Spielberger Inventario de Ansiedad Estado-Rasgo (STAI), respectivamente.	Hiperestesia mecánica y/o alodinia combinada con modificaciones en receptores de detección térmica, podría predecir el desarrollo de NPH. Déficits en ámbitos físicos, calidad de vida o síntomas ansiosos actúan como factores de riesgo en el dolor persistente asociado a NPH.
Drolet	2010	6 meses	Edad: 65.4± 10.8 DE Sexo (σ): 109 (41.8 %)	Zoster Brief Pain Inventory (cuestionario de valoración intensidad del dolor producido tras 24 horas de aparición de lesiones) EuroQol EQ-5D (cuestionario de calidad de vida relacionada con la salud).	El herpes zóster agudo afectó significativamente la calidad de vida y la situación funcional de los sujetos. La calidad del sueño, estado de ánimo , el disfrute de actividades y situación laboral fueron los ámbitos más afectados.
Johnson	2010			Existen dos cuestionarios específicos para evaluar el dolor y el disconfort asociados a HZ y NPH: Zoster Brief Pain Inventory y Zoster Impact Questionnaire.	La alodinia está presente en ≥70% de los pacientes y suele ser considerado como el más angustioso y debilitante componente NPH. Existe una correlación positiva entre el aumento de la intensidad del dolor y el alcance del impacto negativo en la calidad de vida relacionada con enfermedad. Pacientes con NPH presentan con más frecuencia ansiedad, depresión, dificultad en la concentración, polifarmacia y conductas suicidas relacionadas con esta patología.
Cañada-Merino	2009	Cartas al Editor		Ventajas vacunación frente a herpes zóster	Vacunación necesaria porque protege a sujetos mayores de la infección y su afectación a la calidad de vida. Indicaciones: inmunización individuos sanos >50 años, y sujetos con patologías crónicas (diabetes mellitus, asma, EPOC, insuficiencia cardiaca, cirrosis hepática o enfermedad renal). Al tratarse de una vacuna de virus vivos atenuados está contraindicada en embarazo e inmunocomprometidos
Oster	2005	Encuesta/ Transversal	Edad 77.0 ± 7.2 DE Sexo Φ 59.2 σ 39.5	Intensidad de dolor: Brief Pain Inventory Interferencia calidad de vida: Brief Pain Inventory Cuestionario de calidad de vida relacionada con estado de salud: EuroQol EQ-5D Consumo de fármacos para control del dolor neuropático en la semana previa: tipo de medicación	51% sujetos de la muestra había consultado al menos en una ocasión por dolor relacionado con el diagnóstico de herpes zóster con su médico, durante el último mes. 50% sujetos había consumido medicación para el control del dolor neuropático en semana previa, siendo mayoritarios opioides (58%), antiepilépticos (46%), y antidepresivos (35%). 40% sujetos refirió que el dolor interfería de forma moderada-severamente en sus actividades diarias, 45% informó que el dolor influía de forma severa en su estado de ánimo.

Primer Autor	Año publicación	Periodo de seguimiento	Características muestra	Material y Métodos	Resultados
Hampton	2005	Cartas al Editor		Características/Factores de riesgo del dolor neuropático postherpético	La intensidad del dolor en la fase aguda predice la aparición de dolor neuropático posteriormente. Sujetos con dolor neuropático presentan un daño directo sobre los nervios periféricos según localización del herpes, en comparación con aquellos que no desarrollan dolor neuropático, pero si vesículas. 40% sujetos que no reciben tratamiento antiviral en la fase aguda desarrollan dolor.
Coplan	2004	6 meses	Edad: 70.6± 2.3 DE Sexo: Φ 63% σ 37%	Características del dolor (prurito, alodinia, intensidad…), interferencia del dolor en actividades diarias: Zoster Brief Pain Inventory (modificación del cuestionario Brief Pain Inventory para dolor y lesiones de herpes zóster). Afectación de múltiples dominios (mental, social, económico) por dolor: The McGill Pain Questionnaire. Influencia del dolor en calidad de vida: EuroQoL.	De forma proporcional, a medida que severas eran las puntuaciones en la valoración del dolor, empeoraba la puntuación en los cuestionarios de calidad de vida, de forma significativa ($p<0.005$). El uso de un cuestionario adaptado a la valoración del dolor por herpes (ej. Zoster Brief Pain) es una herramienta con validez adecuada, especialmente cuantos peores son las puntuaciones (mayor intensidad del dolor).

Los factores de riesgo involucrados en el desarrollo del dolor persistente, el denominado dolor postherpético o dolor neuropático, descritos en esta revisión, y por tanto, necesarios para su detección precoz por parte del personal médico son:

- A mayor intensidad del dolor presente durante la fase aguda, es decir, aquella donde la manifestación principal son las lesiones cutáneas vesiculosas, mayor riesgo de desarrollar neuralgia postherpética. Esta relación se observa en la literatura en otros estudios (Katz et al., 2004)[16].
- Alodinia, es decir, la percepción anormal del dolor, ante un estímulo, generalmente táctil o térmico, que, en condiciones de ausencia de alodinia, es indoloro; representa el síntoma más frecuente e incapacitante en todos los descritos en la neuralgia postherpética[17]. Esto supone una vía de detección precoz de aquellos sujetos con infección por herpes zóster cuyo riesgo de desarrollar empeoramiento en la calidad de vida sea mayor.
- La presencia concomitante de ansiedad, depresión, edad, conductas suicidas, polifarmacia (≥ 5 fármacos), dificultad en la concentración, constituyen la base fisiopatológica para perpetuar, y por tanto, presentan dificultad en el manejo terapéutico de la neuralgia postherpética[18]. Estos hallazgos se encuentran en concordancia con lo ya descrito previamente en la literatura[19,20]), los cuales observaron síntomas de ansiedad, depresión y conductas suicidas en aquellos sujetos con mayor intensidad del dolor postherpético y peores tasas de respuesta al tratamiento médico.
- Respecto al consumo de fármacos, el 50% de las personas que presentan una infección por herpes zóster tomarán alguna medicación relacionada para el control del dolor, en la última semana. Hallazgos en concordancia con estudios previos tales como Dworkin et al[21] y Kost et al[22].

La fortaleza de esta revisión radica en la inclusión de estudios realizados sobre población comunitaria, a través de los cuales podamos obtener conclusiones y hallazgos semejantes a los que alcanzaríamos si estudiásemos una cohorte de individuos pertenecientes a la población general.

La principal debilidad de esta revisión radica en la existencia de múltiples factores involucrados en la fisiopatología del dolor, y en este caso, de la neuralgia post-herpética, que pueden actuar en algunos casos como elementos de confusión, tal es el caso, del consumo de fármacos analgésicos que en unos estudios se consideraba como criterio de exclusión, pero en otros no, y que conlleva una diversidad en los resultados observados y que han de tomarse con cautela.

De los resultados del estudio se pueden obtener las siguientes utilidades:

En primer lugar la importancia de detectar aquellos síntomas objetivos o subjetivos que presenten los pacientes en el momento del diagnóstico de la infección herpética para poder incluir a estos pacientes en un tratamiento terapéutico más intensivo desde el inicio, por ejemplo, con el comienzo de tratamiento con

fármacos más óptimos o favorecedores del control de la sintomatología, por ejemplo, amitriptilina, en comparación con el uso exclusivo de antiinflamatorios no esteroideos (AINEs).

En segundo lugar, ya que el cribado de estos síntomas favorecedores de neuralgia postherpética es difícil, podría incluirse el uso de aquellos cuestionarios adaptados y que han demostrado validez para considerar de forma exitosa a esta población, por ejemplo el cuestionario Zoster Brief Pain.

En último lugar, la atención del dolor debe considerarse de forma multidimensional, intentando la inclusión de elementos psicológicos y sociales, necesarios para el adecuado abordaje sanitario de esta patología cada vez más frecuente.

Conclusiones

1. Dolor persistente tras infección por herpes zóster (Neuralgia Post-Herpética) está relacionada de forma inversamente proporcional con la calidad de vida, de forma que, a mayor intensidad del dolor, peor es la calidad de vida de los sujetos de la muestra.
2. La alodinia representa el síntoma más frecuente e incapacitante en los sujetos que presentan Neuralgia Post-Herpética.
3. La concordancia de elementos diversos, tales como ansiedad, depresión, conductas suicidas, en el ámbito psicológico, así como dificultad para realizar actividades diarias básicas, dificultad para concentración en el ámbito social, presentan más riesgo de desarrollar neuralgia postherpética y con mayor intensidad.

Conflicto de intereses

Los autores declaran no tener ningún conflicto de inereses.

Bibliografía

1. Patil A, Goldust M, Wollina U. Herpes zoster: A Review of Clinical Manifestations and Management. Viruses. 2022 Jan 19;14(2):192. doi: 10.3390/v14020192. PMID: 35215786; PMCID: PMC8876683.

2. Mareque M, Oyagüez I, Morano R, Casado MA. Systematic review of the evidence on the epidemiology of herpes zoster: incidence in the general population and specific subpopulations in Spain. Public Health. febrero de 2019;167:136-46.

3. Saguil A, Kane S, Mercado M, Lauters R. Herpes Zoster and Postherpetic Neuralgia: Prevention and Management. Am Fam Physician. 15 de noviembre de 2017;96(10):656-63.

4. Gross GE, Eisert L, Doerr HW, Fickenscher H, Knuf M, Maier P, et al. S2k guidelines for the diagnosis and treatment of herpes zoster and postherpetic neuralgia. JDDG: Journal der Deutschen Dermatologischen Gesellschaft. enero de 2020;18(1):55-78

5. Volpi A, Gatti A, Serafini G, Costa B, Suligoi B, Pica F et al. Clinical and psychosocial correlates of acute pain in herpes zoster. J Clin Virol. 2007 Apr;38(4):275-9. doi: 10.1016/j.jcv.2007.01.010. Epub 2007 Mar 6. PMID: 17339131.

6. Goßrau G. Postzosterneuralgie [Postherpetic neuralgia]. Nervenarzt. 2015 Feb;86(2):219-28; quiz 229-30. German. doi: 10.1007/s00115-014-4233-1. PMID: 25659844.

7. Oaklander AL. The pathology of shingles: Head and Campbell's 1900 monograph. Arch Neurol. 1999 Oct;56(10):1292-4. doi: 10.1001/archneur.56.10.1292. PMID: 10520948.

8. Petersen KL, Rice FL, Farhadi M, Reda H, Rowbotham MC. Natural history of cutaneous innervation following herpes zoster. PAIN 2010;150: 75-82.

9. Kramer S, Baeumler P, Geber C, Fleckenstein J, Simang M, Haas L et al. Somatosensory profiles in acute herpes zoster and predictors of postherpetic neuralgia. Pain. 2019 Apr;160(4):882-894. doi: 10.1097/j.pain.0000000000001467. PMID: 30585985.

10. Drolet M, Brisson M, Schmader KE, Levin MJ, Johnson R, Oxman MN et al. The impact of herpes zoster and postherpetic neuralgia on health-related quality of life: a prospective study. CMAJ. 2010 Nov 9;182(16):1731-6. doi: 10.1503/cmaj.091711. Epub 2010 Oct 4. PMID: 20921251; PMCID: PMC2972323.

11. Johnson RW, Bouhassira D, Kassianos G, Leplège A, Schmader KE, Weinke T. The impact of herpes zoster and post-herpetic neuralgia on quality-of-life. BMC Med. 2010 Jun 21;8:37. doi: 10.1186/1741-7015-8-37. PMID: 20565946; PMCID: PMC2905321.

12. Cañada-Merino JL. Herpes Zóster y Neuralgia Post Herpética: Ventajas de la vacunación. Rev Esp Quimioter 2009;22(Suppl.1): 19-21

13. Oster G, Harding G, Dukes E, Edelsberg J, Cleary PD. Pain, medication use, and health-related quality of life in older persons with postherpetic neuralgia: results from a population-based survey. J Pain. 2005 Jun;6(6):356-63. doi: 10.1016/j.jpain.2005.01.359. PMID: 15943957.

14. Hampton T. When shingles wanes but pain does not: researchers target chronic postherpetic neuralgia. JAMA. 2005 May 25;293(20):2459-60. doi: 10.1001/jama.293.20.2459. PMID: 15914732.

15. Coplan PM, Schmader K, Nikas A, et al. Development of a measure of the burden of pain due to herpes zoster and postherpetic neuralgia for prevention trials adaptation of the Brief Pain Inventory. J Pain 2004;5:344-56.

16. Katz J, Cooper EM, Walther RR, Sweeney EW, Dworkin RH. Acute pain in herpes zoster and its impact on health-related quality of life. Clin Infect Dis. 1 de agosto de 2004;39(3):342-8.

17. Jensen TS, Finnerup NB. Allodynia and hyperalgesia in neuropathic pain: clinical manifestations andmechanisms. Lancet Neurol 2014;13:924-35.

18. Schlereth T, Heiland A, Breimhorst M, Fe´ chir M, Kern U, Magerl W, Birklein F. Association between pain, central sensitization and anxiety in postherpetic neuralgia. Eur J Pain 2015;19:193-201.

19. Dworkin RH, Gnann JW, Oaklander AL, Raja SN, Schmader KE, Whitley RJ. Diagnosis and assessment of pain associated with herpes zoster and postherpetic neuralgia. J Pain. enero de 2008;9(1 Suppl 1):S37-44.

20. Opstelten W, Mauritz JW, de Wit NJ, van Wijck AJM, Stalman WAB, van Essen GA. Herpes zoster and postherpetic neuralgia: incidence and risk indicators using a general practice research database. Fam Pract. octubre de 2002;19(5):471-5.

21. Dworkin RH, Gnann JW Jr, Oaklander AL, Raja SN, Schmader KE, Whitley RJ. Diagnosis and assessment of pain associated with herpes zoster and postherpetic neuralgia. J Pain. 2008 Jan;9(1 Suppl 1):S37-44. doi: 10.1016/j.jpain.2007.10.008. PMID: 18166464.

22. Kost RG, Straus SE. Postherpetic neuralgia--pathogenesis, treatment, and prevention. N Engl J Med. 4 de julio de 1996;335(1):32-42.

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ORIGINAL

Evaluation of dietary habits and nutritional needs in women treated for breast cancer in the Balearic Islands

Evaluación de los hábitos dietéticos y las necesidades nutricionales en mujeres tratadas por cáncer de mama en las Islas Baleares

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Abstract

Breast cancer is the most common cancer in women, with more than 700 cases diagnosed each year in the Balearic Islands. There is extensive evidence that lifestyle factors, such as diet and physical activity, may be associated with the onset of tumour-associated malnutrition, but also with prognosis, mortality and relapse. At the same time, evidence suggests that nutrition strategies are often insufficient or non-existent due to lack of resources or infrastructure. The aim of this protocol is to analyse lifestyle factors, such as dietary habits, physical activity and quality of life, in women treated for breast cancer in the Balearic Islands, as well as to evaluate their need of nutritional support. The project proposed consists of a descriptive cross-sectional study in women treated for breast cancer with chemotherapy. The recruitment procedure will be performed in public and private hospitals (n=200) and will comply with current ethical standards and regulations. The strength of this proposal is to establish an objective perspective of the current state of nutritional care for breast cancer patients in the Balearic healthcare system, enabling improved future interventions in women treated for breast cancer but also in other oncologic patients.

Keywords: Breast cancer, Nutrition, Quality of Life, Physical Activity, Clinical practice.

Resumen

El cáncer de mama es el cáncer más común entre las mujeres, con más de 700 casos diagnosticados cada año en Baleares. Existe amplia evidencia de que los factores del estilo de vida, como la dieta y la actividad física, pueden estar asociados con la aparición de desnutrición asociada al cáncer, pero también con el pronóstico, la mortalidad y la recaída. Al mismo tiempo, la evidencia sugiere que las estrategias de nutrición a menudo son insuficientes o inexistentes debido a la falta de recursos o infraestructura. El presente protocolo tiene como objetivo analizar los factores relacionados con el estilo de vida, como los hábitos alimentarios, la actividad física y la calidad de vida, en mujeres tratadas por cáncer de mama en Baleares, así como evaluar su necesidad de apoyo nutricional. El proyecto propuesto consiste en un estudio descriptivo transversal en mujeres tratadas por cáncer de mama con quimioterapia. El procedimiento de reclutamiento se realizará en hospitales públicos y privados (n=200) y cumplirá con las normas y estándares éticos vigentes. La fuerza de esta propuesta es establecer una perspectiva objetiva del estado actual de la nutrición en el sistema sanitario balear, que permita futuras intervenciones en mujeres tratadas por cáncer de mama, pero también en otros pacientes oncológicos.

Palabras clave: Cáncer de mama, Nutrición, Calidad de vida, Actividad física, Práctica clínica.

Background

Cancer is one of the most common causes of death worldwide, according to the World Health Organization, accounting for one in six deaths. In fact, in 2040, the number of new cancer diagnoses is estimated to reach 30.2 million with 16.3 million deaths[1]. Among all cancers, breast cancer is the most common cancer in women[2].

When cancer is diagnosed and treatment starts, many distressing events are usually reported, both physical and psychological[3]. Physical symptoms are classified according whether they are hematological alterations, such as anemia or lymphopenia, and non-hematological, including anorexia, myalgia or gastrointestinal disorders[4]. Most importantly, any of these symptoms will promote malnutrition and decrease physical function, which will ultimately have a deteriorating impact on quality of life.

Women with obesity and breast cancer also present worse quality of life compared to their non-obese counterparts[5]. Furthermore, it has also been observed that not only malnutrition, but also the fat gain associated to breast cancer, are critical prognostic factors for mortality and recurrence[6,7].

There is extensive evidence that lifestyle factors, such as diet and physical activity, may be associated with the onset of malnutrition in its different forms[8,9]. Therefore, interventions which monitor adherence to dietary recommendations and promote an increase in physical activity can have a positive impact on quality of life but also on the prognosis and mortality associated to the tumour and recurrence rates[10-12].

At the same time, it is very well established that in the health systems of many countries nutritional strategies following and/or in conjunction with chemotherapy are often insufficient or non-existent, due to a lack of resources or infrastructure[13-16]. Furthermore, studies reflecting the current status of this service in Spain are scarce and thus it can be assumed that there is a blind spot in the clinical practices surrounding this situation.

In addition, there is little knowledge regarding the dietary habits of women with cancer in the Balearic Islands and therefore it is unknown whether a nutritional support intervention would have an impact on their food habits and medic development. Nevertheless, studies in women with breast cancer conducted in other populations have shown that patients usually modify their regular diet during the course of chemotherapy treatment[17,18].

Thus, the main objective of this study is to perform a nutritional assessment in women diagnosed and treated for breast cancer in the Balearic Islands and explore their need for nutritional support throughout the chemotherapy process.

Methodology

Study design and participants

The project proposed is an observational study, with a descriptive cross-sectional design. Study participants are women treated for breast cancer at the time of chemotherapy treatment. Sample size was calculated in order for it to be representative of the Balearic Islands. Every year, more than 700 women are diagnosed with breast cancer in the Balearic Islands[16]. Of these women, nearly 400 have an age range between 45 and 65 years old. Therefore, a representative sample was considered to be 50% of this major population, resulting in a sample size of approximately 200 participants. The recruitment procedure will be done in public and private hospitals during the period of 2 years. The type of sampling performed will be opportunistic, whereby all subjects will have the same probability of becoming part of the study and will be offered to participate.

Table I: Eligibility criteria.

Inclusion criteria	Exclusion criteria
Sign the informed consent	Terminal clinical situation
Female sex	Psychiatric condition
An established tumour histochemical subtype	Previous disease that could have affected nutritional status
Age range ≥18 and ≤80	Receive exclusive feeding via parenteral nutrition

A pilot study will be performed, where comprehension of the newly developed survey will be conducted, and whether all questions are answered. Changes to improve the survey will be applied if necessary. Ethical approval for this research project was obtained from the Ethical Committee of Research from the University of Balearic Islands (**228CER21**). The study will be carried out in accordance with the principles of the Declaration of Helsinki and the International Conference for Harmonization.

Questionnaire

In order to carry out this nutritional assessment, a new comprehensive survey will be developed based on previously validated and published questionnaires which consider various dimensions (diet, sleep patterns, physical activity, quality of life, sociodemographic factors). The questionnaires used will be: *questionnaire MEDAS of Adherence to the Mediterranean Diet*[19], *Mini Nutritional Assessment*[20], *Subjective global assessment generated by the patient* (VGS)[21], *World Health Organization Quality of Life Questionnaire* (WHOQOL-Bref)[22], *Patient Health Quality* (PHQ9)[23] the *MOS-Sleep*[24] and the *International Questionnaire of Physical Activity* (IPAQ)[25], resulting in around 80 questions with an expected time of completion of 30 minutes. Furthermore, 9 questions regarding adherence to the *World Cancer Research Fund and the American Institute for Cancer Research*, dietary and lifestyle recommendations were also included. Thus, the intention of this survey is to capture

the following information: 1. Quality of the diet; 2. Current nutritional status; 3. Lifestyle behaviours (eating times, sleep); 4. Physical activity levels; 5. Perceived quality of life; 6. Influence of sociodemographic factors; 7. Extent to which patients have received nutritional counselling as well as the quality of counselling. This survey will be implemented by trained nutritionists.

Statistical Analysis

Statistical analysis will be performed using Stata (StataCorp. 2019. Stata Statistical Software). Firstly, an extensive descriptive analysis will be carried out, including: labelling and purification of the data. Also, normality tests and scatters plots will be done for all variables of interest. In the case that high deviations are found, other measures of central tendency will be used, such as medians or modes. Secondly, a bivariate analysis will be carried. Outcomes will be compared with published data, nutritional recommendations and with quality diet indexes in literature.

Discussion

The main limitation of this study relates to the cross-sectional nature of our analyses and the potential for reverse causality bias, and thus it will not be possible to assess the dietary changes that typically occur during chemotherapy and that are reflected in the scientific literature. Furthermore, is it highly plausible that subjects who perceive themselves at risk or as overweight/obese will be more likely to adopt favorable changes in their diets. Lastly, answers may be biased by memory and expectations of which is the best possible or “heathier” answer (also known as Social desirability bias) and to try to sort this limitation, well trained nutritionist interviewers will be part of the project and different dimensions will be inquired by various questions.

The advancement in modern medicine has meant earlier diagnosis of cancer and an increase in the amount of available medications, radiation and surgical interventions. Thus, the number of cancer survivors has increased, and therefore the goal of cancer management is no longer just to treat the disease but also to reduce the risk of further morbidity and mortality. By ensuring survivors develop healthy lifestyle habits, it will be promoted the best possible quality of life in relation to health.

The results of this research will allow the understanding of the current practices and knowledge related to nutrition and oncology in multidisciplinary cooperation and, consequently, enable nutritional interventions in the future. It is expected that this study can provide a general overview in order to develop more studies or nutritional interventions from the start of chemotherapy in future years.

Funding statement

The authors have no conflicts of interest to declare and no financial support has been received to carry out this study.

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References

1. Ferlay J, Colombet M, Soerjomataram I, Parkin D, Piñeros M, Znaor A, et al. Cancer statistics for the year 2020: An overview. Int J cancer . 2021;149(4):778-89.

2. Ganesan K, Du B, Chen J. Effects and mechanisms of dietary bioactive compounds on breast cancer prevention. Pharmacol Res. 2022 Apr 1;178:105974.

3. Salas S, Cottet V, Dossus L, Fassier P, Ginhac J, Latino-Martel P, et al. Nutritional Factors during and after Cancer: Impacts on Survival and Quality of Life. Nutrients. 2022;14(14).

4. Cancer Institute N. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 [Internet]. 2009. Available from: http://www.meddramsso.com

5. Dev R. Measuring cachexia-diagnostic criteria. Ann Palliat Med. 2019;8(1):24-32.

6. Salas S, Cottet V, Dossus L, Fassier P, Ginhac J, Latino-Martel P, et al. Nutritional Factors during and after Cancer: Impacts on Survival and Quality of Life. Nutrients. 2022;14(14).

7. De O Santos K, Gomes F, Da Silva S, Da Silva A, Pinho C. Sarcopenia in oncological patients in chemotherapy treatment. Rev Chil Nutr. 2019;46(4):375-83.

8. Guigni B, Callahan D, Tourville T, Miller M, Fiske B, Voigt T, et al. Skeletal muscle atrophy and dysfunction in breast cancer patients: Role for chemotherapy-derived oxidant stress. Am J Physiol - Cell Physiol. 2018 Nov 1;315(5):744-56.

9. Ballinger TJ, Reddy A, Althouse SK, Nelson EM, Miller KD, Sledge JS. Impact of primary breast cancer therapy on energetic capacity and body composition. Breast Cancer Res Treat. 2018 Nov 1;172(2):445-52.

10. Mantzorou M, Tolia M, Poultsidi A, Vasios G, Papandreou D, Theocharis S, et al. Adherence to Mediterranean Diet and Nutritional Status in Women with Breast Cancer: What Is Their Impact on Disease Progression and Recurrence-Free Patients' Survival? Curr Oncol. 2022;29(10):7482-97.

11. Castro-Espin C, Agudo A. The Role of Diet in Prognosis among Cancer Survivors: A Systematic Review and Meta-Analysis of Dietary Patterns and Diet Interventions. Nutrients. 2022;14(2).

12. Lach K, Peterson SJ. Nutrition Support for Critically Ill Patients With Cancer. Nutr Clin Pract. 2017;32(5):578-86.

13. Keaver L, O'Callaghan N, Douglas P. Nutrition support and intervention preferences of cancer survivors. J Hum Nutr Diet. 2022.

14. Sánchez-Lara K, Ugalde-Morales E, Motola-Kuba D, Green D. Gastrointestinal symptoms and weight loss in cancer patients receiving chemotherapy. Br J Nutr. 2013 Mar 14;109(5):894-7.

15. Smith SL, Singh-Carlson S, Downie L, Payeur N, Wai ES. Survivors of breast cancer: Patient perspectives on survivorship care planning. J Cancer Surviv. 2011 Dec 4;5(4):337-44.

16. Nutrition in Cancer Care (PDQ®): Patient Version. www.cancer.gov. 2022. p. 26389440.

17. Pedersini R, Di Mauro P, Bosio S, Zanini B, Zanini A, Amoroso V, et al. Changes in eating habits and food preferences in breast cancer patients undergoing adjuvant chemotherapy. Sci Rep. 2021 Jun 21;11(1):12975.

18. Carlucci Palazzo C, Cremonezi Japur C, Borges de Araújo L, Diez-Garcia RW. Eating Experiences, Sweet Preference, and Weight Gain in Women During Chemotherapy for Breast Cancer: A Mixed Methods Study. Nutr Cancer. 2019;71(4):594-604.

19. Álvarez-Álvarez I, Martínez-González MÁ, Sánchez-Tainta A, Corella D, Díaz-López A, Fitó M, et al. Adherence to an Energy-restricted Mediterranean Diet Score and Prevalence of Cardiovascular Risk Factors in the PREDIMED-Plus: A Cross-sectional Study. Rev Esp Cardiol (Engl Ed). 2019;72(11):925-34.

20. Salvà Casanovas A. El Mini Nutritional Assessment. Veinte años de desarrollo ayudando a la valoración nutricional. Rev Esp Geriatr Gerontol. 2012 Nov;47(6):245-6.

21. De Groot LM, Lee G, Ackerie A, van der Meij BS. Malnutrition Screening and Assessment in the Cancer Care Ambulatory Setting: Mortality Predictability and Validity of the Patient-Generated Subjective Global Assessment Short form (PG-SGA SF) and the GLIM Criteria. Nutrients. 2020;12(8):1-13.

22. Aydin M, Kose E, Odabas I, Bingul BM, Demirci D, Aydin Z. The Effect of Exercise on Life Quality and Depression Levels of Breast Cancer Patients. Asian Pac J Cancer Prev. 2021;22(3):725-32.

23. Costantini L, Pasquarella C, Odone A, Colucci ME, Costanza A, Serafini G, et al. Screening for depression in primary care with Patient Health Questionnaire-9 (PHQ-9): A systematic review. J Affect Disord. 2021;279:473-83.

24. Oliva D, Andersson B-Å, Lewin F, Jensen LD. Opposing inflammatory biomarker responses to sleep disruption in cancer patients before and during oncological therapy. Front Neurosci. 2022 Sep 21;16.

25. Mantilla Toloza SC, Gómez-Conesa A. El Cuestionario Internacional de Actividad Física. Un instrumento adecuado en el seguimiento de la actividad física poblacional. Vol. 10, Revista Iberoamericana de Fisioterapia y Kinesiologia. Ediciones Doyma, S.L.; 2007. p. 48-52.

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ORIGINAL

Variables influencing the appearance of metabolic syndrome with three different definitions in 418.343 spanish workers

Variables que influyen en la aparición del síndrome metabólico con tres definiciones diferentes en 418.343 trabajadores españoles

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Abstract

Introduction: Metabolic syndrome (MS) is a clinical entity whose prevalence is increasing worldwide. It is a multifactorial condition that increases cardiovascular risk. The aim of this study is to assess the influence of sociodemographic variables and healthy habits on the appearance of MS.
Material and methods: Descriptive and cross-sectional study in 418.343 Spanish workers in which the influence of sex, age, social class, educational level, physical activity, adherence to the Mediterranean diet and tobacco consumption on the prevalence of metabolic syndrome was assessed by applying three different criteria: NCEP ATPIII, IDF and JIS.
Results: Multivariate analysis showed that the variables that most increased the risk of presenting MS were sedentary lifestyle, low adherence to the Mediterranean diet and age. Of all the variables analyzed, the only one that showed no influence was social class.
Conclusions: In our study, all the variables analyzed except social class increased the risk of MS, of which the most influential were low physical activity, low adherence to the Mediterranean diet, and age.

Keywords: Metabolic syndrome, physical activity, adherence to the Mediterranean diet.

Resumen

Introducción: El síndrome metabólico (SM) es una entidad clínica que va aumentando su prevalencia en el mundo. Es un cuadro multifactorial que incrementa el riesgo cardiovascular. El objetivo de este estudio es valorar la influencia de variables sociodemográficas y hábitos saludables en la aparición de SM.
Material y métodos: Estudio descriptivo y transversal en 418.343 trabajadores españoles en los que se valora la influencia del sexo, la edad, la clase social, el nivel de estudios, la actividad física, la adherencia a la dieta mediterránea y el consumo de tabaco en la prevalencia de síndrome metabólico determinado aplicando tres criterios diferentes: NCEP ATPIII, IDF y JIS.
Resultados: En el análisis multivariante se observa que las variables que más incrementan el riesgo de presentar SM son el sedentarismo, la baja adherencia a la dieta mediterránea y la edad. De todas las variables analizadas la única que no muestra influencia es la clase social.
Conclusiones: En nuestro estudio todas las variables analizadas salvo la clase social incrementan el riesgo de SM, de ellas las que más influyen son la baja actividad física, la escas adherencia a la dieta mediterránea y la edad.

Palabras clave: Síndrome metabólico, actividad física, adherencia a la dieta mediterránea.

Introduction

Metabolic syndrome (MS) is a clinical entity that groups together in the same person different metabolic alterations such as abdominal obesity, elevated triglycerides, lower HDL cholesterol, increased blood pressure and hyperglycemia[1].

MS is currently considered one of the most important public health problems[2]. Its presence is five times the prevalence of diabetes mellitus[3] and almost three times the prevalence of cardiovascular disease[4], which translates into a significant increase in health care costs worldwide[5].

MS has been known for a century thanks to the studies of Kylin in Sweden[6]. Since this first approach to the problem, which included hypertension, hyperglycemia and gout, there have been different definitions. Currently, the most commonly used criteria are those of the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP-III)[7] and those of the International Diabetes Federation (IDF)[7].

Many risk factors have been associated with the appearance of MS, including advanced age[8], low socioeconomic level[9], family history[10], genetics[11], obesity[12], polycystic ovary[13], psoriasis[14], sleep disorders[15], and sarcopenia[16], among others.

The aim of this study was to assess whether there is an association between the appearance of MS (applying three different criteria) and different sociodemographic variables (age, sex, social class, and level of education) and healthy habits (physical activity, adherence to the Mediterranean diet, and tobacco consumption).

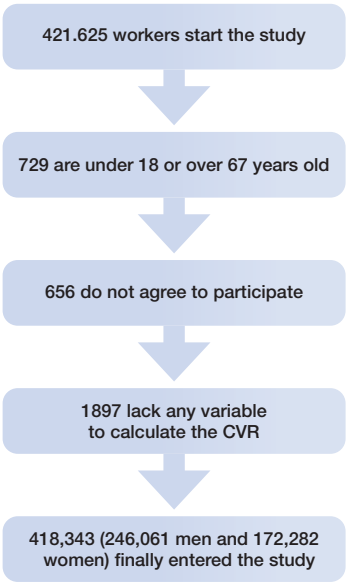
Methods

A descriptive and cross-sectional study was carried out in 418343 workers from different regions of Spain and from different labor sectors, mostly public administration, health, construction and commerce. The workers were selected from those who attended the periodic medical examinations of the companies January 2017 and December 2019.

Inclusion criteria:

- Age between 18 and 67 years.
- Working in one of the companies included in the study.
- Not being in a situation of temporary disability.
- Sign informed consent to participate in the study and to use their data for epidemiological purposes.

Figure 1: Flow diagram of the study participants.



Measurements and data collection

Different anthropometric and analytical parameters were measured in the people who participated in the study.

The anthropometric, clinical and analytical determinations were performed by the occupational health professionals of the companies, after standardization of the different measurement techniques.

Weight and height were obtained from the SECA model scale-measuring scale. Waist circumference (WC) was measured while standing upright, feet together, trunk straight and abdomen relaxed. The measuring tape was placed parallel to the floor at the level of the last floating rib.

Blood pressure was obtained with a calibrated OMRON M3 automatic sphygmomanometer while seated and after at least 10 minutes of rest. Three determinations were made at one-minute intervals and the mean of the three was obtained. Blood parameters were obtained after at least 12h of fasting. Samples were processed in reference laboratories within 48-72 hours. Glycemia, total cholesterol and triglycerides were determined by automated enzymatic methods. HDL-c was determined by a precipitation process with dextran sulfate-MgCl2. LDL-c was calculated indirectly by applying the Friedewald formula, which is valid for triglyceride values below 400 mg/dL. All these parameters are expressed in mg/dL.

Friedewald formula: LDL = cholesterol - HDL - triglycerides/5

Five age groups were established: 18 to 29 years, 30 to 39 years, 40 to 49 years, 50 to 59 years, and 60 to 67 years.

Social class was obtained from the proposal of the social determinants group of the Spanish Society of Epidemiology[17]. Three categories were considered: Class I: directors/managers, university professionals, sportsmen and artists; Class II: intermediate occupations and skilled self-employed workers; Class III: unskilled workers.

The level of education was classified as primary or elementary, secondary and university. We considered smokers to be those who had consumed at least one cigarette daily (or its equivalent in other types of consumption) during the last month, or had quit smoking less than 12 months before.

Heart-healthy eating habits are determined with the "Mediterranean diet adherence questionnaire" used in the PREDIMED study[18]. The questionnaire consists of 14 questions that are scored with 0 and 1 point. Values of 9 or more indicate good adherence and therefore that the diet is heart-healthy.

Physical activity is assessed with the International Physical Activity Questionnaire (IPAQ), which evaluates the physical activity performed in the last week[19].

19 To assess the metabolic syndrome (MS), we used 3 different criteria, those of the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP-III), the Joint Interim Statement (JIS) and the update of the International Diabetes Federation (IDF)[20].

Statistical analysis

A descriptive analysis of the categorical variables was performed, calculating the frequency and distribution of the responses for each of them. For quantitative variables, the mean and standard deviation were calculated following a normal distribution.

Bivariate association analysis was performed using the chi2 test (with correction for Fisher's exact statistic when conditions required it) and Student's t test for independent samples (for comparison of means). Multivariate techniques were used to establish the variables associated with the most significant risk factors. Multinomial logistic regression was used for multivariate analysis, with calculation of the odds ratio and the Hosmer-Lemeshow goodness-of-fit test. Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) version 28.0 (IBM Company, New York, NY, USA) for Windows, with an accepted statistical significance level of 0.05.

Ethical considerations and/or aspects

The research team undertook at all times to follow the ethical principles of health sciences research established nationally and internationally (Declaration of Helsinki), paying special attention to the anonymity of the participants and the confidentiality of the data collected.

Approval was requested from the Ethics and Research Committee of the Balearic Islands (CEI-IB), which was obtained with indicator IB 4383/20. Participation in the study was voluntary, so the participants gave their written and oral consent to participate in the study after receiving sufficient information about the nature of the study. To this end, they were given an informed consent form, as well as an information sheet explaining the objective of the study. The data collected for the study were identified by a code and only the person responsible for the study can relate these data to the participants. The identity of the participants will not be disclosed in any report of this study. The investigators will not disseminate any information that could identify them. In any case, the research team undertakes to strictly comply with the Organic Law 3/2018, of December 5, on the protection of personal data and guarantee of digital rights, guaranteeing the participant in this study that he/she may exercise his/her rights of access, rectification, cancellation and opposition of the data collected.

Results

Table I shows the anthropometric and clinical characteristics of the 418.343 (246.061 men and 172.282 women) persons included in the study. The mean age of the sample was 40.2 ± 11.0 years, the largest group being between 30 and 49 years. Anthropometric, clinical and analytical values were more unfavorable in men. Most people belonged to social class III and had primary education. More than half of them do not engage in regular physical activity and do not have a heart-healthy diet. One out of three workers smoked.

Table II shows the prevalence of metabolic syndrome, applying the three criteria, according to the different sociodemographic variables and healthy habits. The prevalence, applying any of the criteria, increases with age, as one descends in social class or level of education. Smokers, sedentary people or those with low adherence to the Mediterranean diet have higher prevalences of MS. In all cases, the prevalence of MS is higher in men.

Table III shows the results of the multivariate analysis using multinomial logistic regression. The risk of presenting metabolic syndrome with the three criteria is greater in men, with increasing age, in people with a lower level of education, in sedentary people, in those with low adherence to the Mediterranean diet, and in smokers. The variables that most increase the risk of presenting MS are sedentary lifestyle, followed by diet and age. It should be noted that social class showed no effect on the appearance of MS.

Table I: Characteristics of the population.

	Women n=172.282 Mean ± SD	Men n=246.061 Mean ± SD	Total n=418.343 Mean ± SD	p-value
Age	39.6 (10.8)	40.6 (11.1)	40.2 (11.0)	<0.0001
Height	161.8 (6.5)	174.6 (7.0)	169.4 (9.3)	<0.0001
Weight	66.2 (14.0)	81.4 (14.7)	75.1 (16.2)	<0.0001
BMI	25.3 (5.2)	26.7 (4.5)	26.1 (4.8)	<0.0001
Waist	74.8 (10.6)	86.2 (11.1)	81.5 (12.2)	<0.0001
SBP	117.4 (15.7)	128.2 (15.5)	123.7 (16.5)	<0.0001
DBP	72.6 (10.4)	77.8 (11.0)	75.6 (11.0)	<0.0001
Cholesterol	190.6 (35.8)	192.6 (38.9)	191.8 (37.7)	<0.0001
HDL-c	56.8 (8.7)	50.3 (8.5)	53.0 (9.1)	<0.0001
LDL-c	116.1 (34.8)	118.0 (36.7)	117.2 (35.9)	<0.0001
Triglycerides	89.1 (46.2)	123.7 (86.4)	109.5 (74.6)	<0.0001
Glycaemia	87.8 (15.1)	93.3 (21.3)	91.0 (19.2)	<0.0001
	%	**%**	**%**	**p-value**
18-29 years	20.7	18.8	19.6	<0.0001
30-39 years	3.0	27.6	17.4	
40-49 years	29.6	30.0	29.9	
50-59 years	16.8	19.7	18.5	
60-69 years	3.2	3.9	3.6	
Primary school	51.8	61.2	57.3	<0.0001
Secondary school	40.7	34.0	36.8	
University	7.5	4.8	5.9	
Social class I	6.9	4.9	5.7	<0.0001
Social class II	23.4	14.9	18.4	
Social class III	69.7	80.3	75.9	
No physical activity	47.8	54.5	51.7	<0.0001
Yes physical activity	52.2	45.5	48.3	
No mediterranean diet	48.6	59.0	54.7	<0.0001
Yes mediterranean diet	51.4	41.0	45.3	
Non-smokers	67.2	66.6	66.8	<0.0001
Smokers	32.8	33.4	33.2	

SBP systolic bllood pressure. DBP diastolic blood pressure.

Table II: Prevalence of metabolic syndrome with different criteria according to sociodemographic variables and healthy habits.

	Women n	ATPIII %	p-value	IDF %	p-value	JIS %	p-value	Men n	ATPIII %	p-value	IDF %	p-value	JIS %	p-value
18-29 years	35617	0.86	<0.0001	1.39	<0.0001	1.77	<0.0001	46215	2.79	<0.0001	4.08	<0.0001	3.79	<0.0001
30-39 years	5115	1.99		2.69		3.13		67798	6.31		8.32		8.16	
40-49 years	51017	4.19		5.40		7.01		73935	11.51		14.70		14.92	
50-59 years	28951	9.15		7.93		13.13		48522	14.68		19.00		20.20	
60-69 years	5582	12.63		9.98		18.33		9591	14.48		21.44		24.06	
Primary school	89221	4.63	<0.0001	5.16	<0.0001	7.40	<0.0001	150602	9.40	<0.0001	12.20	<0.0001	12.51	<0.0001
Secondary school	70082	2.97		3.37		4.56		83734	8.09		10.86		10.88	
University	12979	2.27		2.34		3.10		11725	6.92		9.01		9.81	
Social class I	11894	2.46	<0.0001	2.38	<0.0001	3.20	<0.0001	11950	6.85	<0.0001	9.07	<0.0001	9.72	<0.0001
Social class II	40266	2.98		3.36		4.58		36590	7.97		10.90		10.77	
Social class III	120122	4.38		4.92		6.98		197521	9.17		11.92		12.21	
No physical activity	82373	7.71	<0.0001	8.63	<0.0001	11.99	<0.0001	134023	16.22	<0.0001	20.71	<0.0001	21.42	<0.0001
Yes physical activity	89909	0.68		0.71		0.78		112038	1.13		1.68		1.69	
No mediterranean diet	83651	7.57	<0.0001	8.48	<0.0001	11.76	<0.0001	145286	14.91	<0.0001	19.09	<0.0001	19.70	<0.0001
Yes mediterranean diet	88631	0.71		0.74		0.81		100775	1.92		2.04		1.89	
Non-smokers	115727	3.77	<0.0001	4.15	<0.0001	5.76	<0.0001	163920	7.35	<0.0001	10.75	<0.0001	10.19	<0.0001
Smokers	56555	3.81		4.38		6.23		82141	11.36		13.02		14.60	
Total	172282	3.78		4.22		5.92		246061	8.84		11.59		11.83	

Table III: Multinomial logistic regression.

	NCEP-ATPIII OR (95% CI)	IDF OR (95% CI)	JIS OR (95% CI)
Women	1	1	1
Men	2.07 (1.98-2.17)	2.62 (2.51-2.73)	1.83 (1.76-1.90)
18-29 years	1	1	1
30-39 years	1.11 (1.02-1.21)	1.18 (1.09-1.28)	1.34 (1.25-1.45)
40-49 years	1.43 (1.32-1.56)	1.39 (1.28-1.50)	1.81 (1.68-1.94)
50-59 years	2.13 (1.95-2.33)	2.04 (1.88-2.21)	2.83 (2.62-3.05)
60-69 years	3.50 (3.13-3.91)	3.01 (2.73-3.32)	4.32 (3.94-4.75)
Primary school	1	1	1
Secondary school	1.17 (1.11-1.24)	1.16 (1.11-1.22)	1.19 (1.13-1.25)
University	1.43 (1.14-1.789)	1.45 (1.19-1.78)	1.46 (1.20-1.77)
Social class I	1	1	1
Social class II	46.44 (35.80-60.23)	13.83 (12.12-15.77)	18.45 (16.05-21.22)
Social class III	1	1	1
No physical activity	5.37 (4.38-6.58)	3.25 (2.86-3.70)	3.73 (3.27-4.24)
Yes physical activity	1	1	1
No mediterranean diet	1.73 (1.67-1.80)	1.39 (1.34-1.44)	1.69 (1.64-1.75)

Discussion

All the sociodemographic variables analyzed, with the exception of social class, influence the appearance of MS applying any of the three criteria. Smoking, level of physical activity and adherence to the Mediterranean diet also have an influence. Of these, the one that most increases the risk of MS is sedentary lifestyle, followed by low adherence to the Mediterranean diet and age.

In our study, the prevalence of MS is considerably higher in men with the three scales and in all age groups, although the differences become smaller as age increases. This data partially coincide with those found in a review by Pucci et al[21], since in this study the prevalence in women exceeds that of men after the age of 50 years, that is, after menopause. The explanation given by the authors is that this is due to several factors, some related to sex and others to gender. Those related to sex are due to hyperandrogenism, insulin resistance and the associated increase in abdominal obesity and reduction of HDL cholesterol that appears after menopause. Those related to gender are sensitive to social and cultural behaviors, dietary habits and psychosocial factors. Women are more likely than men to develop MS in response to work stress and low socioeconomic status. The negative effect of menopause on the prevalence of MS was also highlighted in a meta-analysis by Pu et al[22] in which the main conclusion was that menopause negatively affects all components of MS. Similar results were found in another meta-analysis by Hallajzadeh et al[23].

Our work shows the negative effect of more unfavorable socioeconomic levels on the prevalence of MS. A study carried out in a Mexican population by Bustamante-Villagómez et al[24] in which the influence of quality of life and socioeconomic status on MS was assessed showed that lower quality of life and low socioeconomic status increased the risk of MS; however, if quality of life was improved, the negative effect of low socioeconomic status on MS could be diminished. A study by Zhan et al[25] in the Chinese population found an association between lower levels of income and education and a higher prevalence of MS, although statistical significance was only found in women. In the Iranian population, Gharipour et al[26] also found a higher prevalence of MS in persons with lower socioeconomic levels.

Our study has shown the negative effect of smoking, sedentary lifestyle, and low adherence to the Mediterranean diet on the prevalence of MS.

There is unanimity in considering the beneficial effect of physical activity on MS, and both observational and interventional studies suggest this protective role. Each of the components of MS is, to some extent, favorably influenced by interventions that include physical activity[27-29].

There is also unanimity on the beneficial effect of the Mediterranean diet on MS. The Mediterranean diet can be considered a therapy for MS as it prevents the formation of abnormal fat[30-32].

The negative effect of smoking on MS observed in our study was also seen in a study in Palestinian adolescents by Damiri et al[33]. Another study by Bermudez et al[34] in more than 2000 Venezuelan adults of both sexes showed that smoking was associated with lower HDL values, increased waist circumference and elevated triglycerides.

Strengths and limitations

The strengths of the study include the large sample size (more than 400,000 workers) and the variety of metabolic

syndrome criteria, sociodemographic variables and healthy habits used. Among the possible limitations, we would point out that the study was carried out in the 18-67 age group (working population), which could prevent extrapolation of the results to the entire population. In addition, there may be a sample selection bias since the study included people who go for occupational medical check-ups, so that they could be people who are more concerned about their health.

Conclusions

Male sex, age, educational level, physical activity, adherence to the Mediterranean diet, and tobacco consumption influence the appearance of MS applying any of the three criteria. Social class has shown no influence.

Conflict of Interest

The authors declare that no competing interests exist.

References

1. Engin A. The Definition and Prevalence of Obesity and Metabolic Syndrome. Adv Exp Med Biol. 2017;960:1-17. doi: 10.1007/978-3-319-48382-5_1.

2. Saklayen MG. The Global Epidemic of the Metabolic Syndrome. Curr Hypertens Rep. 2018 Feb 26;20(2):12. doi: 10.1007/s11906-018-0812-z.

3. Li C, Hsieh MC, Chang SJ. Metabolic syndrome, diabetes, and hyperuricemia. Curr Opin Rheumatol. 2013 Mar;25(2):210-6. doi: 10.1097/BOR.0b013e32835d951e.

4. Bovolini A, Garcia J, Andrade MA, Duarte JA. Metabolic Syndrome Pathophysiology and Predisposing Factors. Int J Sports Med. 2021 Mar;42(3):199-214. doi: 10.1055/a-1263-0898.

5. Xu H, Li X, Adams H, Kubena K, Guo S. Etiology of Metabolic Syndrome and Dietary Intervention. Int J Mol Sci. 2018 Dec 31;20(1):128. doi: 10.3390/ijms20010128.

6. Alberti G. Introduction to the metabolic síndrome. European Heart Journal Supplements 2005; (7 suppl D) :D3–D5, https://doi.org/10.1093/eurheartj/sui021

7. Gundogan K, Bayram F, Gedik V, Kaya A, Karaman A, Demir O, et al. Metabolic syndrome prevalence according to ATP III and IDF criteria and related factors in Turkish adults. Arch Med Sci. 2013 Apr 20;9(2):243-53. doi: 10.5114/aoms.2013.34560.

8. Assuncao N, Sudo FK, Drummond C, de Felice FG, Mattos P. Metabolic Syndrome and cognitive decline in the elderly: A systematic review. PLoS One. 2018 Mar 26;13(3):e0194990. doi: 10.1371/journal.pone.0194990.

9. Chen MS, Chiu CH, Chen SH. Risk assessment of metabolic syndrome prevalence involving sedentary occupations and socioeconomic status. BMJ Open. 2021 Dec 13;11(12):e042802. doi: 10.1136/bmjopen-2020-042802.

10. Yao F, Bo Y, Zhao L, Li Y, Ju L, Fang H, et al. Prevalence and Influencing Factors of Metabolic Syndrome among Adults in China from 2015 to 2017. Nutrients. 2021 Dec 15;13(12):4475. doi: 10.3390/nu13124475.

11. Fahed G, Aoun L, Bou Zerdan M, Allam S, Bou Zerdan M, Bouferraa Y, et al. Metabolic Syndrome: Updates on Pathophysiology and Management in 2021. Int J Mol Sci. 2022 Jan 12;23(2):786. doi: 10.3390/ijms23020786.

12. Litwin M, Kułaga Z. Obesity, metabolic syndrome, and primary hypertension. Pediatr Nephrol. 2021 Apr;36(4):825-37. doi: 10.1007/s00467-020-04579-3.

13. Lim SS, Kakoly NS, Tan JWJ, Fitzgerald G, Bahri Khomami M, Joham AE, et al. Metabolic syndrome in polycystic ovary syndrome: a systematic review, meta-analysis and meta-regression. Obes Rev. 2019 Feb;20(2):339-52. doi: 10.1111/obr.12762.

14. Hao Y, Zhu YJ, Zou S, Zhou P, Hu YW, Zhao QX, et al. Metabolic Syndrome and Psoriasis: Mechanisms and Future Directions. Front Immunol. 2021 Jul 23;12:711060. doi: 10.3389/fimmu.2021.711060.

15. Smiley A, King D, Bidulescu A. The Association between Sleep Duration and Metabolic Syndrome: The NHANES 2013/2014. Nutrients. 2019 Oct 26;11(11):2582. doi: 10.3390/nu11112582.

16. Nishikawa H, Asai A, Fukunishi S, Nishiguchi S, Higuchi K. Metabolic Syndrome and Sarcopenia. Nutrients. 2021 Oct 7;13(10):3519. doi: 10.3390/nu13103519

17. Domingo-Salvany A, Bacigalupe A, Carrasco JM, Espelt A, Ferrando J, Borrell C, et al. Propuestas de clase social neoweberiana y neomarxista a partir de la Clasificación Nacional de Ocupaciones 2011. Gac Sanit. 2013 May-Jun;27(3):263-72. doi: 10.1016/j.gaceta.2012.12.009.

18. Ros E. The PREDIMED study. Endocrinol Diabetes Nutr. 2017 Feb;64(2):63-6.

19. Sember V, Meh K, Sorić M, Starc G, Rocha P, Jurak G. Validity and Reliability of International Physical Activity Questionnaires for Adults across EU Countries: Systematic Review and Meta Analysis. Int J Environ Res Public Health. 2020 Sep 30;17(19):7161.

20. Riutord-Sbert P, Riutord-Fe B, Riutord-Fe-N, Arroyo-Bote S, López-González AA, Ramirez-Manent JI. Relationship between physical activity and adherence to the mediterranean diet with metabolic syndrome, hypertriglyceridemic waist phenotype and hypertensive waist. Medicina Balear 2022;37(6):33-8. doi: 10.3306/AJHS.2022.37.06.33

21. Pucci G, Alcidi R, Tap L, Battista F, Mattace-Raso F, Schillaci G. Sex- and gender-related prevalence, cardiovascular risk and therapeutic approach in metabolic syndrome: A review of the literature. Pharmacol Res. 2017 Jun;120:34-42. doi: 10.1016/j.phrs.2017.03.008.

22. Pu D, Tan R, Yu Q, Wu J. Metabolic syndrome in menopause and associated factors: a meta-analysis. Climacteric. 2017 Dec;20(6):583-91. doi: 10.1080/13697137.2017.1386649.

23. Hallajzadeh J, Khoramdad M, Izadi N, Karamzad N, Almasi-Hashiani A, Ayubi E, et al. Metabolic syndrome and its components in premenopausal and postmenopausal women: a comprehensive systematic review and meta-analysis on observational studies. Menopause. 2018 Oct;25(10):1155-64. doi: 10.1097/GME.0000000000001136.

24. Bustamante-Villagómez SK, Vásquez-Alvarez S, Gonzalez-Mejia ME, Porchia LM, Herrera-Fomperosa O, Torres-Rasgado E, et al. Asociación entre síndrome metabólico, nivel socioeconómico y calidad de vida en mexicanos. Rev Med Inst Mex Seguro Soc. 2021 Nov 1;59(6):490-9.

25. Zhan Y, Yu J, Chen R, Gao J, Ding R, Fu Y, et al. Socioeconomic status and metabolic syndrome in the general population of China: a cross-sectional study. BMC Public Health. 2012 Oct 30;12:921. doi: 10.1186/1471-2458-12-921.

26. Gharipour M, Sadeghi M, Nouri F, Nezafati P, Qader SS, Taheri M, et al. Socioeconomic determinants and metabolic syndrome: Results from the Isfahan Healthy Heart Program. Acta Biomed. 2016 Jan 16;87(3):191-8.

27. Myers J, Kokkinos P, Nyelin E. Physical Activity, Cardiorespiratory Fitness, and the Metabolic Syndrome. Nutrients. 2019 Jul 19;11(7):1652. doi: 10.3390/nu11071652.

28. Roberts CK, Hevener AL, Barnard RJ. Metabolic syndrome and insulin resistance: underlying causes and modification by exercise training. Compr Physiol. 2013 Jan;3(1):1-58. doi: 10.1002/cphy.c110062.

29. De Sousa SM Dr, Norman RJ Prof. Metabolic syndrome, diet and exercise. Best Pract Res Clin Obstet Gynaecol. 2016 Nov;37:140-51. doi: 10.1016/j.bpobgyn.2016.01.006.

30. Di Daniele N, Noce A, Vidiri MF, Moriconi E, Marrone G, Annicchiarico-Petruzzelli M, et al. Impact of Mediterranean diet on metabolic syndrome, cancer and longevity. Oncotarget. 2017 Jan 31;8(5):8947-79. doi: 10.18632/oncotarget.13553.

31. Finicelli M, Squillaro T, Di Cristo F, Di Salle A, Melone MAB, Galderisi U, et al. Metabolic syndrome, Mediterranean diet, and polyphenols: Evidence and perspectives. J Cell Physiol. 2019 May;234(5):5807-26. doi: 10.1002/jcp.27506.

32. Sayón-Orea C, Razquin C, Bulló M, Corella D, Fitó M, Romaguera D, et al. Effect of a Nutritional and Behavioral Intervention on Energy-Reduced Mediterranean Diet Adherence Among Patients With Metabolic Syndrome: Interim Analysis of the PREDIMED-Plus Randomized Clinical Trial. JAMA. 2019 Oct 15;322(15):1486-1499. doi: 10.1001/jama.2019.14630.

33. Damiri B, Khatib O, Nazzal Z, Sanduka D, Igbaria S, Thabaleh A, et al. Metabolic Syndrome Associated with Tobacco and Caffeine Products Use Among Refugee Adolescents: Risk of Dyslipidemia. Diabetes Metab Syndr Obes. 2021 Sep 29;14:4121-4133. doi: 10.2147/DMSO.S329675.

34. Bermudez V, Olivar LC, Torres W, Navarro C, Gonzalez R, Espinoza C, et al. Cigarette smoking and metabolic syndrome components: a cross-sectional study from Maracaibo City, Venezuela. F1000Res. 2018 May 10;7:565. doi: 10.12688/f1000research.14571.3.

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ORIGINAL

Prevalence of adverse drug effects of anti-retroviral drugs on hiv-positive patients receiving anti-retroviral treatment in General Hospital Onitsha, Anambra, Nigeria

Prevalencia de los efectos adversos de los medicamentos antirretrovirales en pacientes seropositivos que reciben tratamiento antirretroviral en el Hospital General de Onitsha, Anambra, Nigeria

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Abstract

Background: The wide use and acceptability of antiretroviral treatment has really helped in fighting HIV and keeping infected patients healthy and reducing the risk of further transmission and because of that HIV has become less life threatening. The general objective of this study was to determine the prevalence of adverse drug reactions of antiretroviral drugs on HIV patients receiving care in General Hospital Onitsha.
Methods: A descriptive cross sectional study was adopted to obtain findings on the Prevalence of Adverse Drug Reaction of Antiretroviral Drugs on HIV-positive patient in General Hospital Onitsha. A non-probability convenient sampling technique was used to determine a sample size of 310 respondents for the study and data was collected from all of them with the use of a detailed questionnaire. Data was analyzed using the SPSS version 22 and Microsoft excel. Chi-square was used to test association between variables.
Results: From the analysis, it showed that 65.8% of the respondents are female and adults in the age bracket of 29-48 years. 51.9% were married and majority of the respondents (80%) are of the Igbo origin. Also a good number of them (n=200, 64.5%) are using TDF+3TC+DTG. Only 37.1% of the respondents are found to have had an experience of adverse drug reactions in which skin rash, peripheral neuropathy and gastrointestinal problems are prevalent with percentages of 32.2, 23.5 and 22.6 respectively.
Conclusion: Adverse drug reactions associated with antiretroviral drugs in General Hospital Onitsha was found not to be prevalent and they occur mostly in people who are in the early years of treatment initiation. This study emphasized the need to monitor at risk and vulnerable patients to know when they have developed an event as a result of treatment. It is highly recommended that intensive and close follow-up of patients, especially for those in their early years of treatment initiation for early detection and quick management of adverse drug reaction.

Keywords: Adverse Drug Effects, HIV, Anti-retroviral Drugs, HIV-Positive Patients, Prevalence.

Resumen

Antecedentes: El amplio uso y la aceptación del tratamiento antirretroviral han ayudado realmente a luchar contra el VIH y a mantener sanos a los pacientes infectados y a reducir el riesgo de nuevas transmisiones, por lo que el VIH se ha convertido en una amenaza para la vida. El objetivo general de este estudio fue determinar la prevalencia de las reacciones adversas a los medicamentos antirretrovirales en los pacientes con VIH que reciben atención en el Hospital General de Onitsha.
Métodos: Se adoptó un estudio transversal descriptivo para obtener resultados sobre la Prevalencia de Reacciones Adversas a los Medicamentos Antirretrovirales en pacientes VIH positivos en el Hospital General de Onitsha. Se utilizó una técnica de muestreo conveniente no probabilístico para determinar un tamaño de muestra de 310 encuestados para el estudio y se recogieron datos de todos ellos con el uso de un cuestionario detallado. Los datos se analizaron con el SPSS versión 22 y Microsoft Excel. Se utilizó el chi-cuadrado para probar la asociación entre las variables.
Resultados: Del análisis se desprende que el 65,8% de los encuestados son mujeres y adultos en la franja de edad de 29 a 48 años. El 51,9% estaban casados y la mayoría de los encuestados (80%) son de origen igbo. Además, un buen número de ellos (n=200, 64,5%) utiliza TDF+3TC+DTG. Sólo el 37,1% de los encuestados ha experimentado reacciones adversas al fármaco, en las que prevalecen las erupciones cutáneas, la neuropatía periférica y los problemas gastrointestinales, con porcentajes de 32,2, 23,5 y 22,6 respectivamente.
Conclusión: Se encontró que las reacciones adversas a los medicamentos antirretrovirales en el Hospital General de Onitsha no son prevalentes y ocurren principalmente en las personas que están en los primeros años de la iniciación del tratamiento. Este estudio enfatiza la necesidad de monitorizar a los pacientes de riesgo y vulnerables para saber cuándo han desarrollado un evento como resultado del tratamiento. Se recomienda encarecidamente realizar un seguimiento intensivo y estrecho de los pacientes, especialmente de los que se encuentran en los primeros años de inicio del tratamiento, para la detección precoz y el manejo rápido de las reacciones adversas a los medicamentos.

Palabras clave: Efectos adversos de los medicamentos, VIH, medicamentos antirretrovirales, pacientes seropositivos, prevalencia.

Introduction

Anti-retroviral treatment is the most effective tool in helping fight the Human Immunodeficiency Virus (HIV) by keeping infected patients healthy and reducing the risk of further transmission. As countries implement the 2017 World Health Organization (WHO) treatment guidelines, which require all people living with HIV to be on long-term treatment[1],It is proven that effective treatment results in a decrease in viral load, a boost in the number of CD4 counts, and clinical improvement of the HIV-infected patient[2]. Therefore, ARV drugs have brought highly significant hope to people living with HIV as millions of eligible HIV-infected patients have access to life-prolonging ARV drugs, which has led to a reasonable decrease in HIV-related morbidity and mortality[3]. As a result, HIV has gone from a life-threatening to a chronic condition as a result of the wide use and accessibility of anti-retroviral treatment (ART) among HIV patients[4]. It is estimated that out of the 35.3 million people living with HIV worldwide, only 10.6 million were receiving ART in 2012, with nearly 6.6 million HIV/AIDS related deaths worldwide having been prevented using ART[5]. According to[6], the sub-Saharan African region is most affected by HIV; more than 67% of the people were infected with HIV, and 72% of the patients have died since 2008 due to Acquired Immune Deficiency Syndrome (AIDS)[7]. At the same time[6], reports indicated that approximately 36.7 million people were living with HIV/AIDS, with only 18.2 million receiving anti-retroviral treatment globally.

In 2004, Nigeria received over 400 million dollars in funding to scale up ART —a funding that was partly implemented by Family Health International under the Global HIV/AIDS Initiative Nigeria (GHAIN) project— and this resulted in the influx of ART into the country at an increased level[3]. The establishment of eligibility is attained using clinical staging and CD4 count (Stage I or II with a CD4 count less than 350 or stage IV irrespective of CD4 counts for adults; CD4 less than 25% for children less than 11 months and CD4 less than 20% for children between the ages of 12-35 months) as a criteria regarding Nigerian national guidelines[8].

Despite these gains, adverse reactions to these medicines remain a highly significant public health concern, which stands to contradict the effectiveness of anti-retroviral treatment[2]. Adverse drug reactions are a critical component of HIV/AIDS care and treatment as they should be evaluated for the prevalence and pathogenesis of ADRs to inform clinical management[9]. The occurrence of ADRs may negatively affect the quality of life of patients as well as adherence to the treatment, and the spectrum of ADRs is wide and varied, making it difficult to identify the principal cause[10]. ADRs are highly significant in the effort to diminish toxicities that are most likely to increase the prevalence of chronic diseases of ageing in the HIV-positive population[4]. A better understanding of the ADRs of ARV drugs among HIV patients could help specialists to optimize therapy and also improve the care given to HIV-positive patients[9].

Adverse drug reactions are the most common reason for poor adherence to ART[3]. Non-adherence to anti-retroviral treatment regimens remains common, leading to considerable deterioration of the disease and enhanced HC expenditure[11]. Noncompliance is also thought to increase viral load, drug resistance, and treatment failure[12]. Chronic use of ARV drugs, multiple pills taken at once, exclusion from society and being lonely due to stigma and discrimination, and treatment failure are the major problems associated with highly active anti-retroviral treatment[13]. Adverse drug reactions (ADRs) are regarded as the most prevailing cause of mortality among people living with HIV/AIDS as they are significantly involved in treatment interruptions, regimen changes, treatment failure, and non-adherence among patients on ART[13]. ADRs are brought about by many factors, including stock-out of drugs, poor health service quality, and treatment interruptions, which limit the treatment options, increase the cost of treatment programs, and might increase resistant viruses to the point of being transmissible if left untreated[14]. ADRs are not exactly life-threatening but can impact negatively on the quality of life as it impairs the patients' willingness to adhere to their regimen and influences the decisions made about health care[15].

The stock out of drugs interrupts the treatment and may contribute to ARV drug resistance. That could urge regimen change to deter ARV drug resistance. The longer a patient is on ART, the less likely they will experience ADRs, possibly as a result of stability in the ARV regimen, coming after many changes and eventually settling on an acceptable regimen[16]. Previous research has shown that patients over the age of 38 years have a significantly higher recurrence of ADRs than those under the age of 30 years[17,3]. Also, gender differentials were also found with females having higher risks of adverse drug effects than males, as females experienced higher abnormal fat distribution and peripheral neuropathy that occurred at a significantly younger age compared to males[16]. In a multisite trial in Africa, it was found that tenofovir therapy was associated with a 1.3% rate of significant nephrotoxicity, which was comparable to other regimens, thereby showing no significant toxicity difference between tenofovir and other regimens[3]. This raises a sentinel sign that perhaps drug response to TDF in this setting is not in conformity with the results from other studies where the drug profile of TDF has been superior over AZT and d4T.

The problematic occurrence of widespread underreporting of ADRs and the importance of addressing shortcomings effectively in pharmacovigilance activities in the public healthcare setting need to be appropriately addressed[18]. Furthermore, knowledge regarding antiretroviral (ARV) toxicity in developing countries is limited. These toxicities

can result in unknown long-term effects and compromise patient confidence and adherence[19]. Poor adherence, particularly at levels lower than 95%, has a negative impact on HIV outcome[20]. Over the years, some adverse drug reactions have been observed in every course of anti-retroviral therapy[7]. The occurrence of adverse drug reactions negatively affects the quality of life of patients as well as adherence to the treatment, and the spectrum of adverse events is wide and varied, thereby making it difficult to identify the principal cause sometimes[10]. Different types of anti-retroviral adverse drug reactions occur commonly among patients. Because the ADRs vary in their severity, a common cause of ADR is therefore poor adherence. Also, monitoring safety and toxicity related to ART remains a challenge facing the public health sector. Spontaneous reporting of ADRs is a very inefficient system for detecting drug-related conditions, leading to an underestimation of the burden due to adverse drug reactions. Structured surveillance tracks HIV positive patients who are on ART to assess drug-related morbidity and mortality over time. The objective of this study was to determine the prevalence of adverse drug effects of anti-retroviral drugs on HIV-positive

Methods

Design

A descriptive cross-sectional design was adopted in the study on the prevalence of adverse drug effects of anti-retroviral drugs on HIV-positive patients who are receiving anti-retroviral treatment in General Hospital Onitsha.

Study Setting

This study was carried out at General Hospital Onitsha, Onitsha South Local Government Area, Anambra State. General Hospital Onitsha is a government-owned tertiary healthcare facility located in the cosmopolitan city of Onitsha in the southeastern zone of Nigeria. It has several departments, just like every other government hospital. Services at the ART unit are provided by a group of competent health and non-health professionals. The unit provides comprehensive HIV-related services such as voluntary counselling and testing (VCT), provider-initiated testing and counselling (PITC), PMTCT, pediatric HIV care, and treatment and support for PLWHAs.

Inclusion Criteria

The study recruited HIV-positive patients less than 18 years who were receiving anti-retroviral treatment in General Hospital Onitsha, at least for a minimum of 6 months.

Exclusion Criteria

The study excluded HIV-positive patients receiving treatment in General Hospital Onitsha who refused to give in their consent for the study. The study also excluded HIV-positive patients who are absent at the time of study, those who are below the age of 18, and those who picked up ARVs only once at the pharmacy.

Sampling

The researcher made use of only three hundred and ten HIV-infected patients receiving anti-retroviral care in General Hospital Onitsha. The respondents will be interviewed in order to gather information for the progress of the study.

Sample Size determination

The sample size was determined using the Yamene formula (1967) for sample size determination.

$$n = \frac{N}{1+Ne^2}$$

Where;
n is the desired sample size
N is the population size (953)
e is margin of error (0.05)

$$n = \frac{953}{1+953(0.05)^2}$$

$$n = \frac{953}{1+953*0.0025}$$

Therefore,
n = 281.74

Furthermore, to account for Non Response Rate, the sample size was increased by 10% = 0.10 = 281.74 x 0.10 = 28.1

n =281.7+28.17 =309.9

Approximately =**310**

Sampling Techniques

A non-probability-based convenience sampling technique was employed for the study on the prevalence of adverse drug effects of anti-retroviral drugs on HIV-1 and HIV-2 patients who are receiving anti-retroviral treatment in General Hospital Onitsha.

Data Collection

A self-administered structured questionnaire was used for the study on the prevalence of adverse drug effects of anti-retroviral drugs on HIV-positive patients who are receiving anti-retroviral treatment in General Hospital Onitsha. Data was obtained using a self-administered, semi-structured questionnaire. This was done with the aid of two (2) field assistants who work in the ART department unit of the hospital to aid the researcher in the data collection process. Both the researcher and the research assistants were involved in retrieving the administered questionnaire for data analysis.

Validity and Reliability of the Research Instrument

The questionnaire as the instrument of data collection was developed by the researcher and submitted to the project supervisor for face validity and proper scrutiny as

well as two other lecturers in order to ensure that the questionnaire meets the objectives of study before the distribution of questionnaires for reliability testing.

The reliability of the data instrument was determined using the test retest method. The researcher gave copies of the questionnaire to some respondents outside the area of study by the researcher, thereby pre-testing the questionnaire twice before administering it to the respondents. This area shares similar characteristics with General Hospital Onitsha, which was used for this study. On reliability correlation testing using SPSS, the Cronbach alpha value of 0.76 was obtained. The closeness of this value to 1 indicates that the instrument of data collection is very reliable.

Method of Data Analysis

The data that was gathered from the questionnaire was analyzed using the statistical package for social sciences (SPSS) version 22 and Microsoft Excel. Descriptive statistics, which were expressed in frequency tables and percentages, were used to describe the characteristics in the study of the subjects. Inferential statistics were used with a confidence interval of 95% and a P-value of 0.05 for interpreting significance and correlation.

Ethics

A letter of introduction was obtained from the ethics committee, department of public health, Federal University of Technology Owerri (FUTO). The letter was handed over to the Head of Department, Anti-retroviral Therapy (ART) unit, General Hospital Onitsha, in order to get his consent before carrying out the research in the unit. The purpose of the research was explained to each respondent and verbally informed consent was obtained from them before inclusion in the study. Also, the anonymity of the respondents was assured and ensured. The confidentiality of the information they gave had to be maintained.

Results

A total of 310 respondents were included in the final analysis. 310 questionnaires were carefully distributed and collected by the researcher for the study. The questionnaires were filled properly and cross-checked for accuracy. The flow diagram below (**Figure 1**) summarizes the distribution of patients according to their antiretroviral treatment regimen. This study final analysis includes only HIV-positive patients above the age of 18 who are receiving antiretroviral treatment in General Hospital Onitsha.

The flow diagram (**Figure 1**) summarizes the distribution of respondents according to their antiretroviral treatment regimen. As shown in the figure above, 66.5% (n=206) of the total population use combination of two nucleoside reverse transcriptase inhibitors (NRTI) and an integrase inhibitor (II); 29.6% (n=92) use combination of two NRTI and a non-nucleoside reverse transcriptase inhibitor (NNRTI); and the remaining 3.9% (n=12) use the combination of two NRTI and a protease inhibitor (PI).

Figure 1: Flow diagram of patients and ART regimen received at treatment initiation.

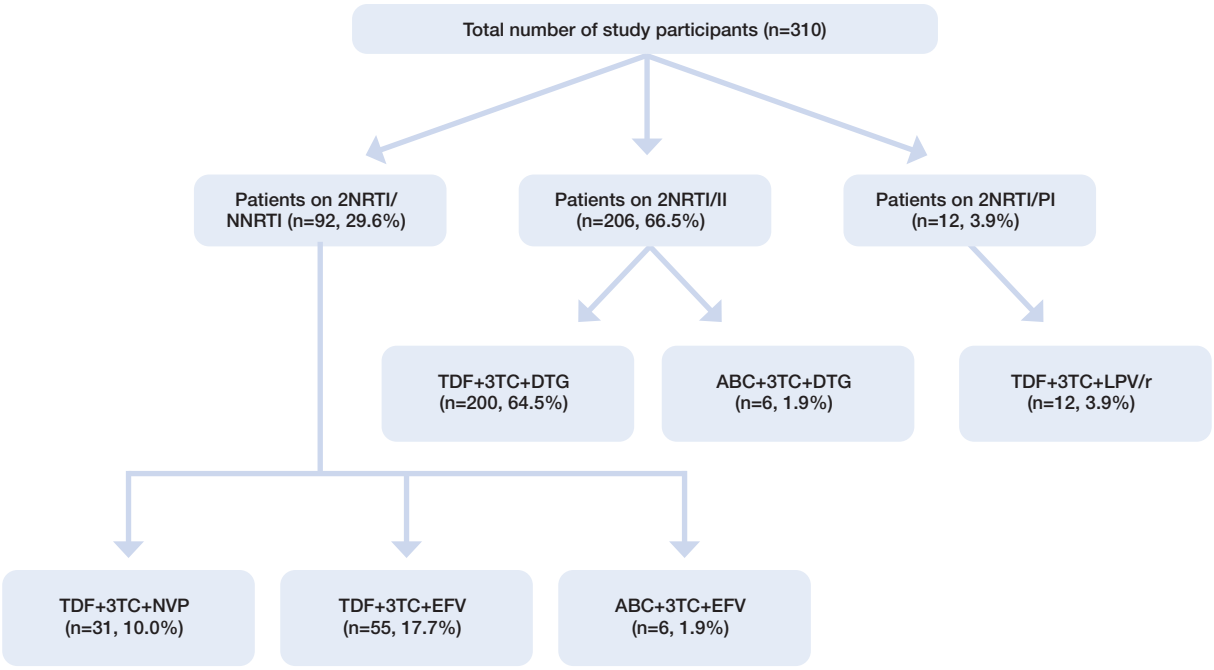


Table I: Socio-demographic Characteristics of Study Participants. (N=310).

Variables	Subgroup	Frequency (N=310)	Percentage (100%)
Age	18-28	59	19.0
	29-38	71	22.9
	39-48	115	37.1
	49-58	35	11.3
	58 and above	30	9.7
Gender	Male	106	34.2
	Female	204	65.8
Marital status	Single	66	21.3
	Married	161	51.9
	Divorced/Separated	31	10.0
	Widowed	52	16.8
Ethnicity	Igbo	248	80
	Hausa	37	11.9
	Yoruba	17	5.5
	Others	8	2.6
Educational level	Primary	44	14.2
	Secondary	75	24.2
	Tertiary	104	33.5
	Uneducated	87	28.1
Occupation	Trader	137	44.2
	Farmer	95	30.6
	Civil servant	33	10.6
	Student	21	6.8
	Others	7	2.3
	Unemployed	17	5.5

Source: Field data, 2021.

Table I above shows that a good number of the study participants were females (n=204, 65.8%) and adults in the age bracket of 39-48 years. Many of the participants (n=104, 33.5%) have attained tertiary education, 87 (28.1%) are uneducated, 75 (24.2%) are recorded to have achieved only secondary education and 44(14.2%) attained only primary education. Regarding marital status, married people are highest accounting for 51.9% of the total population, seconded by the singles (n=66, 21.3%), then the widowed (n=52, 16.8%) and the divorced/separated (n=31, 10%). Considering ethnicity, Igbos are leading amounting to 80% of the population, followed by the Hausas (11.9%), then the Yorubas (5.5%) and then few people from other tribes(2.6%). It is also shown in the table above that most of the study participants are traders with a percentage of 44.2, seconded by farmers with a percentage of 30.6, then comes civil servants, students, people of other occupations not mentioned and unemployed people with a percentage of 10.6, 6.8, 2.3, and 5.5 respectively.

Figure 2: A bar chart representing the age distribution of respondents.

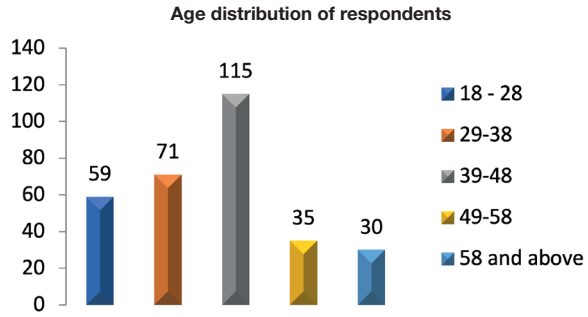


Figure 2 shows a diagrammatic representation of the age distribution of the respondents plotted against the frequency of respondents found to be within these age groups. As shown in the diagram, the leading age group is those within the ages of 39-48 years (n=115), while the least one is found to be those who are 58 years and above (n=30).

Table II indicates that 139(44.8%) to have been on treatment for the first 2 years, 57 are reported to fall within those receiving treatment for the past 2-6 years, 98 have been on treatment for about 7-10 years and the rest (n=16,5.2%) have been on treatment for over

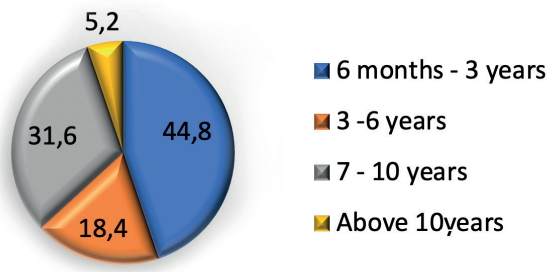
Table II: Ascertaining Type, Frequency and Dosage of ARV in Use.

Characteristics	Sub-group	Frequency (n=310)	Percent (100%)
How long the patient has been on treatment	6 months-2 years	139	44.8
	2-6 years	57	18.4
	7-10years	98	31.6
	Above 10 years	16	5.2
The ARV combination in use	2NRTI/II	206	66.5
	2NRTI/NNRTI	92	29.6
	2NRTI/PI	12	3.9
The exact drug combination in use	TDF+3TC+DTG	200	64.5
	TDF+3TC+EFV	55	17.7
	TDF+3TC+LPV/r	12	3.9
	ABC+3TC+EFV	6	1.9
	TDF+3TC+NVP	31	10.0
	ABC+3TC+DTG	6	1.9
Prescribed dosage of the drug	1 tab/daily	288	92.9
	2 tabs/daily	22	7.1
Adherence to everyday use of drug	Yes	199	64.2
	No	35	11.3
	Sometimes	76	24.5
Adherence of everyday use of drug with respect to time and dosage	Yes	178	57.4
	No	46	14.8
	Sometimes	86	27.7

Source: Field data, 2021

10 years. It also shows that all that study participants make use of ARV drugs of which the common ones are TDF+3TC+DTG (66.5%), TDF+3TC+EFV (17.7%) and TDF+3TC+NVP (10.0%) while the least common ones areTDF+3TC+LPV/r (3.9%) and ABC+3TC+EFV and ABC+3TC+DTG with percentages of 1.9% each. Almost all the respondents (92.9%) report their prescription to be 1tab/day and the rest (7.1%) take theirs twice daily. 64.2% of the study participants adhere to everyday use of drug, 11.3% do not adhere while 24.5% adhere sometimes. 57.4% of the total population adhere to everyday use with respect to time and dosage, 14.8% do not and the remaining 27.7% sometimes adhere to everyday use of drugs with respect to time and dosage.

Figure 3: A pie chart representing how long a patient has been on treatment



The figure above (**Figure 3**) is a pie chart representing the how long respondents have been on treatment, hence the time treatment initiation. From the chart, it is seen that 44.8% of the total population are within the first three years of treatment, 18.4% reported to have been on treatment for about 3-6 years, 31.6% have been on treatment for about 7-10 years, and the remaining 5.2% have been on antiretroviral treatment for more than 10 years.

Table III: Ascertaining the incidence of ADRs resulting from ARV drugs.

Variables	Sub-groups	Frequency	Percent
Ever experienced any ADR	Yes	115	37.1
	No	195	62.9
What type of ADR experienced	Neuropathy	27	23.5
	Skin rash/itching	37	32.2
	Insomnia	10	8.7
	Dizziness	15	13.0
	Gastro-intestinal	26	22.6
Presence of severe condition as a result of ADR	Yes	26	22.6
	No	89	77.4

Source: Field data, 2021.

Table III shows that only 37.1% (n=115) adverse drug reaction of antiretroviral drugs of which 22.6% experience severe conditions as a result and 77.4% never had such experience. The adverse events experienced by the respondents include skin rash/itching, neuropathy, insomnia, dizziness and gastro-intestinal symptoms with percentages of 32.2, 23.5, 22.6, 13.0 and 8.7 respectively.

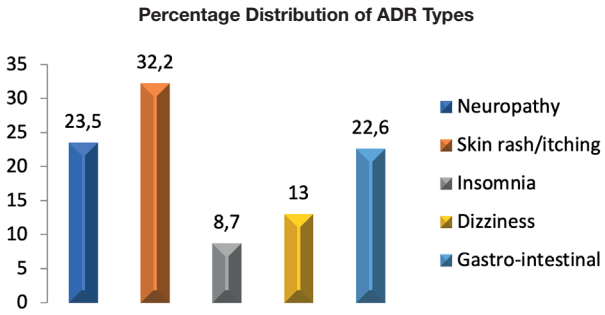
Table IV: Determining rate of occurrence and result on switching.

Variables	Sub-group	Frequency	Percent
Rate of occurrence	Weekly	0	0
	Monthly	21	18.3
	Yearly	40	34.8
	Rarely	54	46.9
Ever had a change in regimen	Yes	73	63.5
	No	42	36.5
Result of ADRs after drug switching	Disappeared	29	39.7
	Reduced/contained	44	60.3

Source: Field data, 2021.

Table IV shows that of 115 patients that experience adverse events, 21 (18.3%) have them occur every month, 40 (34.8%) experience it yearly and 54 (46.9%) rarely have the experience. 63.5% of those that experience adverse events have had a change in regimen, of which 39.7% had the adverse events disappear after switching and 60.3% had their adverse events reduced or contained.

Figure 4: A bar chart showing percentage distribution of ADR types.



The above figure (**Figure 4**) is another bar chart representing the percentage distribution of the types of adverse drug reactions (ADRs) experienced by the respondents. As shown above, the most prevalent ADRs are skin rash, neuropathy and nausea/vomiting with percentages of 32.2, 23.5 and 22.6 respectively. The least occurring ones are dizziness and insomnia with percentages of 13.0 and 8.7 respectively.

Test of Hypothesis

Table V shows that age, gender, educational level, the time of treatment initiation and the patients' adherence to everyday use of drugs with respect to prescribed dosage and time all appear to have a correlation with the patients' experience of adverse effect with p value of 0.0001 each. Marital status is not significant in determining the experience of adverse drug reaction of antiretroviral drugs.

Table V: Association of participants' demographic factors and adherence to prescribed dosage and frequency of drug use.

Variables	Sub-group	Patients with ADR	Patients without ADR	Chi-square test value	Df	P value	Decision
Age	18 - 28 29 - 38 39 - 48 49 - 58 59 and above	3 20 48 14 30	36 51 67 21 0	80.393	4	.0001	Sig
Gender	Male Female	55 60	51 144	15.100	1	.0001	Sig
Educational Level	Primary Secondary Tertiary Uneducated	24 20 28 43	20 55 76 44	19.517	3	.0001	Sig
Marital Status	Single Married Divorced Windowed	28 58 9 20	38 103 22 32	1.788	3	.618	Not Sig.
How long patient has been on treatment	6 mths - 3yrs 3 - 6 years 7 - 10 years Above 10 years	75 27 12 1	64 30 86 15	51.972	3	.0001	Sig
Adherence to with respect to dosage and time	Yes No Sometimes	36 29 50	142 17 36	51.305	2	.0001	Sig

Source: Field data, 2021

Discussion

From the analysis, it is revealed that the majority of the respondents (80%)of the study are of Igbo origin. This is because the study was conducted in the Southern part of Nigeria as the hospital is located in Onitsha, Anambra State. Considering the socio-demographic characteristics of the respondents, with regards to gender and age, a good number of respondents (65.8%) are females, and most respondents are within the age range of 29-48 years old. This is in accordance with the findings of[21], that the majority of these patients are females and young adults in the age bracket of 25-45 years old. This gender difference, though not statistically significant, is found in much other related research carried out in African countries. It is also consistent with other studies conducted in Nigeria that show a feminization of the HIV epidemic[22,23,21]. Findings from the study show that 44.8% of the respondents are within their first three years of treatment, 18.4% reported to have been on treatment for about 3-6 years, 31.6% have been on treatment for about 7-10 years, and the remaining 5.2% have been on antiretroviral treatment for more than 10 years. A good percentage of the respondents (66.5%) use a combination of two nucleoside reverse transcriptase inhibitors (NRTI) and an integrase inhibitor (II). Following suit is the group using the 2NRTI/NNRTI combination. People who make use of the ABC+3TC+EFV and ABC+3TC+DTG are 6 and 6, respectively, which is a minority representative of the study participants. This is because the patients who use these drugs are ones with special cases, for instance, patients with kidney and liver diseases and children (which we didn't use for this study).

Almost all the respondents (n = 200, 64.5%) make use of TDF + 3TC + DTG. This is because it is the first line regimen and it is suitable for virtually every adult, including pregnant and lactating mothers, and also for adolescents. Meanwhile, TDF + 3TC + LPV is taken by a small number of people (n = 12,3.9%) because it is a second-line regimen.

Considering the frequency and dosage, it is denoted here that the majority of the study participants (n = 199, 64.2%) adhere to everyday use of their drugs, of which 89.4% adhere to everyday use of the drugs with respect to the time and required dosage. 11% of the study participants do not adhere at all, and 24.5% do not adhere all the time as their answers to questions are sometimes. This argues the study conducted by[24] that says this presents less than optimal adherence among HIV-positive patients. Almost all respondents (n = 288,92.9%) are taking one tablet per day, while the remainder (n = 22,7.1%) are taking two tablets per day because they are on second-line therapy TDF + 3TC+LPV and abacavir-based regimens. From the findings, 115 participants out of the 310 used for the study were reported to have experienced or be experiencing adverse drug reactions as a result of the use of ARV drugs[23]. This represents 37.1% of the total population and is in accordance with[23]. Of the people that have experienced ADRs, 26 (22.6%) have experienced a chronic condition as a result of the ADRs, while 89 (77.6%) haven't had such experience. The prevalent ADRs are skin rash/itching, neuropathy and gastro-intestinal symptoms (which include vomiting, nausea, abdominal pain and diarrhea) with percentages

of 32.2%, 23.5% and 22.6%, respectively, which is the same as reported by other Nigerian studies[3,22,21]. In comparison to[23], the study found a lower incidence of antiretroviral drug adverse drug reactions. Adverse events are reported to be most prevalent among people who are in the early years of treatment initiation, and this supports the study[3] that found ADRs are more likely to occur within the first 6 months of treatment. The study shows that the 54 respondents(46.9%) out of 115 that were reported to have had an experience of ADR rarely have the occurrence, 40 (34.8%) experience it yearly and 21 (18.3%) experience it monthly. Also, 63.5% of those reported to be with ADR have had a change in regimen, of which 39.7% (n = 29) reported that the ADR had disappeared and 60.3% (n = 44) reported ADRs to be reduced or contained. This is because most respondents are still adjusting to the treatment while few are allergic to a combination of the regimen.

Conclusion

Adverse drug reactions to antiretroviral treatment were common in this study and were reported to occur mostly within the early years of treatment initiation. The most prevalent ADRs were skin rash/itching (n = 37, 32.2%), neuropathy (n = 27, 23.5%) and gastro-intestinal symptoms (n = 26, 22.6%). Other rarely occurring but serious cases of ADR include insomnia (n = 10,8.7%) and dizziness (n = 15,13%), which were also observed. Adverse Drug Reactions are significantly predicted by the time of therapy initiation as people within the early years of initiation were reported to experience ADRs more than others, with a percentage of 65.2%. This study emphasizes the need to monitor at-risk and vulnerable or low-immune patients to know when they have developed an event as a result of treatment.

Recommendations

As a result of this study, an intensive and close follow-up of patients, especially in the early years of treatment initiation, is highly recommended for early detection of ADR and quick management. These ADRs should be properly documented in order to provide accurate data for further studies or research. Patients who are not able to respond effectively to first-line therapies should be identified and placed on effective second-line therapies. Valuable information on patients' responsiveness to treatment should be made available to physicians in-charge and concerned NGOs like USAID when there is a need to modify HAART regimens. Further study using larger and more complete data is also recommended.

Limitations of the Study

With regards to the study, there is a tendency that non-clinical ADRs were overlooked. There is a possibility of under-reporting of ADRs by patients and caregivers. The researcher was not able to relate the factors that caused the ADRs, which would have played an important role in the interpretation of the result.

Ethics Approval and consent to Participate

Not Applicable.

Consent to Publish

Not applicable.

Availability of Data and Materials

The Data set from the study are available to the corresponding author upon request.

Competing Interests

Authors have declared that they have no competing interests.

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Not Applicable.

References

1. World Health Organization. HIV Drug Resistance surveillance guideline-2015 Update. www.who.int

2. WHO. Assuring safety of preventive chemotherapy interventions for neglected tropical diseases. practical advice for national program managers on the prevention, detection and management of serious adverse effects 2010. Available at: http://whqlibdoc.who.int/publications/2011/9789241502191_eng.pdf

3. Eluwa GI, Badru T. Akpoigbe KJ. Adverse drug reactions to antiretroviraltherapy (ARVs): incidence, type and risk factors in Nigeria. BMC Clinical Pharmacology 2012 12:7. doi:10.1186/1472-6904-12-7

4. Hawkins T. Understanding and managing the adverse effects of antiretroviral therapy. Antiretroviral Resource 2010. 85: 201-9.

5. Joint United Nations Program on HIV/AIDS. Global report: UNAIDS reports on the global AIDS Epidemic 2013. Geneva: Switzerland

6. UNAIDS. Global report: UNAIDS report on the global AIDS epidemic UNAIDS Geneva; 2010.

7. Tatiparthi R, Mamo Y. Prevalence of ADRs and associated factors of antiretroviral treatment on HIV positive adults at Jush. Indian Journal of Pharmacological Practice 2014;7(4):8-15

8. Federal Ministry of Health, Nigeria. National guidelines for HIV/AIDS treatment and care in adolescents and adults 2010.

9. Takaki I, Quirelli L, Cuman R. Adverse drug reaction in HIV infected people treated with HAART in Maringa, Southern Brazil. Tropical Journal of Pharmaceutical Research 2017; 16(4):939-45. http://www.tjpr.org

10. Lartey M, Asante-Quashie A, Essex A, Kenu E, Gang V, Neequaye A. Adverse drug reaction to anti-retroviral therapy during the early ART period at Tertiary Hospital in Ghana. Pan African Medicine Journal 2014; 18:25. Doi:10.11604/pamj.2014.18.25.3886

11. Gelaw Y, Adugna B, Tsegave A, Melaku T, Kefale B. Coping strategies for Adverse Effects of Antiretroviral Therapy among Adult HIV patients attending University of Gondar Hospital, Gondar, Northwest Ethiopia: a cross-sectional study. AIDS Research and Treatment 2018;18(7):91-8

12. Rajesh R, Vidyasagar S, Nandakumar K. Highly active anti-retroviral therapy induced adverse drug reactions in Indian human immuno-deficiency virus positive patients. Pharmacy Practice 2011;9(1):48-55.

13. Parchure R, Kulkami V, Darak T. Growth pattern of HIV infected Indian children in response to ART: a clinic based cohort study. Indian Journal of pediatricians 2015; 82(6):519-24

14. WHO. Using early warning indicators to prevent HIV Drug resistance 2010. www.who.int

15. Ermias A, Gurmesa G, Mesfin M, Mengistu A. Adverse drug reaction monitoring in Ethiopia: Analysis of case reports, 2002-2007. Ethiopian Journal of Health Development 2011;25(2):168-73

16. Dube M, Summers R, Tint K-S, Mayayise G. A pharmacovigilance study of adults on highly active anti-retroviral therapy, South Africa: 2007-2011. Pan African Medical Journal 2012;11:39.

17. Srikanth A, Babu S, Yadav H, Jain SK. Incidence of Adverse Drug Reactions in human immunodeficiency virus positive patients using high active anti-retroviral therapy. Journal of advanced pharmacological technology resource 2012; 3:62-67.

18. Ruud KW, Srinivas SC, Toverud EL. Addressing gaps in pharmacovigilance practices in the antiretroviral therapy program in the Eastern Cape Province, South Africa. Res Social Adm Pharm. 2010 Dec;6(4):345-53. doi: 10.1016/j.sapharm.2009.11.006.

19. Kyeyune R, Saathoff E, Ezeamama AE, Löscher T, Fawzi W, Guwatudde D. Prevalence and correlates of cytopenias in HIV-infected adults initiating highly active antiretroviral therapy in Uganda. BMC Infect Diseases 2014; 10;14:496. doi: 10.1186/1471-2334-14-496.

20. Sweileh WM. Global research output on HIV/AIDS-related medication adherence from 1980 to 2017. BMC Health Serv Res. 2018 Oct 10;18(1):765. doi: 10.1186/s12913-018-3568-x.

21. Abah IO. Adverse Drug Reaction to Antiretroviral Drugs: Effect on Virologic failure in a Nigerian Cohort of HIV-infected Adults on First Line Antiretroviral Therapy. Journal of International Association of Providers of AIDS care 2017; 2325957414589192.

22. Agu KA, Oparah AC. Adverse Drug Reactions to Antiretroviral Therapy: Results on spontaneous reporting system in Nigeria. Perspectives in Clinical Research 2014;4(2): 117-24

23. Masenyetse L, Manda S, Mwambi H. An assessment of adverse drug reactions among HIV positive patients receiving antiretroviral treatment in South Africa. AIDS research therapy 2015; 12(6):1-8

24. Ndashimye E, Arts EJ. The urgent need for more potent antiretroviral therapy in low-income countries to achieve UNAIDS 90-90-90 and complete eradication of AIDS by 2030. Infect Dis Poverty. 2019 Aug 2;8(1):63. doi: 10.1186/s40249-019-0573-1.

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ORIGINAL

A Quantitative Assessment of Coping Strategies among Jamaican Males 18+ years old: Post-COVID-19

Una evaluación cuantitativa de las estrategias de afrontamiento entre los varones jamaicanos mayores de 18 años: Post-COVID-19

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Abstract

Introduction: The importance of a gendered perspective on men's unhealthy coping strategies for mental health is becoming more widely recognized in the literature. There is no literature on Jamaican males and how they are coping and what coping strategies they are engaged in during the post-COVID-19 period.
Objectives: The aim is to examine the types of coping strategies used by Jamaican males who are 18 years and older used to address problematic situations that arose in their life during the COVID-19 pandemic.
Methods and materials: The study used cross-sectional web-based survey data on Jamaican men 18 years and older from the fourteen parishes of Jamaica, the survey commenced on October 1, 2022, and ended on November 25, 2022. The Systematic Sampling Technique was utilized to draw a sample of 1088 respondents utilizing a randomized selection of every fifth male in the population.
Results: Substance use has been strongly employed by Jamaican males to address the challenges of life post-COVID-19 (three in every four Jamaican males have been using hard drugs). In addition, religion and denial have been strongly employed by sampled Jamaicans to address the challenges of life post-COVID-19. Furthermore, self-blame and self-distraction have also been a part of the strategies employed by Jamaican males to deal with life post-COVID-19. In addition to the aforementioned issues, Jamaican males have been venting and acceptance of the challenges experienced in their lives post-COVID-19.
Conclusion: This research has provided insight into the stressors experienced by Jamaican males post-COVID-19 and is as such forwarding a need for social intervention programmes to assist them to deal with the new normal set by the pandemic..

Keywords: Coping, coping strategies, stress.

Resumen

Introducción: La importancia de una perspectiva de género en las estrategias de afrontamiento no saludables de los hombres para la salud mental es cada vez más reconocida en la literatura. No existe literatura sobre los hombres jamaicanos y cómo están afrontando y qué estrategias de afrontamiento están llevando a cabo durante el período posterior a COVID-19.
Objetivos: El objetivo es examinar los tipos de estrategias de afrontamiento utilizadas por los varones jamaicanos mayores de 18 años para hacer frente a las situaciones problemáticas que surgieron en su vida durante la pandemia COVID-19.
Métodos y materiales: El estudio utilizó datos de encuestas transversales basadas en la web sobre hombres jamaicanos de 18 años o más de las catorce parroquias de Jamaica, la encuesta comenzó el 1 de octubre de 2022 y finalizó el 25 de noviembre de 2022. Se utilizó la técnica de muestreo sistemático para extraer una muestra de 1088 encuestados utilizando una selección aleatoria de uno de cada cinco varones de la población.
Resultados: Los varones jamaicanos han recurrido en gran medida al consumo de sustancias para hacer frente a los retos de la vida tras el COVID-19 (tres de cada cuatro varones jamaicanos han consumido drogas duras). Además, los jamaicanos de la muestra han recurrido en gran medida a la religión y a la negación para hacer frente a los retos de la vida tras el COVID-19. Además, la autoculpabilización y la autodistracción también han formado parte de las estrategias empleadas por los varones jamaicanos para hacer frente a la vida posterior a COVID-19. Además de las cuestiones mencionadas, los varones jamaicanos se han desahogado y han aceptado los retos experimentados en su vida tras el COVID-19.
Conclusiones: Esta investigación ha proporcionado una visión de los factores de estrés experimentados por los varones jamaicanos después del COVID-19 y, como tal, plantea la necesidad de programas de intervención social para ayudarles a hacer frente a la nueva normalidad establecida por la pandemia.

Palabras clave: Afrontamiento, estrategias de afrontamiento, estrés.

Introduction

The importance of a gendered perspective on men's unhealthy coping strategies for mental health is becoming more widely recognized in the literature. According to Mental Health Foundation[1], in 2017, nearly 6000 suicides were recorded in Great Britain. Of these, 75% were men. In a study by CBHS Health[2], it was compared that more men than women turn to negative coping strategies such as anger, alcohol, drugs, gambling, excessive use of technology and binge eating in an attempt to deal with mental health issues; on the other hand, there are several positive coping strategies that men may choose from when coping with their problems such as eating healthy, keeping busy, exercising, using humour, and helping someone.

According to Lazarus and Folkman[3], coping strategies are "constantly changing cognitive and behavioural efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of the person." The COPE Inventory created by Charles Carver has two main components namely problem-focused coping and emotion-focused coping. Research done by Endler and Parker as well Matud[4,5], proved that men are more likely to utilise problem-focused coping strategies to deal with stressful situations, which involves taking action to resolve stressful situations by addressing the underlying cause.

Emotion-focused coping involves directing one's feelings and emotional response to the problem instead of addressing the problem[6,7]. Coping strategies are cognitive tactics that have been used to evaluate the consequences of various stressful events. Using suicides in Jamaica, the majority of the cases were committed by males and this speaks to the males' difficulties to cope with life's challenges compared to females (Annexe). The question is 'what strategies did Jamaican males employ post-COVID-19 (October 1 - November 25, 2022)? Hence, in this research, the aim is to examine the types of coping strategies used by Jamaican males who are 18 years and older used to address problematic situations that arose in their life during the COVID-19 pandemic.

Theoretical Framework

The theoretical framework that will be utilized for this research is the cognitive theory of coping coined by Folkman and Lazarus[3]. This theory was selected as it correlates to the construct central to our study, 'An Examination of Coping Strategies among Males during COVID-19'. According to the theory, learning can be partially attributed to studying other people through social interactions, experiences, and external media influences. Folkman and Lazarus[3] defined coping as a change in cognitive and behavioural efforts to cope with specific external and internal demands that are perceived as extreme. The theory posits three meta-theoretical assumptions: transaction, process, and context that claim one's coping strategy are determined by their emotional experience and the context of the environment, rather than its effectiveness. This framework is consistent with the topic of this study and allows a thorough examination of survival techniques used by men in COVID-19 in the context of human, environmental and social interactions[8-10].

Literature Review

COVID-19 has impacted a lot of men negatively, and as such, it is key for them to seek help[11-14]. One way that men had to cope was to seek assistance[15-17]. Coupled with what we already highlighted, there are more ways that men have used to cope during the pandemic. "Getting informed about their current mental and physical health conditions." "Put that knowledge into practice by working on improving yourself to improve stress conditions." "Asking your friends or even getting professionals to help you during times of duress is always a good idea." "Connecting with others on social media platforms." "Overcome the stigma and the negative attitudes when it comes to personal development." "Shifting your mind toward positive thoughts should be a daily recurring activity[18].

"Dr Peter Bajic, a physician associated with the Cleveland Clinic survey, notes that men are "not great about going to the doctor," and physicians need to stress to men that taking care of themselves is important. "Many men see depression and anxiety as weakness, and by seeking mental or physical health treatment, they are vulnerable or weak"[10]. The stress and the implications of the COVID-19 pandemic have left most men tight-lipped about their struggles and stress[19-21]. As a result, men have opted to bottle their inner feelings as a means to cope with tough times, to them, they see this as a sign of strength. This accounts for the rise in alcohol consumption and the use of other stimulants during the COVID-19 pandemic[22-24]. According to Roberts et al.,[22], the proportion of people consuming other substances during the pandemic ranged from 3.6% to 17.5% in the general population."

Stress has always been an issue that affects men on a large scale, as men tend to have great difficulty dealing with stress which causes their stress levels to be very high. Quote from Hans Selye "Adopting the right attitude can convert a negative stress into a positive one"[25]. From Selye's statement, we can notice that focusing on negative stress can only affect us negatively, whether psychical or mentally. Applying this to the additional stress brought on by the COVID-19 pandemic, one can argue that these additional stressors negatively impact an individual's health[26]. The World Health Organization found that there has been a 25% increase in selected mental health conditions during the COVID-19 pandemic (i.e., anxiety and depression).

COVID-19 has proven to be unpredictable and a pandemic the world was not prepared for. The frequency of its transmission and how lethal it is causing the most developed countries economic and healthcare systems to go under severe stress or near collapse causing stress on everyone. Jamaica recorded its first case of COVID-19 on March 10, 2020; COVID-19 affects individuals differently based on social class, ethnicity and gender. As known males tend to have higher rates of mortality including suicides than females and this is owing to their risky behaviour, engagement in stressful activities, healthcare hesitancy, and COVID-19 may have brought with it a different state of stress on them.

Pre-COVID-19 studies indicate men's self-reported coping strategies, avoidance-0riented strategies typified by excessive use of drugs or alcohol to cope with one's distress[28,29]. Over-focusing at work as a distraction from issues, along with trying to hide or minimize symptoms by withdrawing and disengaging from relationships; are avoidance-oriented strategies that typically exacerbate distress in the long term. Many of these strategies are linked to traditionally masculine norms, concealing and avoiding negative emotions and partaking in risk-taking behaviours; represent efforts of men to regain a feeling of control and power or discordant emotions when a sense of emasculation is noted. Men's mental health and other illnesses play a role in poverty, and unhealthy coping mechanisms and make people more vulnerable to prolong mental health issues[30,31]. Hence, this study used a national probability study to examine the coping strategies employed by Jamaican males post-COVID-19.

Materials and Methods

The study used cross-sectional web-based survey data on Jamaican men 18 years and older from the fourteen parishes of Jamaica, the survey commenced on October 1, 2022, and ended on November 25, 2022. The Systematic Sampling Technique was utilized to draw a sample of 1088 respondents utilizing a randomized selection of every fifth male in the population. The Statistical Institute of Jamaica (STATIN) reported that there are 1,350.633 males 18+ years in Jamaica as of the end of 2018[33] The sample size was calculated based on the 2018 male population for Jamaica, which was 1,350, 633. The researcher used the 2018 male population, a 95% confidence level, and a 2.97% margin of error.

The survey was anonymous, so participants were not required to disclose any personal information. Informed consent was implied based on the participants that completed the survey. Participants completed the survey voluntarily and were able to withdraw at any time without any form of liability. A 32-item questionnaire was used to collect the data. The 32-item questionnaire was subdivided into 4 general demographic profiles of the sample and 28 items from the Brief Cope Scale (coping orientation to a problem experienced). The Brief Cope Scale was divided into eight subscales namely, Resting, Guarding, Relaxation, Asking for assistance, Task persistence, Seeking social support, Coping self-statements and exercise/strength and each item was scored using the following statements; I haven't been doing this at all, I've been doing this a little bit, I've been doing this a medium amount and I've been doing this a lot[8]. The researcher sought and received permission from the late Dr Charles Carver's wife who was also a collaborator in the development of the Brief Cope Scale[8].

Data were stored, retrieved and analyzed, using the Statistical Packages for the Social Sciences (SPSS) for Windows, Version 28.0. The data were analyzed by way of descriptive statistics, reliability analysis, and per cents, and presented using tables and graphs. Evans' interpretation of correlation coefficients was used to assess the reliability valuations[34]. Evans forwarded that a very weak correlation ranges from 0 to 0.19; weak is 0.20 to 0.39; moderate is 0.40 to 0.59; strong is 0.60 to 0.79; and, a very strong correlation is 0.80 to 1.00[34]. Based on Evans' interpretation of statistical correlation coefficients, 0.70 (or 70%) is used to indicate a good Cronbach alpha, and construct validity of Brief Coping strategies.

Results

Table I presents the sociodemographic characteristics of the sampled male respondents. Of the sampled male respondents (n=1088), most of them were less than 28 years old (29.0%, n=31%, lived in St. Catherine (18.85, 204), where single people (43.1%, 469), and have tertiary level education (40.6%, 442).

Table II presents the reliability testing of the subscales and overall Brief Coping Inventory using a sample of 1088 Jamaican males 18 years and older. Using Evans' interpretation of correlation coefficients [Evans, 1996], items for the subscales and overall Brief Coping Inventory are very good to employ for assessing the construct of coping among Jamaican males.

Table III presents descriptive statistics for fourteen[14] pairs of double coping subscales. The fourteen[14] pairs of double coping subscales provide insights into the various types of coping strategies employed by Jamaican males post-COVID-19 to deal with the hardship of life. Based on the mean values for each of the pair double coping strategies, Jamaican males have been employing all fourteen pairs of coping strategies post-COVID-19. The results revealed that substance use has been strongly employed by Jamaican males to address the challenges of life post-COVID-19. In addition, religion and denial have been strongly employed by sampled Jamaicans to address the challenges of life post-COVID-19.

Furthermore, self-blame and self-distraction have also been a part of the strategies employed by Jamaican males to deal with life post-COVID-19. In addition to the aforementioned issues, Jamaican males have been venting and acceptance of the challenges experienced in their lives post-COVID-19.

Table I: Sociodemographic Characteristics of the Sampled Male Respondents, n=1088.

Details	% (n)
Age cohort	
18 - 27 Years Old	29.0 (315)
28 - 38 Years Old	23.1 (251)
39 - 48 Years Old	15.3 (167)
49 - 58 Years Old	11.7 (127)
59 - 68 Years Old	8.6 (94)
69 - 78 Years Old	6.7 (73)
79+ Years Old	5.6 (61)
Parish of residence	
Manchester	6.9 (75)
St. Elizabeth	5.4 (59)
Westmoreland	5.2 (57)
Trelawny	2.8 (30)
Hanover	2.5 (27)
Kingston	18.5 (201)
St. Catherine	18.8 (204)
Portland	3.2 (35)
St. Andrew	5.6 (61)
St. James	7.5 (82)
St. Mary	4.6 (50)
St. Ann	6.3 (68)
St. Thomas	3.4 (37)
Clarendon	9.4 (102)
Marital status	
Single	43.1 (469)
Divorced	8.4 (91)
Married	37.1 (404)
Widowed	11.4 (124)
Educational level	
None	3.3 (36)
Primary level	8.9 (97)
Secondary level	28.9 (314)
Vocational training	18.3 (199)
Tertiary level	40.6 (442)

Table II: Reliability Testing of Subscales and Overall Brief Coping Inventory.

Details	Cronbach alpha
Problem-focused Coping Inventory	0.935
Emotion-focused Coping Inventory	0.947
Avoidant Coping Inventory	0.929
Overall Brief Coping Inventory	0.976

Table IV presents descriptive statistics for the three general subscales of coping strategies employed by Jamaican males as well as the overall Brief Coping strategies employed by them to deal with the hardship of life post-COVID-19. Jamaican males have been moderately employing various coping strategies to deal with the hardship of life post-COVID-19 (overall Brief Coping Index = 69.3±22.6, maximum value = 120). On disaggregating the various sub-components of coping strategies, the results revealed that the sampled males have been strongly employing problem-focus, emotion-focused, and avoidant coping strategies to deal with life's difficulties post-COVID-19. Based on the results of the current study, a potent deduction is that males are not effectively dealing with the hardship of life post-COVID-19. This extrapolation from the findings is based on the widespread utilization of all the established coping strategies as developed by Carver (1997), and Carver and colleagues (1989), particularly the avoidant coping strategies.

The high utilization of avoidant coping strategies speaks to delay behaviour, penned-up feelings, and challenges that must be addressed in the future. Some of the avoidant coping strategies and their degree of employment of these are presented in **table V**.

Table III: Descriptive Statistics for the 14 pairs of double coping subscales.

Details	Mean±SD, 95% CI
Self-distraction	4.9±1.85, 4.8 - 5.1
Active coping	5.1±1.86, 5.0 - 5.2
Denial	4.8±1.91, 4.7 - 4.9
Substance use	4.8±2.01, 4.7 - 4.9
Use Emotional	4.8±1.89, 4.7 - 5.0
Instrumental Support	4.9±1.87, 4.8 - 5.0
Behavioural Disengagement	4.8±1.93, 4.7 - 5.0
Venting	5.0±1.85, 4.8 - 5.1
Positive Reframing	5.1±1.88, 4.9 - 5.2
Planning	5.1±1.90, 5.0 - 5.2
Humour	4.9±1.91, 4.8 - 5.1
Acceptance	5.1±1.91, 5.0 - 5.3
Religion	5.0±1.91, 4.9 - 5.2
Self-blame	5.0±1.89, 4.8 - 5.1

Note: The maximum value for each subscale is eight[8].

Table IV: Descriptive Statistics of the 3 subscales.

Details	Mean±SD, 95% CI
Problem-focused Coping	20.1±6.8, 19.7 - 20.5; maximum = 32
Emotion-focused Coping	30.0±9.8, 29.3 - 30.5; maximum = 48
Avoidant Coping	19.3±6.8, 18.9 - 19.8; maximum = 32
Overall Brief Coping Index	69.3±22.6, 68.0 - 70.7; maximum = 120

Table V: Descriptive Statistics for Avoidant Coping Strategy.

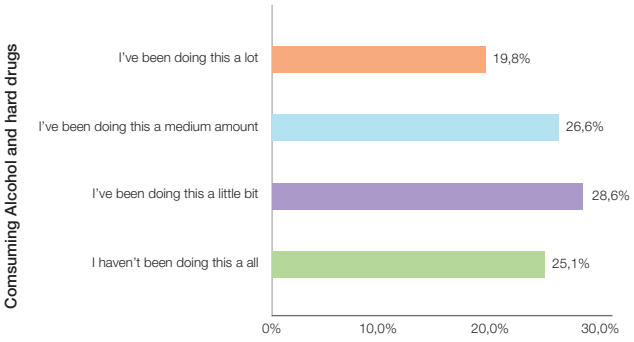
Details	Mean	SD	N
1. I've been turning to work or other activities to take my mind off things	2.46	0.998	1088
3. I've been saying to myself "this isn't real"	2.44	1.069	1088
4. I've been using alcohol or other drugs to myself feel better	2.39	1.070	1088
6. I've been giving up trying to deal with it	2.40	1.046	1088
8. I've been refusing to believe that it has happened	2.38	1.022	1088
11. I've been using alcohol or other drugs to help me get through it	2.41	1.068	1088
16. I've been giving up the attempt to cope	2.38	1.049	1088
19. I've been doing something to think about it less, such as going to movies, watching TV, reading, daydreaming, sleeping, or shopping	2.48	1.024	1088

Notes: The maximum value is 4 for each item.

Table V presents the descriptive statistics for the items in the avoidant coping strategies. On average, Jamaican males have been turning to work or other activities to take their minds off things (2.46±0.998, out of 4), I've been doing something to think about it less, such as going to movies, watching TV, reading, daydreaming, sleeping, or shopping (2.48±1.024, out of 4), I've been saying to myself "this isn't real" (2.44±1.069, out of 4), and so forth. A point of emphasis of this study is the utilization of substances as a coping mechanism (2.41±1.068, out of 4).

Figure 1 depicts the prevalence of Jamaican males using alcohol and hard drugs post-COVID-19. Of the sampled male respondents (n=1088), the response rate to the statement 'I've been using alcohol or other drugs to help me get through it.' The results revealed that three in every four Jamaican males have been using hard drugs and consuming alcohol post-COVID-19. In addition, one in every 5 Jamaican males has been utilizing hard drugs or consuming alcohol frequently post-COVID-19 as a coping mechanism.

Figure 1: Using Alcohol and Hard drugs.



Discussion

The COVID-19 pandemic has changed the population/demographic composition of the world's human population. Many measures were implemented by governments across the globe to address the COVID-19 pandemic, and the byproducts of these measures include unemployment, low social interventions, reduced living standards, increased frustrations, and fright of the pandemic. The pandemic has been lifted by the World Health Organization and the Centers for Disease Control and Prevention; but, there are many challenges during this post-COVID-19 period. In fact, "Experiencing post-COVID conditions can be confusing and frustrating, and a person who feels sick long-term may feel isolated. Everyone experiences these conditions differently and may want different types of support or even no support at all" [35]. The current study revealed that the psychological/mental health status of Jamaican males has been exponentially compromised and has left them searching for solutions, and as a result employing many coping strategies in this post-COVID-19 era. 1) three in every four Jamaican males have been using hard drugs and consuming alcohol post-COVID-19. In addition, one in every 5 Jamaican males has been utilizing hard drugs or consuming alcohol frequently post-COVID-19 as a coping mechanism, 2) on average, Jamaican males have been turning to work or other activities to take their minds off things (2.46±0.998, out of 4), I've been doing something to think about it less, such as going to movies, watching TV, reading, daydreaming, sleeping, or shopping (2.48±1.024, out of 4), I've been saying to myself "this isn't real" (2.44±1.069, out of 4), and so forth, 3) Jamaican males have been moderately employing various coping strategies to deal with the hardship of life post-COVID-19 (overall Brief Coping Index = 69.3±22.6, maximum value = 120). On disaggregating the various sub-components of coping strategies, the results revealed that the sampled males have been strongly employing problem-focus, emotion-focused, and avoidant coping strategies to deal with life's difficulties post-COVID-19.

The present study highlights that Jamaican males are engaged in various activities to address the challenges encountered as a result of the COVID-19 pandemic. The reality is, they are engaging in different activities only because of wanting to cope with post-COVID-19. The Centers for Disease Control and Prevention provides a rationale for men employing various measures to live, post-COVID-19, which is aptly "Learning to cope with stress healthily will help you, the people you care about, and those around you become more resilient"[36]. Jamaican males are in the process of dealing with the challenges that emerged during COVID-19, which has been equally presented in the literature[37-42].

During this learning process, they have employed both negative and positive measures to learn the right measures to deal with issues that emerged during the pandemic. Hence, this accounts for the substance use that has been strongly engaged by Jamaican males to address the challenges of life post-COVID-19. This study is not forwarding that a judgement should be ascribed to Jamaican males, but the literature provides a context for understanding the behaviour of people post-COVID-19. The Mount Sinai Hospital cited, "It makes a lot of sense that people are feeling anxious and unsettled right now. Just when we were finally adjusting to a new normal with some predictability and flow, the world is preparing to change all over again. Future uncertainty and a sense of not knowing what to expect can fuel anticipatory anxiety. There is even a diagnosis for this feeling: adjustment disorder"[40]. As a result, they are engaged in destruction practices simply because of the anxiety, uncertainty, unsettled mental state, unknown, and wanting to settle their experiences

post-COVID-19. The employment of the various coping strategies by Jamaican males is simply in keeping with what Bhattacharjee and Ghosh[43] referred to as 'Coping with the new normal.

Conclusion

The current study revealed that **1)** three in every four Jamaican males have been using hard drugs and consuming alcohol post-COVID-19, **2)** Jamaican males have been turning to work or other activities to take their minds off things (2.46±0.998, out of 4), I've been doing something to think about it less, such as going to movies, watching TV, reading, daydreaming, sleeping, or shopping (2.48±1.024, out of 4), I've been saying to myself "this isn't real" (2.44±1.069, out of 4), Jamaican males have been moderately employing various coping strategies to deal with the hardship of life post-COVID-19 (overall Brief Coping Index = 69.3±22.6, maximum value = 120). On disaggregating the various sub-components of coping strategies, the results revealed that the sampled males have been strongly employing problem-focus, emotion-focused, and avoidant coping strategies to deal with life's difficulties post-COVID-19. This research has provided insight into the stressors experienced by Jamaican males post-COVID-19 and is as such forwarding a need for social intervention programmes to assist them to deal with the new normal set by the pandemic.

Annexe

Table Number of Suicides by Gender and Male to Female Ratio.

Year	Male	Female	Total[1]	Male to Female[2]
2000	66	11	77	6:1
2001	62	13	75	5:1
2002	51	6	57	9:1
2003	55	9	64	6:1
2004	6	4	10	2:1
2005	48	10	58	5:1
2006	42	5	47	8:1
2007	46	4	50	12:1
2008	41	6	47	7:1
2009	51	3	54	17:1
2010	29	6	35	5:1
2011	47	5	52	9:1
2012	45	8	53	6:1
2013	45	10	55	5:1
2014	46	6	52	8:1
2015	51	8	59	6:1
2016	50	5	55	10:1
2017	42	5	47	8:1
2018	56	5	61	11:1
2019	51	7	58	7:1
2020	37	6	43	6:1
2021	44	7	51	6:1
2022*	46	4	50	12:1

*This figure is for January 1 to November 28, 2022
[1]Source: Jamaica Constabulary Force. (various years)
[2]Computed by Paul Andrew Bourne

Competing Interests

Authors have declared that they have no competing interests.

References

1. Mental Health Foundation. Men and mental health. Mental Health Foundation: England and Wales, 2022. https://www.mentalhealth.org.uk/explore-mental-health/a-z-topics/men-and-mDo mental-health.

2. CBHS Health. What coping mechanisms do men really use to stay mentally healthy? CBHS; 2019. https://www.cbhs.com.au/mind-and-body/blog/what-coping-mechanisms-do-men-really-use-to-stay-mentallyhealthy

3. Lazarus RS, Folkman S. Stress, Appraisal and Coping. New York: Springer; 1984.

4. Endler NS, Parker JD. Multidimensional assessment of coping: A critical evaluation. Journal of Personality and Social Psychology, 1990; 58(5), 844–54. https://doi.org/10.1037/0022-3514.58.5.844

5. Matud MP. Gender Differences in Stress and Coping Styles. Personality and Individual Differences, 2004; 37, 1401-15.

6. http://dx.doi.org/10.1016/j.paid.2004.01.010

7. Carver CS. You want to measure coping but your protocol is too long: Consider the brief cope. International journal of behavioural medicine, 1997; 4(1), 92-100.

8. Raypole C. 7 emotion-focused coping techniques for uncertain times. Evolve Health Center: Vancouver; 2022. https://evolvewellnessvancouver.ca/2020/05/08/7-emotion-focused-coping-techniques-for-uncertain-times/

9. Suratana S, Tamornpark R, Apidechkul T, Srichan P, Mulikaburt T, Wongnuch P, et al. Impacts of and survival adaptations to the COVID-19 pandemic among the hill tribe population of northern Thailand: A qualitative study. PLOS ONE, 2021; 16(6), e0252326. https://doi.org/10.1371/journal.pone.0252326

10. Mofijur M, Fattah IMR, Alam MA, Islam ABMS, Ong HC, Rahman SMA, et al. Impact of COVID-19 on the social, economic, environmental and energy domains: Lessons learnt from a global pandemic. Sustain Prod Consum. 2021 Apr;26:343-59. DOI: 10.1016/j.spc.2020.10.016. Epub 2020 Oct 14. PMID: 33072833; PMCID: PMC7556229.

11. Woodruff Family Law Group. COVID and the mental and physical effects on men's health. North Carolina: Woodruff Family Law Group; 2021. https://www.northcarolinadivorcelawyersblog.com/covid-and-the-mental-and-physical-effects-on-mens-health/

12. White A. Men and COVID-19: the aftermath, Postgraduate Medicine, 2020; 132:sup4, 18-27, DOI: 10.1080/00325481.2020.1823760

13. Sousa AR, Santana TS, Moreira WC, Sousa AFL, Carvalho ESS, Craveiro I. Emotions and coping strategies of men to the COVID-19 pandemic in Brazil. Texto Contexto Enferm [Internet]. 2020 [cited YEAR MONTH DAY]; 29:e20200248. Available from: https://doi.org/10.1590/1980-265X-TCE-2020-0248.

14. Ellison JM, Semlow AR, Jaeger EC, Griffth DM. COVID-19 and MENtal Health: Addressing Men's Mental Health Needs in the Digital

World. Am J Mens Health. 2021 Jul-Aug;15(4):15579883211030021. DOI: 10.1177/15579883211030021. PMID: 34229530; PMCID: PMC8267042.

15. Wilson MJ, Seidler ZE, Oliffe JL, Toogood N, Kealy D, Ogrodniczuk JS, Walther A, Rice SM. "Appreciate the Little Things": A Qualitative Survey of Men's Coping Strategies and Mental Health Impacts During the COVID-19 Pandemic. Am J Mens Health. 2022 May-Jun;16(3):15579883221099794. doi: 10.1177/15579883221099794.

16. National Center for Chronic Disease Prevention and Health Promotion, Division of Population Health. Coping with stress. Atlanta; CDC: 2022. https://www.cdc.gov/mentalhealth/stress-coping/cope-with-stress/index.html.

17. Livingston JD, Youssef GJ, Francis LM, Greenwood CJ, Olsson CA, Macdonald JA. Hidden in Plain Sight? Men's Coping Patterns and Psychological Distress Before and During the COVID-19 Pandemic. Front Psychiatry. 2022 Jan 5;12:772942. doi: 10.3389/fpsyt.2021.772942. PMID: 35069282; PMCID: PMC8766713.

18. Gottert A, Shattuck D, Pulerwitz J, Betron M, McLarnon C, Wilkins JD, et al. Meeting men's mental health needs during COVID-19 and beyond: a global health imperative. BMJ Glob Health. 2022 Apr;7(4):e008297. doi: 10.1136/bmjgh-2021-008297.

19. Ede H. The link between your body's physical and mental health is explained. PACT: Bradford: 2020. https://physiciansallianceofconnecticut.com/blog/link-between-physical-and-mental-health/

20. Manchia M, Gathier AW, Yapici-Eser H, Schmidt MV, de Quervain D, van Amelsvoort T, et al. The impact of the prolonged COVID-19 pandemic on stress resilience and mental health: A critical review across waves. Eur Neuropsychopharmacol. 2022 Feb;55:22-83. doi: 10.1016/j.euroneuro.2021.10.864. Epub 2021 Oct 29. PMID: 34818601; PMCID: PMC8554139.

21. Voltmer E, Köslich-Strumann S, Walther A, Kasem M, Obst K, Kötter T. The impact of the COVID-19 pandemic on stress, mental health and coping behavior in German University students - a longitudinal study before and after the onset of the pandemic. BMC Public Health. 2021 Jul 13;21(1):1385. doi: 10.1186/s12889-021-11295-6.

22. Cleveland Clinic. Coping with COVID Survey Illustrates the mental and physical toll of pandemic is taking on men. Cleveland: Cleveland Clinic; 2020. https://newsroom.clevelandclinic.org/2020/09/02/cleveland-clinic-coping-with-covid-survey-illustrates-the-mental-and-physical-toll-the-pandemic-is-taking-on-men/

23. Roberts A, Rogers J, Mason R, Siriwardena AN, Hogue T, Whitley GA, et al. Alcohol and other substance use during the COVID-19 pandemic: A systematic review. Drug Alcohol Depend. 2021 Dec 1;229(PtA):109150. doi: 10.1016/j.drugalcdep.2021.109150. Epub 2021 Oct 29. PMID: 34749198; PMCID: PMC8559994.

24. Bourne PA, Reid, D-A, Plummer S, Lewis T, Ferguson J, Foster C, et al. The Influence of Alcohol Consumption on Sexual Promiscuity among Young Jamaican Males during the COVID-19 Pandemic. *International Journal of Recent Advances in Medical & Pharma Research*, 2020; 3(1): 23-35.

25. Bonsaksen T, Ekeberg Ø, Skogstad L, Heir T, Grimholt TK. Use of Alcohol and Addictive Drugs During the COVID-19 Outbreak in Norway: Associations With Mental Health and Pandemic-Related Problems. Frontiers in Public Health, 2020. https://doi.org/10.3389/fpubh.2021.667729.

26. Magellan Health. Embracing lifelong wellness. https://www.bnl.gov/hr/occmed/hpp/files/pdf/lifelongwellness-newsletter.pdf

27. World Health Organization (WHO). He believed stress was necessary to have an exciting life but too much negative stress would lead to illness and death. Geneva: WHO; 2022. https://www.who.int/news-room/feature-stories/detail/the-impact-of-covid-19-on-mental-health-cannot-be-made-light-of.

28. World Health Organization. COVID-19 pandemic triggers 25% increase in prevalence of anxiety and depression worldwide. Geneva: WHO; 2022. https://www.who.int/news/item/02-03-2022-covid-19-pandemic-triggers-25-increase-in-prevalence-of-anxiety-and-depression-worldwide.

29. Wilson MJ, Seidler ZE, Oliffe JL, Toogood N, Kealy D, Ogrodniczuk JS, et al. "Appreciate the Little Things": A Qualitative Survey of Men's Coping Strategies and Mental Health Impacts During the COVID-19 Pandemic. Am J Mens Health. 2022 May-Jun;16(3):15579883221099794. DOI: 10.1177/15579883221099794. PMID: 35608377; PMCID: PMC9134443.

30. Livingston JD, Youssef GJ, Francis LM, Greenwood CJ, Olsson CA, Macdonald JA. Hidden in Plain Sight? Men's Coping Patterns and Psychological Distress Before and During the COVID-19 Pandemic. *Frontiers in Psychiatry*. https://doi.org/10.3389/fpsyt.2021.772942

31. Frech A, Damaske S. Men's Income Trajectories and Physical and Mental Health at Midlife. AJS. 2019 Mar;124(5):1372-1412. DOI: 10.1086/702775. PMID: 34176948; PMCID: PMC8231310.

32. World Health Organization. Mental health: strengthening our response. Geneva: WHO; 2022. https://www.who.int/news-room/fact-sheets/detail/mental-health-strengthening-our-response

33. Statistical Institute of Jamaica. Mid-year population by age and sex. Kingston: SATTIN;2022. https://statinja.gov.jm/Demo_SocialStats/newMidYearPopulationbyAgeandSex2008.aspx

34. Evans JD. Straightforward Statistics for the Behavioral Sciences. Brooks/Cole Publishing; Pacific Grove, California; 1996.

35. National Center for Immunization and Respiratory Diseases (NCIRD), Division of Viral Diseases. Caring for People with Post-COVID Conditions. Atlanta: CDC; 2022. https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/care-post-covid.html#:~:text=Ways%20to%20Cope%20with%20Stress&text=Take%20breaks%20from%20watching%2C%20reading,%2C%20meditate%2C%20or%20practice%20mindfulness.

36. National Center for Immunization and Respiratory Diseases (NCIRD), Division of Viral Diseases. Coping with Stress. Atlanta: CDC; 2022. https://www.cdc.gov/mentalhealth/stress-coping/cope-with-stress/index.html.

37. Fluharty M, Fancourt D. How have people been coping during the COVID-19 pandemic? Patterns and predictors of coping strategies amongst 26,016 UK adults. BMC Psychol 2021; 9, 107. https://doi.org/10.1186/s40359-021-00603-9

38. Kavanagh BE, Ashton MM, Lotfaliany M, McCallum M, Wrobel AL, Croce S, et al. Saunders L, Lai J, Berk L. Coping with COVID-19: Exploring coping strategies, distress, and post-traumatic growth during the COVID-19 pandemic in Australia. *Frontiers in Psychiatry*, 2022; 13. https://doi.org/10.3389/fpsyt.2022.1025767.

39. Gökalp ZŞ, Koç H, Kozan HİÖ. Coping and Post-traumatic Growth Among COVID-19 Patients: A Qualitative Study. J Adult Dev. 2022;29(3):228-39. doi: 10.1007/s10804-022-09398-4. Epub 2022 Mar 15. PMID: 35308045; PMCID: PMC8921436.

40. Mount Sinai. How to cope with post-pandemic anxiety. New York: Mount Sinai; 2022. https://health.mountsinai.org/blog/how-to-cope-with-post-pandemic-anxiety/

41. World Health Organization (WHO). Coping with the unknown – a family's story of living with long COVID. Geneva: WHO; 2022. https://www.who.int/europe/news-room/feature-stories/item/coping-with-the-unknown---a-family-s-story-of-living-with-long-covid

42. Kira IA, Shuwiekh HAM, Ahmed SAE, Ebada EE, Tantawy SF, Waheep NN, Ashby JS. Coping with COVID-19 Prolonged and Cumulative Stressors: the Case Example of Egypt. Int J Ment Health Addict. 2022 Jan 8:1-22. doi: 10.1007/s11469-021-00712-x.

43. Bhattacharjee A, Ghosh T. COVID-19 Pandemic and Stress: Coping with the New Normal. Journal of Prevention and Health Promotion, 2022;3(1):30-52. https://doi.org/10.1177/26320770211050058

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ORIGINAL

Association between different cardiometabolic risk scales and metabolic syndrome scales in 418.343 Spanish workers

Asociación entre diferentes escalas de riesgo cardiometabólico y escalas de síndrome metabólico en 418.343 trabajadores españoles

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Abstract

Introduction: Cardiometabolic diseases are currently a public health problem in all countries of the world due to their high prevalence and high morbidity and mortality.
Material and methods: Descriptive, cross-sectional study to assess the association between various cardiometabolic risk scales and metabolic syndrome assessed with three different criteria.
Results: Both the mean values and the prevalence of elevated values of the different cardiometabolic risk scales analyzed (atherogenic indices, vascular age, REGICOR and SCORE scales, atherogenic dyslipidemia, lipid triad, and diabesity) were higher in persons with metabolic syndrome with any of the criteria. The scales that most increase the risk of presenting metabolic syndrome are the atherogenic indices, AD, LT and diabesity.
Conclusions: There is a good relationship between the cardiometabolic risk scales analyzed and metabolic syndrome with any of the three criteria. The variables most associated with an increased risk of developing metabolic syndrome are atherogenic indices, atherogenic dyslipidemia, lipid triad and diabesity.

Keywords: Metabolic syndrome, atherogenic indices, diabesity, atherogenic dyslipidemia, cardiometabolic risk.

Resumen

Introducción: Las enfermedades cardiometabólicas son en la actualidad un problema de salud pública en todos los países del mundo tanto por su elevada prevalencia como por su alta morbimortalidad.
Material y métodos: Estudio descriptivo y transversal para valorar la asociación entre diversas escalas de riesgo cardiometabólico y el síndrome metabólico valorado con tres criterios diferentes.
Resultados: Tanto los valores medios como la prevalencia de valores elevados de las diferentes escalas de riesgo cardiometabólico analizadas (índices aterogénicos, edad vascular, escalas REGICOR y SCORE, dislipemia aterogénica, triada lipídica y Diabesity) presentan cifras superiores en las personas con síndrome metabólico con cualquiera de los criterios. Las escalas que más incrementan el riesgo de presentar síndrome metabólico son los índices aterogénicos, DA, LT y Diabesity.
Conclusiones: Existe buena relación entre las escalas de riesgo cardiometabólico analizadas y el síndrome metabólico con cualquiera de los tres criterios. Las variables que más se relacionan con un aumento del riesgo de presentar síndrome metabólico son los índices aterogénicos, dislipemia aterogénica, triada lipídica y Diabesity.

Palabras clave: Síndrome metabólico, actividad física, adherencia a la dieta mediterránea.

Introduction

Cardiometabolic diseases, due to their high prevalence[1] and the high morbimortality they cause[2], are considered one of the main public health problems in most countries, and not only in developed countries[3].

Metabolic syndrome (MS) is a pathological entity that has been known for more than a century and encompasses different alterations such as obesity (mainly abdominal), elevated lipid profile, insulin resistance that results in elevated blood glucose levels and elevated blood pressure[4].

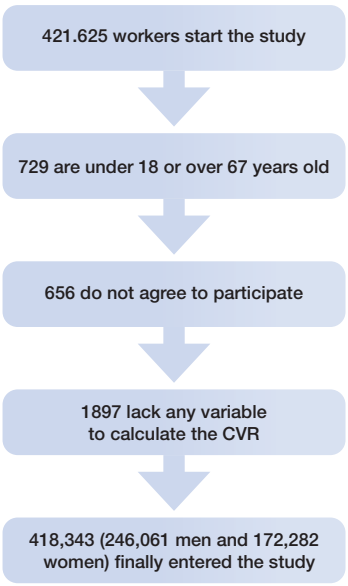
The similar pathophysiology of both pathological conditions suggests that there should be a close relationship between them, so the aim of this study is to assess the association between the values of different cardiometabolic risk scales and MS determined with different criteria in the Spanish working population.

Material and methods

A descriptive, cross-sectional study was carried out in 418.343 Spanish workers from different regions and work sectors and selected from occupational medical examinations between the months of January 2017 and December 2019. The following inclusion criteria were established: age between 18 and 69 years, working in one of the companies included in a study, not being in a situation of temporary disability, signing the informed consent to participate in the study and to use their data for epidemiological purposes.

Figure 1 shows the flow diagram of the study participants.

Figure 1: Flow chart.



Measurements and data collection

Anthropometric (height, weight and waist circumference), clinical and analytical measurements were performed by the health professionals of the companies participating in the study, after standardization of the measurement techniques.

Weight (in kg) and height (in cm) were obtained with a SECA 700 scale-measuring device. Waist circumference (WC) was measured with a SECA measuring tape with the person standing, feet together, trunk erect and abdomen relaxed. The tape was placed parallel to the ground at the height of the last floating rib.

A calibrated OMRON M3 automatic sphygmomanometer was used to determine blood pressure while the person was seated and after a 10-minute rest. Three determinations were made one minute apart and the mean of the three was obtained. The analytical parameters were obtained after 12 h of fasting. Glycemia, total cholesterol and triglycerides were obtained by automated enzymatic methods while HDL-c was obtained by a precipitation process with dextran sulfate-MgCl2. LDL-c was calculated indirectly using the Friedewald formula (only valid for triglycerides below 400 mg/dL). All analytical parameters were expressed in mg/dL.

Friedewald formula: LDL = cholesterol - HDL - triglycerides/5

Metabolic syndrome (MS) was determined using three different criteria: the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP-III), the Joint Interim Statement (JIS), and the International Diabetes Federation (IDF) update[5].

As cardiometabolic risk scales, the following were assessed:

a. Cardiovascular risk scales
- Years of life lost due to vascular age (ALLY) SCORE and Framingham[6].
- REGICOR and SCORE[7] scales.

b. Atherogenic indices
- Cholesterol/HDL, triglycerides/HDL and LDL/HDL[8].

c. Other
- Diabesity[9].
- Atherogenic dyslipidemia (AD) and lipid triad (LT)[10].

A smoker is defined as a person who has consumed at least one cigarette a day (or its equivalent in other types of consumption) in the last 30 days or has quit smoking less than 1 year ago.

Based on the profession and applying the proposal of the social determinants group of the Spanish Society of Epidemiology[11], the social class was obtained, establishing three categories: Class I: directors/

managers, university professionals, sportsmen and artists; Class II: intermediate occupations and skilled self-employed workers; Class III: unskilled workers.

The level of education was classified as primary or elementary, secondary and university. We considered smokers to be those who had consumed at least one cigarette daily (or its equivalent in other types of consumption) during the last month, or had quit smoking less than 12 months before.

Heart-healthy eating habits are determined with the "Mediterranean diet adherence questionnaire" used in the PREDIMED study[12]. The questionnaire consists of 14 questions that are scored with 0 and 1 point. Values of 9 or more indicate good adherence and therefore that the diet is heart-healthy.

Physical activity is assessed with the International Physical Activity Questionnaire IPAQ (International Physical Activity Questionnaire), which assesses physical activity in the last week[13].

Statistical analysis

A descriptive analysis of the categorical variables was performed, calculating the frequency and distribution of the responses for each of them. For quantitative variables, the mean and standard deviation were calculated following a normal distribution.

Bivariate association analysis was performed using the chi2 test (with correction for Fisher's exact statistic when conditions required it) and Student's t test for independent samples (for comparison of means). Multivariate techniques were used to establish the variables associated with the most significant risk factors. For multivariate analysis, logistic regression was used, with calculation of the odds ratio and the Hosmer-Lemeshow goodness-of-fit test. ROC curves were performed, and the area under the curve

(The statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) version 28.0 (IBM Company, New York, NY, USA) for Windows, with an accepted statistical significance level of 0.05.

Ethical considerations and/or aspects

The research team undertook at all times to follow the ethical principles of health sciences research established nationally and internationally (Declaration of Helsinki), paying special attention to the anonymity of the participants and the confidentiality of the data collected. Approval was requested from the Ethics and Research Committee of the Balearic Islands (CEI-IB), which was obtained with indicator IB 4383/20. Participation in the study was voluntary, so the participants gave their written and oral consent to participate in the study after receiving sufficient information about the nature of the study. To this end, they were given an informed consent form, as well as an information sheet explaining the objective of the study.

The data collected for the study were identified by a code and only the person responsible for the study can relate these data to the participants. The identity of the participants will not be disclosed in any report of this study. The investigators will not disseminate any information that could identify them. In any case, the research team undertakes to strictly comply with the Organic Law 3/2018, of December 5, on the protection of personal data and guarantee of digital rights, guaranteeing the participant in this study that he/she may exercise his/her rights of access, rectification, cancellation and opposition of the data collected

Results

Table I shows the anthropometric and clinical characteristics of the 418.343 workers (246.061 men and 172.282 women) who were included in the study. The mean age of the sample was 40.2 ± 11.0 years, the majority being in the group between 30 and 49 years of age. All variables presented more unfavorable values in men. Three out of four workers belonged to social class III, one out of three smoked and slightly more than half did not engage in regular physical activity or have high adherence to the Mediterranean diet.

Table II shows the mean values of the different cardiometabolic risk scales analyzed according to the presence or absence of metabolic syndrome applying the different criteria in men and women. The mean values of all the cardiometabolic risk scales were much higher, in both sexes, in those who presented metabolic syndrome applying any of the three criteria. In all cases, the differences observed were statistically significant.

Table III shows that the prevalence of high values of the different cardiometabolic risk scales behaved similarly to the mean values, that is, they were higher in workers with metabolic syndrome, and the differences observed were statistically significant.

Table IV shows the results of the multinomial logistic regression, showing that the risk of presenting MS with the different criteria increases in parallel with the increase in the values of the cardiometabolic risk scales. The highest odds ratios were found for atherogenic dyslipidemia, lipid triad and diabesity.

Table I: Characteristics of the population.

	Women n=172.282 Mean ± SD	Men n=246.061 Mean ± SD	Total n=418.343 Mean ± SD	p-value
Age	39.6 (10.8)	40.6 (11.1)	40.2 (11.0)	<0.0001
Height	161.8 (6.5)	174.6 (7.0)	169.4 (9.3)	<0.0001
Weight	66.2 (14.0)	81.4 (14.7)	75.1 (16.2)	<0.0001
BMI	25.3 (5.2)	26.7 (4.5)	26.1 (4.8)	<0.0001
Waist	74.8 (10.6)	86.2 (11.1)	81.5 (12.2)	<0.0001
SBP	117.4 (15.7)	128.2 (15.5)	123.7 (16.5)	<0.0001
DBP	72.6 (10.4)	77.8 (11.0)	75.6 (11.0)	<0.0001
Cholesterol	190.6 (35.8)	192.6 (38.9)	191.8 (37.7)	<0.0001
HDL-c	56.8 (8.7)	50.3 (8.5)	53.0 (9.1)	<0.0001
LDL-c	116.1 (34.8)	118.0 (36.7)	117.2 (35.9)	<0.0001
Triglycerides	89.1 (46.2)	123.7 (86.4)	109.5 (74.6)	<0.0001
Glycaemia	87.8 (15.1)	93.3 (21.3)	91.0 (19.2)	<0.0001
	%	%	%	p-value
18-29 years	20.7	18.8	19.6	<0.0001
30-39 years	3.0	27.6	17.4	
40-49 years	29.6	30.0	29.9	
50-59 years	16.8	19.7	18.5	
60-69 years	3.2	3.9	3.6	
Primary school	51.8	61.2	57.3	<0.0001
Secondary school	40.7	34.0	36.8	
University	7.5	4.8	5.9	
Social class I	6.9	4.9	5.7	<0.0001
Social class II	23.4	14.9	18.4	
Social class III	69.7	80.3	75.9	
No physical activity	47.8	54.5	51.7	<0.0001
Yes physical activity	52.2	45.5	48.3	
No mediterranean diet	48.6	59.0	54.7	<0.0001
Yes mediterranean diet	51.4	41.0	45.3	
Non-smokers	67.2	66.6	66.8	<0.0001
Smokers	32.8	33.4	33.2	

SBP systolic bllood pressure. DBP diastolic blood pressure.

Table II: Mean values of different cardiometabolic risk scales according to the presence or absence of metabolic syndrome with the different criteria by sex.

	No MS ATPIII	Yes MS ATPIII		No MS IDF	Yes MS IDF		No MS JIS	Yes MS JIS	
Men	n=98425	n=33115	p-value	n=107921	n=23619	p-value	n=80890	n=50650	p-value
ALLY VA SCORE	6.7 (6.6)	10.7 (7.1)	<0,001	7.2 (6.8)	9.9 (7.0)	<0.001	6.1 (6.4)	10.1 (7.1)	<0,001
SCORE	1.5 (2.0)	2.6 (2.8)	<0,001	1.7 (2.2)	2.2 (2.5)	<0.001	1.3 (1.8)	2.5 (2.7)	<0,001
ALLY VA Framingham	4.3 (8.9)	16.4 (10.7)	<0,001	5.3 (9.8)	14.6 (10.7)	<0.001	3.1 (8.2)	14.5 (10.7)	<0,001
REGICOR	3.2 (2.2)	3.9 (2.6)	<0,001	3.2 (2.2)	3.7 (2.5)	<0.001	3.1 (2.1)	3.7 (2.5)	<0,001
Cholesterol/HDL	3.7 (1.0)	5.1 (1.3)	<0,001	3.8 (1.0)	5.0 (1.3)	<0.001	3.6 (0.9)	4.8 (1.2)	<0,001
Triglycerides/HDL	2.1 (1.4)	4.9 (3.2)	<0,001	2.3 (1.8)	4.5 (3.0)	<0.001	2.0 (1.2)	4.3 (2.9)	<0,001
LDL/HDL	2.3 (0.9)	3.1 (1.1)	<0,001	2.3 (0.9)	3.1 (1.1)	<0.001	2.2 (0.8)	3.0 (1.1)	<0,001
Women	n=72329	n=12967	p-value	n=73270	n=12026	p-value	n=70168	n=15128	p-value
ALLY VA SCORE	3.7 (5.0)	7.1 (5.4)	<0,001	3.8 (5.0)	6.5 (5.4)	<0.001	3.6 (4.9)	7.0 (5.4)	<0,001
SCORE	0.4 (0.8)	1.0 (1.4)	<0,001	0.4 (0.9)	0.9 (1.3)	<0.001	0.4 (0.8)	1.0 (1.4)	<0,001
ALLY VA Framingham	-1.2 (10.1)	16.5 (13.1)	<0,001	-0.8 (10.6)	14.5 (13.1)	<0.001	-1.4 (9.9)	15.8 (13.1)	<0,001
REGICOR	2.8 (2.2)	3.5 (2.3)	<0,001	2.8 (2.2)	3.4 (2.3)	<0.001	2.8 (2.2)	3.5 (2.3)	<0,001
Cholesterol/HDL	3.3 (0.8)	4.3 (0.9)	<0,001	3.4 (0.8)	4.3 (0.9)	<0.001	3.3 (0.8)	4.3 (0.9)	<0,001
Triglycerides/HDL	1.5 (0.7)	3.0 (1.7)	<0,001	1.5 (0.8)	2.8 (1.5)	<0.001	1.5 (0.7)	2.9 (1.7)	<0,001
LDL/HDL	2.1 (0.8)	2.8 (0.8)	<0,001	2.1 (0.8)	2.7 (0.8)	<0.001	2.0 (0.7)	2.7 (0.8)	<0,001

ALLY VA Years of life lost of vascular age. SCORE REGICOR Gironí heart registry. HDL High-density lipoproteins. LDL Low-density lipoproteins. MS ATPIII Metabolic syndrome Adult Treatment Panel III. MS IDF Metabolic syndrome International Diabetes Federation. MS JIS Metabolic Syndrome Joint Interim Statement.

Table III: Prevalence of high values of different cardiometabolic risk scales according to the presence or absence of metabolic syndrome with the different criteria by sex.

	No MS ATPIII	Yes MS ATPIII		No MS IDF	Yes MS IDF		No MS JIS	Yes MS JIS	
Men	**n=98425**	**n=33115**	**p-value**	**n=107921**	**n=23619**	**p-value**	**n=80890**	**n=50650**	**p-value**
SCORE high	8.1	20.8	<0.001	10.2	16.0	<0.001	6.7	18.7	<0,001
REGICOR high-very high	1.7	3.5	<0.001	1.9	2.9	<0.001	1.6	3.0	<0,001
CT/HDL moderate-high	10.1	49.5	<0.001	12.2	46.6	<0.001	7.7	40.4	<0,001
TG/HDL high	16.4	77.5	<0.001	20.2	69.2	<0.001	12.2	64.6	<0,001
LDL/HDL high	20.1	54.6	<0.001	21.7	53.4	<0.001	17.0	49.3	<0,001
Diabesity	0.6	16.9	<0.001	1.1	17.6	<0.001	0.2	11.6	<0,001
Atherogenic dyslipidemia	1.3	39.7	<0.001	3.8	33.4	<0.001	1.0	25.3	<0,001
Lipid triad	0.3	11.4	<0.001	1.1	9.2	<0.001	0.3	7.2	<0,001
Women	**n=72329**	**n=12967**	**p-value**	**n=73270**	**n=12026**	**p-value**	**n=70168**	**n=15128**	**p-value**
SCORE high	0.8	3.4	<0.001	1.0	2.5	<0.001	0.8	3.1	<0,001
REGICOR high-very high	1.5	2.3	<0.001	1.5	2.2	<0.001	1.5	2.3	<0,001
CT/HDL moderate-high	8.5	39.4	<0.001	9.0	35.8	<0.001	8.2	38.0	<0,001
TG/HDL high	3.4	41.6	<0.001	4.3	33.6	<0.001	3.2	38.2	<0,001
LDL/HDL high	10.5	35.9	<0.001	10.8	33.8	<0.001	10.2	35.2	<0,001
Diabesity	0.2	14.8	<0.001	0.2	15.3	<0.001	0.2	13.6	<0,001
Atherogenic dyslipidemia	1.0	31.8	<0.001	1.8	24.9	<0.001	1.0	27.9	<0,001
Lipid triad	0.3	7.9	<0.001	0.5	5.7	<0.001	0.2	7.0	<0,001

SCORE Systematic Coronary Risk Estimation REGICOR Gironi Heart Registry. CT Total cholesterol. TG Triglycerides. HDL. High-density lipoproteins. LDL. Low-density lipoproteins. TG Triglycerides. MS ATPIII Metabolic syndrome Adult Treatment Panel III. MS IDF Metabolic syndrome International Diabetes Federation. MS JIS Metabolic syndrome Joint Interim Statement.

Table IV: Multinomial logistic regression.

	MS ATPIII OR (95% CI)	MS IDF OR (95% CI)	MS IDF OR (95% CI)
SCORE low	1	1	1
SCORE moderate	1.50 (1.44-1.56)	1.16 (1.11-1.22)	1.59 (1.53-1.66)
SCORE high	4.14 (4.00-4.28)	2.00 (1.93-2.08)	5.08 (4.91-5.26)
REGICOR low	1	1	1
REGICOR moderate	1.41 (1.20-1.66)	1.38 (1.15-1.65)	1.44 (1.24-1.68)
REGICOR high	1.76 (1.51-2.06)	1.51 (1.27-1.79)	1.69 (1.46-1.95)
REGICOR very high	3.01 (2.58-3.50)	2.18 (1.89-2.59)	2.80 (2.42-3.24)
CT/HDL low	1	1	1
CT/HDL moderate	2.41 (2.05-2.84)	1.60 (1.37-1.87)	1.86 (1.57-2.20)
CT/HDL high	20.11 (17.09-23.65)	9.88 (8.46-11.54)	14.26 (12.03-16.90)
TG/HDL normal	1	1	1
TG/HDL high	17.04 (16.70-17.39)	8.63 (8.45-8.80)	16.28 (15.99-16.58)
LDL/HDL normal	1	1	1
LDL/HDL high	5.12 (5.03-5.22)	4.28 (4.20-4.37)	5.34 (5.25-5.43)
No Atherogenic dyslipidemia	1	1	1
Yes Atherogenic dyslipidemia	50.86 (49.12-52.66)	14.37 (13.99-14.77)	34.31 (33.05-35.61)
No Lipid triad	1	1	1
Yes Lipid triad	39.66 (37.13-42.37)	9.97 (9.50-10.45)	29.73 (27.67-31.94)
No Diabesity	1	1	1
Yes Diabesity	45.42 (43.00-47.98)	26.34 (25.21-27.52)	83.36 (76.43-90.91)

SCORE Systematic Coronary Risk Estimation REGICOR Gironi Heart Registry. CT Total cholesterol. HDL. High-density lipoproteins. LDL. Low-density lipoproteins. TG Triglycerides. MS ATPIII Metabolic syndrome Adult Treatment Panel III. MS IDF Metabolic syndrome International Diabetes Federation. MS JIS Metabolic syndrome Joint Interim Statement.

Discussion

The mean values and prevalence of elevated values of the different cardiometabolic risk scales analyzed (atherogenic indices, vascular age, REGICOR and SCORE scales, atherogenic dyslipidemia, lipid triad, and diabesity) show higher figures in persons with metabolic syndrome with any of the criteria.

The scales that most increase the risk of presenting metabolic syndrome are atherogenic indices, AD, LT and diabesity.

We have not found articles that relate the metabolic syndrome with most of the cardiometabolic scales analyzed in this study, so we will focus on those that relate the MS with cardiovascular risk scales.

A cohort of persons aged between 20 and 75 years (mean age 59 years) with metabolic syndrome presented a prevalence of high-risk values with the SCORE scale of 50% in men and 29.6% in women, higher figures than those found in our study, perhaps due to the higher mean

age of the sample[14]. A review of the literature[15] concluded that, based on prospective studies, the cardiovascular risk in women with MS is equal to or somewhat higher than that of men with MS; these data differ from those found in our study. Another review conducted in Italy showed that the metabolic syndrome seems to modestly increase cardiovascular risk[16].

Strengths and limitations

The greatest strengths of the study are the large sample size (more than 400 000 workers) and the large number of cardiometabolic risk and metabolic syndrome scales used. As limitations, we would highlight the fact that it was carried out in the working population, which excludes people under 18 and over 69 years of age, so we do not know whether we can extrapolate our results to the general population.

Conclusions

The high values of all the cardiometabolic risk scales analyzed have a very good relationship with the presence of MS with the three criteria. The variables that most increase the risk of presenting MS with any of the three criteria are high atherogenic cholesterol/HDL and triglycerides/HDL indices, atherogenic dyslipidemia, lipid triad, and diabesity.

Conflict of Interest

The authors declare that no competing interests exist.

Bibliography

1. Sattar N, Gill JMR, Alazawi W. Improving prevention strategies for cardiometabolic disease. Nat Med. 2020 Mar;26(3):320-325. doi: 10.1038/s41591-020-0786-7.

2. Bedogni G, Gastaldelli A, Foschi FG. Fatty liver, cardiometabolic disease and mortality. Curr Opin Lipidol. 2020 Feb;31(1):27-31. doi: 10.1097/MOL.0000000000000652.

3. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. GBD-NHLBI-JACC Global Burden of Cardiovascular Diseases Writing Group. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. J Am Coll Cardiol. 2020 Dec 22;76(25):2982-3021. doi: 10.1016/j.jacc.2020.11.010.

4. Saklayen MG. The Global Epidemic of the Metabolic Syndrome. Curr Hypertens Rep. 2018 Feb 26;20(2):12. doi: 10.1007/s11906-018-0812-z.

5. Riutord-Sbert P, Riutord-Fe B, Riutord-Fe-N, Arroyo-Bote S, López-González AA, Ramirez-Manent JI. Relationship between physical activity and adherence to the mediterranean diet with metabolic syndrome, hypertriglyceridemic waist phenotype and hypertensive waist. Medicina Balear 2022;37(6):33-8. doi: 10.3306/AJHS.2022.37.06.33

6. Cuende JI. Vascular Age, RR, ALLY, RALLY and Vascular Speed, Based on SCORE: Relations Between New Concepts of Cardiovascular Prevention. Rev Esp Cardiol (Engl Ed). 2018 May;71(5):399-400. English, Spanish. doi: 10.1016/j.rec.2017.02.043.

7. Gómez-Vaquero C, Corrales A, Zacarías A, Rueda-Gotor J, Blanco R, González-Juanatey C, et al. SCORE and REGICOR function charts underestimate the cardiovascular risk in Spanish patients with rheumatoid arthritis. Arthritis Res Ther. 2013 Aug 21;15(4):R91. doi: 10.1186/ar4271.

8. López González ÁA, Rivero Ledo YI, Vicente Herrero MT, Gil Llinás M, Tomás Salvá M, Riutord Fe B. Índices aterogénicos en trabajadores de diferentes sectores laborales del área Mediterránea Española. Clin Investig Arterioscler. 2015 May-Jun;27(3):118-28. Spanish. doi: 10.1016/j.arteri.2014.10.004.

9. Ng ACT, Delgado V, Borlaug BA, Bax JJ. Diabesity: the combined burden of obesity and diabetes on heart disease and the role of imaging. Nat Rev Cardiol. 2021 Apr;18(4):291-304. doi: 10.1038/s41569-020-00465-5.

10. Busquets-Cortés C, López C, Paublini H, Arroyo Bote S, López-González ÁA, Ramírez-Manent JI. Relationship between Atherogenic Dyslipidaemia and Lipid Triad with Different Scales of Overweight and Obesity in 418,343 Spanish Workers. J Nutr Metab. 2022 Aug 9;2022:9946255. doi: 10.1155/2022/9946255.

11. Domingo-Salvany A, Bacigalupe A, Carrasco JM, Espelt A, Ferrando J, Borrell C, et al. Propuestas de clase social neoweberiana y neomarxista a partir de la Clasificación Nacional de Ocupaciones 2011. Gac Sanit. 2013 May-Jun;27(3):263-72 doi: 10.1016/j.gaceta.2012.12.009.

12. Ros E. The PREDIMED study. Endocrinol Diabetes Nutr. 2017 Feb;64(2):63-6.

13. Sember V, Meh K, Sorić M, Starc G, Rocha P, Jurak G. Validity and Reliability of International Physical Activity Questionnaires for Adults across EU Countries: Systematic Review and Meta Analysis. Int J Environ Res Public Health. 2020 Sep 30;17(19):7161.

14. Ruiz-Villaverde G, Sánchez-Cano D, Ruiz-Villaverde R, Abalos-Medina GM, Ramírez-Rodrigo J, Villaverde-Gutiérrez C. Agreement between Framingham-DORICA and SCORE scales in estimation of cardiovascular risk in the patients suffering from metabolic syndrome in Granada (Spain). Ir J Med Sci. 2011 Jun;180(2):351-4. doi: 10.1007/s11845-011-0673-9.

15. Pucci G, Alcidi R, Tap L, Battista F, Mattace-Raso F, Schillaci G. Sex- and gender-related prevalence, cardiovascular risk and therapeutic approach in metabolic syndrome: A review of the literature. Pharmacol Res. 2017 Jun;120:34-42. doi: 10.1016/j.phrs.2017.03.008.

16. Vanuzzo D, Pilotto L, Mirolo R, Pirelli S. Cardiovascular risk and cardiometabolic risk: an epidemiological evaluation]. G Ital Cardiol (Rome). 2008 Apr;9(4 Suppl 1):6S-17S.

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ORIGINAL

Efectos de una intervención educativa médica personalizada sobre la percepción del riesgo de padecer un cáncer ginecológico y de las actitudes para controlarlo: un modelo de investigación asistencial

Effects of a personalized medical educational intervention on the perception of the risk of gynecological cancer and attitudes to control it: a healthcare research model

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Resumen

Se plantea a partir de la necesidad de aplicar criterios de Medicina Personalizada la conveniencia de averiguar cuál es la percepción del riesgo de sufrir un cáncer ginecológico que siente una mujer y qué hace para prevenirlo, y se contrasta esta información con la evidencia disponible para su edad de cual es realmente el cáncer ginecológico que más la amenaza y cuál debería ser su actitud preventiva, practicándose una intervención educativa para corregir, si los hubiere, déficits en el concepto y en la actuación derivada.

Palabras clave: Educación, cáncer ginecológico, prevención.

Abstract

Based on the need to apply Personalized Medicine criteria, the convenience of finding out what is the perception of the risk of suffering a gynaecological cancer that a woman feels and what she does to prevent it is considered. This information is contrasted with the evidence available for her age, which is really the gynaecological cancer that threatens the most and what should be its preventive attitude, practicing an educational intervention to correct, if any, deficits in the concept and in the derived action.

Keywords: Education, gynecological cancer, prevention.

La Medicina se está dirigiendo hacia la aplicación de pautas personalizadas de atención, incluyendo las de prevención y tratamiento de los cánceres ginecológicos, adaptadas a cada grupo de edad y al riesgo de cada paciente, la llamada Medicina de Precisión, bien definida en sus aspectos oncológicos por el National Cancer Institute [1]. Establecer pautas por un lado fieles a las recomendaciones de los organismos nacionales e internacionales que se ocupan del asunto y al mismo tiempo adaptar los procedimientos al perfil de la persona que consulta. En prevención del cáncer ginecológico, los esquemas de aplicación clínica están recientemente publicados a nivel nacional e internacional y son absolutamente coincidentes[2,3].

Entre las mujeres que acuden a la consulta ginecológica para revisiones de salud los autores han percibido un desconocimiento de cuál es el riesgo real personal de padecer un cáncer ginecológico y, especialmente, qué tipo de cáncer es el que por razones de edad e historia personal o familiar más les amenaza. Una estimación inicial realizada por uno de los autores demostró esta ignorancia y/o esta confusión[4] hasta niveles que perjudican seriamente la acción preventiva

primaria –eliminar la causa identificada– o secundaria –diagnóstico precoz– a realizar cuando son posibles, y lo son de manera muy relevante en todos los cánceres del área de preocupación y acción ginecológicas, incluido el cáncer de mama[5].

Gracias al Registro de Tumores Poblacional operativo en la Isla de Mallorca, de cobertura poblacional y de alta calidad contrastada, sabemos con precisión cual es la incidencia en Mallorca por grupos de edad de los cánceres ginecológicos[6] y sabemos cuáles deberían ser las prácticas preventivas primarias y secundarias para cada uno de ellos a aplicar en la consulta[6].

Desconocemos de manera clara y precisa cuales son los hábitos preventivos habituales desarrollados por las mujeres, y también el impacto real que una intervención educativa personalizada según edad y antecedentes puede tener en la percepción del riesgo de sufrir determinados cánceres y en la modificación de las conductas preventivas relativas a ellos.

En este contexto, el proyecto de investigación que aquí se comenta plantea:

1. Encuestar a las mujeres para conocer:
   a. Su estimación de riesgo de presentar algún o algunos de los cánceres ginecológicos.
   b. Las prácticas preventivas que llevan a cabo frente a ellos.

2. Realizar una intervención educacional personal para:
   a. Informar sobre su riesgo personal de sufrir estos cánceres más incidentes.
   b. Educar en prácticas preventivas.

3. Estimar pasado un año cual ha sido el impacto de esta intervención educativa sobre la percepción del riesgo de presentar un cáncer ginecológico y sobre las conductas preventivas desarrolladas.

Se plantea una metodología con un Grupo Control (GC) dividido en tres franjas de edad (30-39, 40-49, 50-59 años), con una "N" de 100 para cada franja, y un Grupo de Intervención (GI) con los mismos subgrupos y el mismo tamaño muestral. A cada paciente se le pasará un cuestionario previo para situarle en su contexto socioeconómico y evaluar su percepción de riesgo de padecer cáncer ginecológico. El GC recibirá posteriormente una información generalizada estándar sobre pautas de prevención y conductas de riesgo, mientras que el GI recibirá una información educativa preventiva dirigida específicamente a su perfil personal, incluyendo edad y antecedentes personales y familiares. Un año después se pasará un nuevo cuestionario a ambos grupos con el que se evaluará si se ha dado algún cambio en la percepción del riesgo y en las conductas derivadas.

Los resultados de este estudio nos permitirán conocer la utilidad de la intervención educativa personalizada realizada y, en caso de que se demuestre útil, sentarían las bases para la implementación de intervenciones educativas personalizadas en las consultas ginecológicas. Es intención del grupo realizar y publicar un análisis interino de procedimiento y resultados provisionales cuando la intervención se haya ya realizado en aproximadamente el 70% de la N planteada.

Conflicto de intereses

Los autores declaran no incurrir para esta publicación en ningún conflicto de intereses.

Bibliografía

1. Disponible en https://www.cancer.gov/publications/dictionaries/cancer-terms/def/precision-medicine Acceso 06.03.2023.

2. Disponible en https://www.semnim.es/wp-content/uploads/2019/07/349.pdf Acceso 06.03.2023.

3. Disponible en https://www.cdc.gov/ Acceso 06.03.2023.

4. Cortés J.: Comunicación a la Reunión Anual de la Sociedad Balear de Ginecología y Obstetricia. 2017.

5. Cortés J, Dexeus D, López AC, Palacios S, Serrano L.: La prevención del cáncer ginecológico en la asistencia privada. Prog Obstet Ginecol 2017 ; 60: 160-75.

6. Disponible en https://redecan.org/es/registros-de-cancer/15/registre-de-cancer-de-mallorca Acceso 06.03.2023.

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SPECIAL ARTICLE

Eliminación del cáncer de cérvix

Elimination of cervical cancer

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Resumen

A partir de la declaración de la Organización Mundial de la Salud que identificó al cáncer de cérvix como el primer cáncer erradicable de nuestro mundo, se presentan las causas de esta propuesta y su situación en Islas Baleares y España.

Palabras clave: cáncer, cérvix, prevención.

Abstract

Based on the declaration of the World Health Organization that identified cervical cancer as the first eradicable cancer in the world, the causes of this proposal and its situation in the Balearic Islands and Spain are presented.

Keywords: cancer, cervix, prevention.

La Organización Mundial de la Salud (OMS) ha declarado al cáncer de cérvix (CC) como el primer cáncer eliminable, erradicable, de nuestro mundo[1]. En esta declaración se dice textualmente que "ha llegado el momento de poner en marcha una estrategia ambiciosa e inclusiva para acelerar la eliminación del cáncer de cérvix como problema de salud pública. La eliminación está al alcance de todos los países. Todos podemos dejar un gran legado si aprovechamos las oportunidades que están a nuestro alcance ahora, para que las niñas que nazcan hoy vivan para ver un mundo libre de esta enfermedad".

Las razones que dan soporte a este posicionamiento son obvias:

- Conocemos la causa necesaria para el desarrollo de un CC, la infección por virus papiloma humano (VPH)[2,3].
- Disponemos de una prevención primaria altamente segura, eficaz y eficiente frente a la infección por VPH, la vacunación[4].
- Tenemos muy bien identificadas a las lesiones precancerosas del CC y somos capaces de detectarlas y de tratarlas de manera altamente cómoda y eficaz[5].

Las condiciones para lograr esta erradicación se resumen según la OMS en tres cifras: 90-70-90[6], es decir:

- 90% de cobertura de vacunación frente al VPH.
- 70% de cobertura en los programas de prevención secundaria del CC.
- 90% de cobertura en los tratamientos de las lesiones precancerosas detectadas.

¿Cuál es la situación al respecto de estos tres objetivos en Islas Baleares y en España? La que se resume a continuación:

- Cobertura de vacunación frente al VPH en segunda dosis[7]:
  - Islas Baleares: No notificada y por tanto no incluida en la tabla facilitada por el Ministerio.
  - España: Cobertura media del 81,8%, con un rango que va desde el 33,3% de Asturias al 94,9 de La Rioja.
- Cobertura de los programas de prevención secundaria (cribado) del CC 8:
  - 71% de las mujeres no se realiza un cribado de CC de forma regular.
- Cobertura en los tratamientos de las lesiones precancerosas detectadas: No se dispone de datos, aunque la accesibilidad a los equipos de tratamiento – en Sanidad Pública y Privada– parece correcta[5,9].

¿Qué incidencia[10] y qué mortalidad[11] presenta el CC en Islas Baleares y en España, ahora y en los años pasados? Pueden consultarse en las **tablas I** y **II**: se objetiva un aumento apreciable en las cifras 2022 comparadas con las de 2012 en las dos variables analizadas.

Tabla I: Incidencia del cáncer de cuello de útero.

	2012	2022
Islas Baleares	43	47
España	1.883	1.965

Fuente: Ref. 10.

Tabla II: Mortalidad por cáncer de cuello de útero.

	2012	2022
Islas Baleares	18	29
España	666	684

Fuente: Ref. 11.

¿Es esta una situación equiparable a la documentada en el resto del mundo? En una reciente publicación de la OMS[12] se dice textualmente que "la carga del cáncer de cuello uterino sigue siendo alta en muchas partes del mundo y, en la mayoría de los países, la incidencia y la mortalidad de la enfermedad siguen siendo muy superiores al umbral establecido por la iniciativa de la OMS sobre la eliminación del cáncer de cuello uterino. Identificamos desigualdades geográficas y socioeconómicas sustanciales en el cáncer de cuello uterino a nivel mundial, con un claro gradiente de tasas crecientes para países con niveles más bajos de desarrollo humano". Esta apreciación coincide sustancialmente con las conclusiones de un estudio global liderado por la Universidad de Tianjin, en la República de China[13], en el que se concluye que "las políticas de prevención y control del cáncer en países con índices de desarrollo altos han logrado efectos de implementación relativamente ideales relativos a la probable eliminación del cáncer de cérvix. En los países con un nivel de desarrollo social y económico relativamente atrasado, las políticas de prevención y control del cáncer tuvieron poco efecto, dada la menor cobertura de vacunación contra el VPH, una asignación regional deficiente de recursos de salud, incluyendo las prácticas de prevención secundaria y tratamiento de las lesiones pre-invasoras, y una escasa concienciación de la educación pública".

¿Qué ocurre en los países de nuestro entorno? Italia ha publicado su situación[14], con esta conclusión: "La evaluación del estado actual de la eliminación de CC como objetivo general más allá del logro de los objetivos de vacunación, detección y tratamiento representa el primer paso para la identificación de las intervenciones que se implementarán para acelerar el camino hacia la eliminación de CC. En base a esto y siguiendo el llamado de la OMS, se propone un enfoque basado en valores para desentrañar el beneficio total de las estrategias de eliminación de los cánceres relacionados con el VPH e identificar las prioridades y las mejores prácticas".

Añadamos que está documentada una alta inequidad española en el acceso a las tres variables preventivas, ya denunciada en dos estudios que han devenido en clásicos[15,16], con datos reproducidos recientemente 8: 71% de las mujeres no se realiza en España un cribado de manera regular. En estas mujeres no controladas que básicamente viven en zonas no ciudadanas y que pertenecen a estratos sociales de nivel medio / bajo se concentra el 70% del CC incidente: 7 de cada 10 mujeres con CC no tienen una historia previa de cribado. Puede concluirse que el trabajo preventivo debe concentrarse en corregir estos déficits clamorosos y esto solamente podrá hacerse reestructurando los programas ahora en aplicación –mayoritariamente oportunistas– transformándolos en poblacionales que garanticen máximas coberturas independientemente de nivel de riqueza, de educación o de lugar de residencia.

Este es, este debe ser el camino. Alcanzar este 90-70-90 es un objetivo alcanzable siempre que los esfuerzos se coordinen, desde todos los puntos de vista, desde todas las instancias político-sanitarias involucradas. Tal como se reclama desde la Sociedad Española de Vacunología[17] "para lograr el máximo impacto, las intervenciones encaminadas a alcanzar estos tres objetivos deben realizarse de manera simultánea y a la escala apropiada". Un esfuerzo de coordinación es mandatorio, adaptando las decisiones a los protocolos estratégicos en vigor promulgados por los organismos supranacionales y nacionales.

Como dice el Dr. Fernando Moraga, Vice-Presidente primero de la Asociación Española de Vacunología,[17] "se estima que si se consigue implementar la triple estrategia 90-70-90 en 2030, para 2050 ya podría haber disminuido a la mitad la incidencia del cáncer de cuello uterino, y en los próximos 100 años se evitarán más de 74 millones de casos de este cáncer y se salvarán más de 62 millones de vidas de mujeres. Un gran triunfo de la vacunología y de la medicina preventiva". Un gran triunfo factible si hacemos, entre todos, las cosas bien. Un gran triunfo que puede y debe ser extendido a la aplicación poblacional de programas de cribado de otros cuatro cánceres, mama femenina, colon-recto, pulmón y próstata, tal como se recomienda en la última propuesta ejecutiva 14770/22 del Consejo de la Unión Europea[18].

Conflicto de intereses

Ninguno para los tres autores.

Bibliografía

1. Disponible en https://www.who.int/es/news-room/events/detail/2020/11/17/default-calendar/launch-of-the-global-strategy-to-accelerate-the-elimination-of-cervical-cancer Acceso 27.12.2022.

2. zur Hausen H, Meinhof W, Scheiber W, Bornkamm GW. Attempts to detect virus-secific DNA in human tumors. I. Nucleic acid hybridizations with complementary RNA of human wart virus. Int J Cancer. 1974 May 15;13(5):650-6. doi: 10.1002/ijc.2910130509.

3. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 1999; 189: 12 - 9.

4. WHO Weekly Epidemiological Record Nº 50, 2022, 97, 645–672.

5. https://www.aepcc.org/wp-content/uploads/2022/11/Guia-Prevencion-cancer-cervix-2022.pdf

6. Disponible en https://www.who.int/ Acceso 27.12.2022.

7. Disponible en https://www.sanidad.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/calendario-y-coberturas/coberturas/docs/Todas_las_tablas2020.pdf Acceso 28.12.22.

8. Disponible en https://www.seap.es/c/document_library/get_file?uuid=e0ecfbbc-9f49-4054-8ed6-9c7a40a40186&groupId=10157 Acceso 28.12.22.

9. Disponible en https://seepidemiologia.es/wp-content/uploads/2022/03/S.E.Epidemiologia-NOTA-Webinar-Cervix-del-GT-de-Cribado-OK-.pdf Acceso 28.12.2022.

10. Disponible en https://observatorio.contraelcancer.es/informes/informe-dinamico-incidencia Acceso 28.12.2022.

11. Disponible en https://observatorio.contraelcancer.es/informes/informe-dinamico-mortalidad Acceso 28.12.2022.

12. Singh D , Vignat J, Lorenzoni V, Eslahi M, Ginsburg O, Lauby-Secretan B et al. Global estimates of incidence and mortality of cervical cancer in 2020: a baseline analysis of the WHO Global Cervical Cancer Elimination Initiative. Lancet Glob Health.2022; S2214-109X (22) 00501-0.

13. Xu T, Yang X, He X, Wu J. The Study on Cervical Cancer Burden in 127 Countries and Its Socioeconomic Influence Factors. J Epidemiol Glob Health. 2022. doi: 10.1007/s44197-022-00081.

14. Calabro GE, Riccardi MT, D'Ambrosio F, Castagna C, Sapienza M, Millevolte R et al. Cervical cancer elimination in Italy: Current scenario and future endeavors for a value based prevention. Front Public Health. 2022; 10: 1010237.

15. Bosch FX, Castellsagué X, Cortés J, Puig-Tintoré LL, Roura E, de Sanjosé S et al. Estudio AFRODITA: Cribado del cáncer de cuello uterino en España y factores relacionados. GSK Eds. 2009. ISBN 978-84-69l-8490-S.

16. Castellsagué X, Iftner T, Roura E, Vidart JA, Kjaer SK, Bosch FX et al. Prevalence and genotype distribution of human papillomavirus infection of the cervix in Spain: the CLEOPATRE study. J Med Virol.2012; 84(6): 947-56.

17. Disponible en https://www.vacunas.org/un-mundo-sin-cancer-de-cuello-uterino-la-estrategia-90-70-90/ Acceso 04.01.23.

18. Disponible en Cribado Unión Europea 11.22.pdf Acceso 04.01.23.

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CASE REPORT

Acute pancreatitis due to diverticular compression of the gland

Pancreatitis aguda por compresión diverticular de la glándula

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Abstract

Diverticula are commonly located in the colon and are less frequent in other parts of the gastrointestinal tract. Diverticula of the duodenum are the most common in the small intestine and are usually asymptomatic. In rare cases they can lead to abdominal pain, bleeding and obstruction of the bowel or biliary system. In exceedingly rare cases they may be the cause for acute pancreatitis, usually when they are located near the major papilla. We present a rare case where the pancreas was compressed by a large 38 mm by 49.7 diverticulum of the horizontal part of the duodenum, and was managed conservatively.

Keywords: pancreas, duodenal diverticulum, acute pancreatitis, diet.

Resumen

Los divertículos suelen localizarse en el colon y son menos frecuentes en otras partes del tracto gastrointestinal. Los divertículos del duodeno son los más frecuentes en el intestino delgado y suelen ser asintomáticos. En raras ocasiones pueden provocar dolor abdominal, hemorragia y obstrucción intestinal o del sistema biliar. En casos extremadamente raros pueden ser la causa de pancreatitis aguda, normalmente cuando se localizan cerca de la papila mayor. Presentamos un caso poco frecuente en el que el páncreas estaba comprimido por un gran divertículo de 38 mm por 49,7 de la parte horizontal del duodeno, y fue tratado de forma conservadora.

Palabras clave: páncreas, divertículo duodenal, pancreatitis aguda, dieta.

Introduction

Diverticula are commonly located in the colon and are less frequent in other parts of the gastrointestinal tract[1,2]. Diverticula of the duodenum are the most common in the small intestine. They are usually asymptomatic except for cases of pain, bleeding and obstruction of the bowel or biliary system[1].Pancreatitis due to duodenal diverticulum are rare and usually are caused by juxtapapillary diverticula[3]. We report a rare case of a large diverticula located in the horizontal portion of duodenum that caused acute pancreatitis due to its compression of the pancreas.

Case summary

A 57-year-old male patient was admitted with complaints of pain in the upper abdomen with irradiation to the back, nausea, and vomiting. According to the patient, he considers himself ill for about a year, when he began to notice epigastric pain and nausea after eating. During the last year he lost 5 kg. At the time of examination, he had pain in the epigastric region. Laboratory values were normal, with the exception of an increased amylase (309 U/L, normal value 28-100 U/L). Ultrasound of the abdominal cavity revealed an increase in the size

Figure 1: Upper gastrointestinal endoscopy. DD – duodenal diverticulum, DL – duodenal lumen.

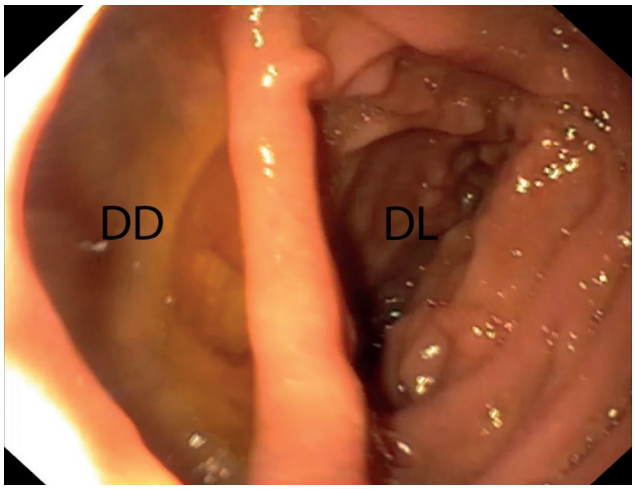


Figure 2: Abdominal X-ray with oral contrasting.

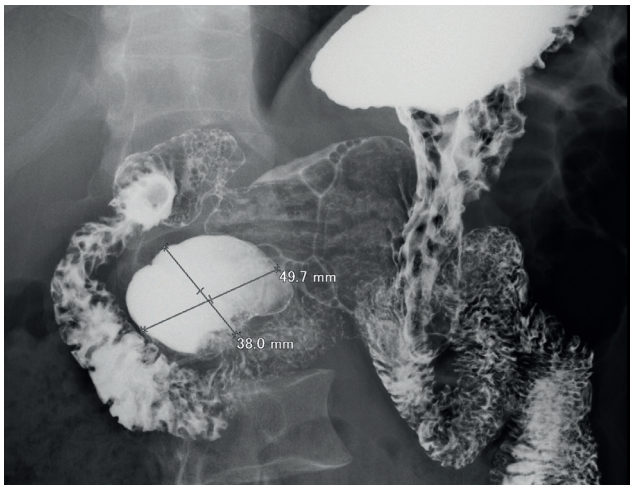
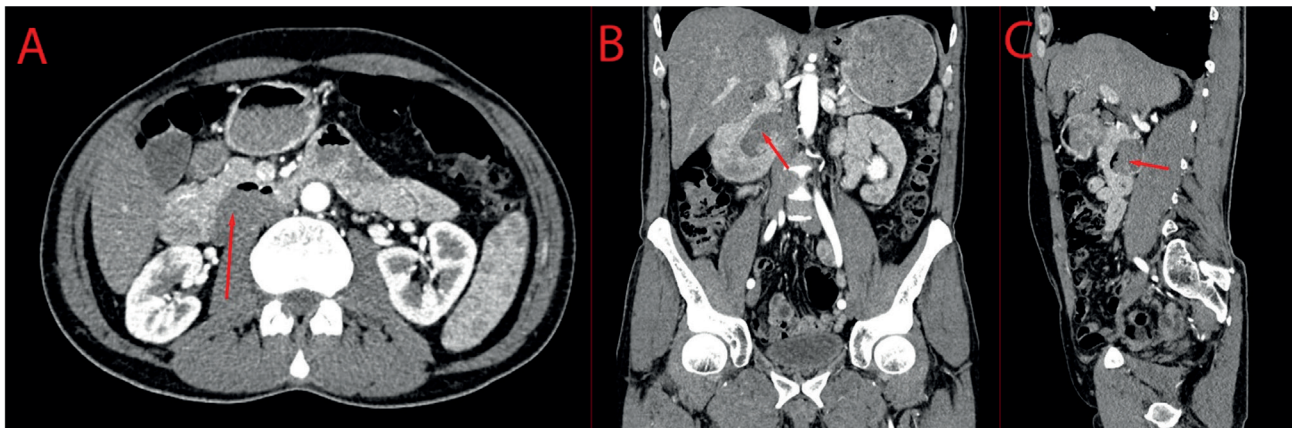


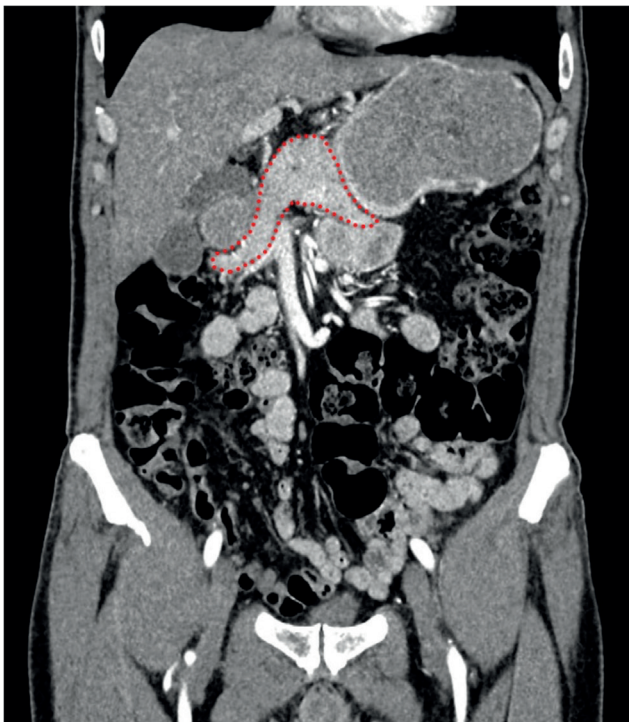
Figure 3: Abdominal CT showing large diverticulum that compresses the pancreas (arrow indicates the duodenal diverticulum). A – Axial plane, B – coronal plane, C – sagittal plane.



of the pancreas with diffuse changes in its structure. For the purpose of differential diagnosis, an upper gastrointestinal endoscopy was performed, which revealed a diverticulum of the horizontal duodenal part without signs diverticulitis (**Figure 1**).

Contrast abdominal X-ray (**Figure 2**) and abdominal CT scan (**Figures 3a, 3b, 3c**) revealed a 38 mm by 49.7 mm diverticulum, which exerted pressure on the pancreas causing an inverted V shape lie (**Figure 4**). Against the background of conservative therapy, withhold of food and fluid there was an improvement in the condition. Amylase level decreased to 107 U/L when re-examined after two days. The patient was discharged 9 days after hospitalization with normal laboratory values and improved overall condition. One year follow up revealed no exacerbation of his condition on diet of smaller but more frequent meals with high amounts of fluid.

Figure 4: Abdominal CT demonstrating an inverted V shape of the pancreas (the pancreas is marked in red).



Discussion

Duodenal diverticula are encountered in up to 23% of cases, depending on the mode of diagnosis. They

can be congenital or acquired, while the last are more frequent. The acquired type represents a protrusion of the mucosa, muscularis mucosa, or submucosa through a local weakness in the duodenal wall. They are symptomatic in approximately 5-10% of cases. In the majority of cases duodenal diverticula are small and are located in the periampullary region or in the medial aspect of the second and third portions of the duodenum. They can mimic a variety of conditions of the duodenum and pancreas including pancreatic pseudocyst or abscess[3,4].

Giant or large diverticula are rare and there are only a few cases reported in the literature with measurements up to 11 cm, typically in the second or third part of the duodenum[1,5,6]. However, there is no measurement scale when a diverticulum is considered to be giant. None of these cases caused symptoms related to pancreatic diseases. Periampullary diverticula are traditionally associated with diseases of the biliary or pancreatic tree. Nevertheless, the association with acute pancreatitis is rare and there are only several cases reported in the literature. The pathogenetic mechanism is usually compression of the duodenal papilla, diverticular inflammation or compression of the common bile duct[7,8]. The present case demonstrates a different mechanism when the size of the diverticula permitted constant compression on the pancreatic parenchyma after a heavy meal. Dietary modifications allowed to decrease the symptoms of the disease. Conservative management is possible for cases where the duodenal neck is wide, therefore allowing fast emptying of the diverticular content.

There are no commonly accepted guidelines on the management of duodenal diverticula. However, commonly accepted approach is to treat a duodenal diverticulum when it becomes symptomatic or causes complications[6,9]. The most common surgical treatment is open or laparoscopic resection, but there are several reports of successful conservative management[6,9].

Acute pancreatitis is a condition when the pancreas becomes inflamed in a short period of time. The most common reasons for acute pancreatitis are alcohol use, gallstones, and hypertriglyceridemia cause. However, the list of causes is extensive and includes other etiological factors such as anomalies of development of the gland, viral infections, systemic conditions, medications, trauma etc[10,11,12]. Acute pancreatitis due to external compression from adjacent anatomical structures is an exceedingly rare condition and there are only a few case reports in the literature. The current case describes successful conservative management of such patients, however, surgical management is possible in refractory cases or when complications occur.

Conflict of interest
The authors have no conflict of interest to declare

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Author contribution
SC - concept and design of the study, editing, analysis of the literature; INL - concept and design of the study, editing, collecting material, text writing; AIE - research concept and design, editing, literature analysis, text writing; AAK - collection and processing of material, editing, analysis of literature; DSB - collection and processing of material, text writing, editing.

References

1. Bierton C, Gupta A. Giant duodenal diverticulum-an incidental finding. J Surg Case Rep. 2019(4):rjz120-rjz. https://doi.org/10.1093/jscr/rjz120

2. Shabunin AV, Bedin VV, Yakomaskin VN, Grekov DN, Covantev S. Clinical Case of a Gastric Diverticulum Operated by Laparoscopic Approach. Online J Health Allied Scs. 2018;17(4):9.

3. Barat M, Dohan A, Dautry R, Barral M, Boudiaf M, Hoeffel C, et al. Mass-forming lesions of the duodenum: A pictorial review. Diagnostic and Interventional Imaging. 2017;98(10):663-75. https://doi.org/10.1016/j.diii.2017.01.004

4. Dusunceli Atman E, Erden A, Ustuner E, Uzun C, Bektas M. MRI Findings of Intrinsic and Extrinsic Duodenal Abnormalities and Variations. Korean J Radiol. 2015;16(6):1240-52. https://doi.org/10.3348/kjr.2015.16.6.1240

5. Millard JR, Ziter FM, Jr., Slover WP. Giant duodenal diverticula. The American journal of roentgenology, radium therapy, and nuclear medicine. 1974;121(2):334-7. https://doi.org/ 10.2214/ajr.121.2.334

6. Ter Horst M, Boer MC, Raber MH, Klaase JM. Giant Diverticulum of the Duodenum. Gastroenterology research. 2011;4(6):289-93. https://doi.org/10.4021/gr359w

7. Rizwan MM, Singh H, Chandar V, Zulfiqar M, Singh V. Duodenal diverticulum and associated pancreatitis: case report with brief review of literature. World J Gastrointest Endosc. 2011;3(3):62-3. https://doi.org/10.4253/wjge.v3.i3.62

8. Yildirgan MI, Başoğlu M, Yilmaz I, Atamanalp SS, Balik AA, Aydinli B, et al. Periampullary diverticula causing pancreaticobiliary disease. Digestive diseases and sciences. 2004;49(11-12):1943-5. https://doi.org/10.1007/s10620-004-9597-9

9. Moysidis M, Paramythiotis D, Karakatsanis A, Amanatidou E, Psoma E, Mavropoulou X, Michalopoulos A. The challenging diagnosis and treatment of duodenal diverticulum perforation: a report of two cases. BMC Gastroenterol. 2020 Jan 8;20(1):5. doi: 10.1186/s12876-019-1154-2.

10. Covantev S. Pancreas divisum: a reemerging risk factor for pancreatic diseases. Rom J Intern Med. 2018;56(4):233-242. doi: 10.2478/rjim-2018-0022. PMID: 30521477

11. Gapp J, Chandra S. Acute Pancreatitis. [Updated 2022 Jun 21]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482468/

12. Covantsev S, Chicu C, Mazuruc N, Belic O. Pancreatic ductal anatomy: more than meets the eye. Surg Radiol Anat. 2022;44(9):1231-1238. https://doi.org/10.1007/s00276-022-03002-w.

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CASE REPORT

Surgical treatment of a patient with hemangiopericytoma and subsequent abdominoplasty: a clinical case

Tratamiento quirúrgico de una paciente con hemangiopericitoma y posterior abdominoplastia: un caso clínico

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Abstract

Hemangiopericytoma is a rare neoplasm of mesenchymal tissue, which is mentioned in the literature mainly in the form of clinical observations. The tumor usually occurs at the age of 20-70 years in the soft tissues of the neck, lower extremities, retroperitoneal space and pelvis. There have been only 20 cases of hemangiopericytoma of the anterior abdominal wall. In rare cases they are associated with paraneoplastic syndromes. In the presented clinical observation, the patient underwent a wide excision of soft tissue tumor, initially regarded as a desmoid, followed by abdominoplasty. The combination of wide excision with abdominoplasty leads an optimal cosmetic result while not violating oncological principles.

Keywords: desmoid tumor, hemangiopericytoma, wide excision, abdominoplasty.

Resumen

El hemangiopericitoma es una neoplasia poco frecuente del tejido mesenquimal, que se menciona en la literatura principalmente en forma de observaciones clínicas. El tumor suele aparecer entre los 20 y los 70 años de edad en los tejidos blandos del cuello, las extremidades inferiores, el espacio retroperitoneal y la pelvis. Sólo se han registrado 20 casos de hemangiopericitoma de la pared abdominal anterior. En raras ocasiones se asocian a síndromes paraneoplásicos. En la observación clínica presentada, la paciente fue sometida a una escisión amplia del tumor de partes blandas, considerado inicialmente como un desmoide, seguida de abdominoplastia. La combinación de escisión amplia con abdominoplastia conduce a un resultado cosmético óptimo sin violar los principios oncológicos.

Palabras clave: tumor desmoide, hemangiopericitoma, escisión amplia, abdominoplastia.

Introduction

Hemangiopericytomas are abundantly vascularized mesenchymal tissue tumors that are currently classified as solitary fibrous tumors. They were first described by Stout and Murray in 1942 as a group of vascular tumors derived from Zimmerman's pericytes[1,2]. Depending on the cellular composition, they are classified as hemangiopericytomas if the cellular component predominates and solitary fibrous tumors if the hyalinizing form of neoplasia predominates. Most commonly, this tumor occurs in the neck, meninges, pleura, retroperitoneum, pelvis, and lower extremities[3]. The incidence is 0.06 per 100,000 examined, and localization within the abdominal wall has been described in only 20 cases[3-5]. There are two types of tumor: malignant and benign; in turn, the latter can become malignant over time. Due to the rare occurrence of the disease and the diverse localization, there are currently no precise recommendations on the tactics of treating these patients. Surgical intervention is considered optimal, which, if necessary, is supplemented by subsequent adjuvant chemotherapy or radiotherapy and active monitoring over time. In the presented clinical observation, the patient underwent a wide excision of soft tissue tumor, initially regarded as a desmoid, followed by abdominoplasty.

Clinical case

In 2019 a 43 years old woman drew attention to the appearance of a mass of the anterior abdominal wall in the umbilical region. She observed the mass until June 2022 and due to the increase in size the patient consulted a surgeon, then was referred for a consultation to an oncologist. On examination the entire anterior abdominal wall below the umbilicus was represented by a voluminous multinodular mass measuring 18x15 cm with clear, even contours, the skin over the tumor was hyperemic but without changes around the mass (**Figure 1A, 1C**). On palpation, the tumor was painless, it was displaced along with the skin relative to the underlying tissues and the inguinal lymph nodes were not enlarged.

On July 25, 2022, the patient undergone a core-needle biopsy of the lesion. The histological conclusion was desmoid type fibromatosis. Immunohistochemical study revealed that tumor cells were Actin- CD34+ Beta-caternin+. She underwent computed tomography (CT) of the abdominal cavity and pelvis with intravenous contrast enhancement. The CT scan revealed a solid multinodular tumor in the soft tissues of the anterior abdominal wall, 5 mm below the umbilical ring measuring 193x98x42 mm with clear, even contours, most likely originating from the left rectus abdominis muscle and accumulating contrast (**Figure 1B, 1D**). Taking into account the size of the tumor and its location, we decided to perform a wide excision of the mass followed by abdominoplasty. The preoperative marking of the anterior abdominal wall is indicated in **figure 2A**. The patient received preoperative antibiotic prophylaxis with 1 g of cefotaxime 30 minutes before surgery. Surgery was performed under combined endotracheal anesthesia. After preparing the skin with antiseptic solution, the skin and subcutaneous fat were dissected with two incisions. A skin flap with dimensions of 20.0 x 13.0 cm with the mass was isolated up to the fascia. Tumor invasion into the underlying muscles was not detected intraoperatively. The navel was excised and skin flaps were dissected in the cranial direction to the edges of the costal arches and the xiphoid process. The diastasis and the umbilical ring were sutured. The wound was sutured in layers with a cosmetic suture, two vacuum drainages were left, brought out through counter-openings in the region of the inguinal folds.

Figure 4: Preoperative picture of the mass. A - anterior projection of the mass B - CT image of the mass (axial section), C - anterior projection of the mass, D - CT image of the mass (sagittal section).

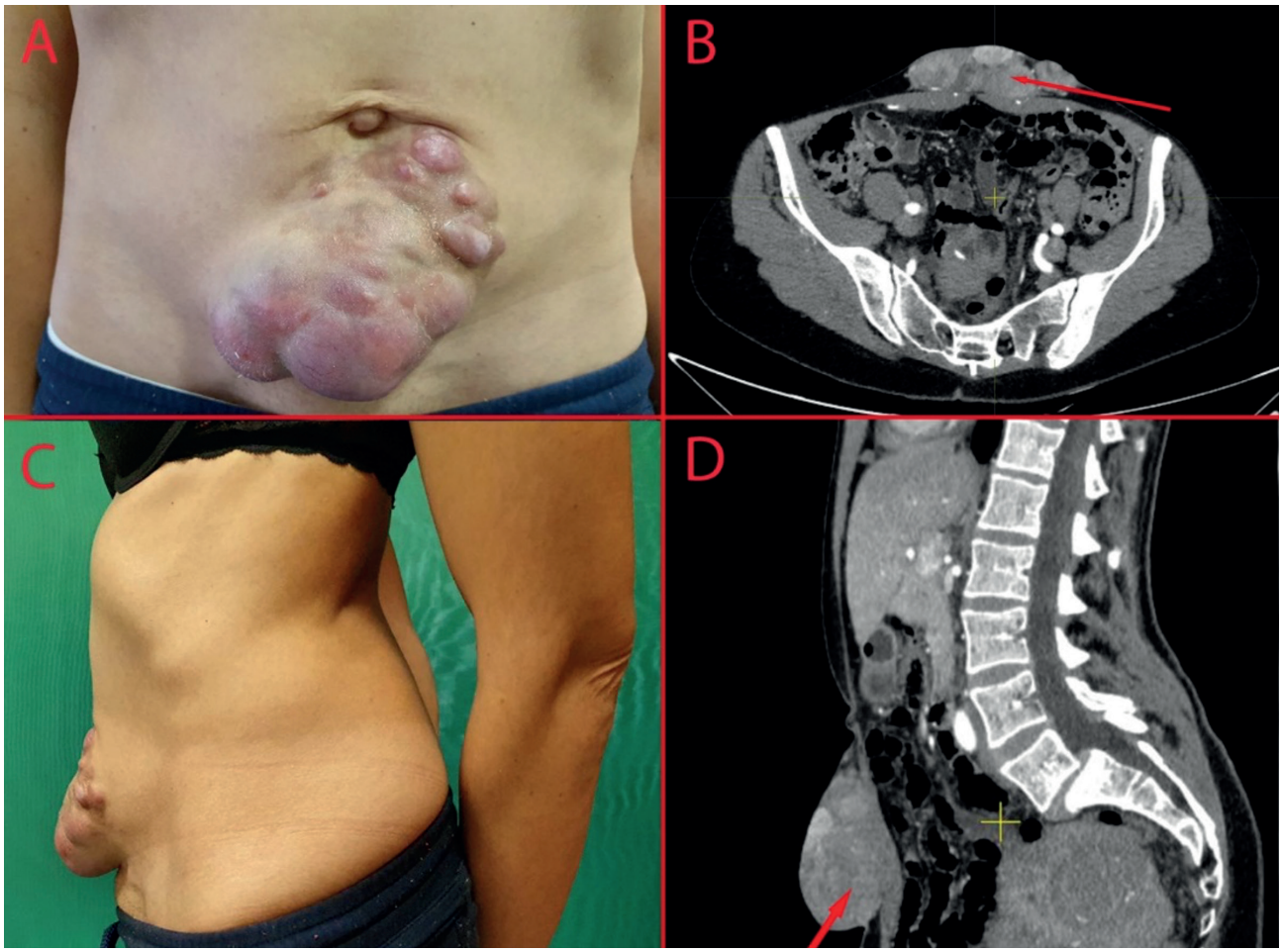
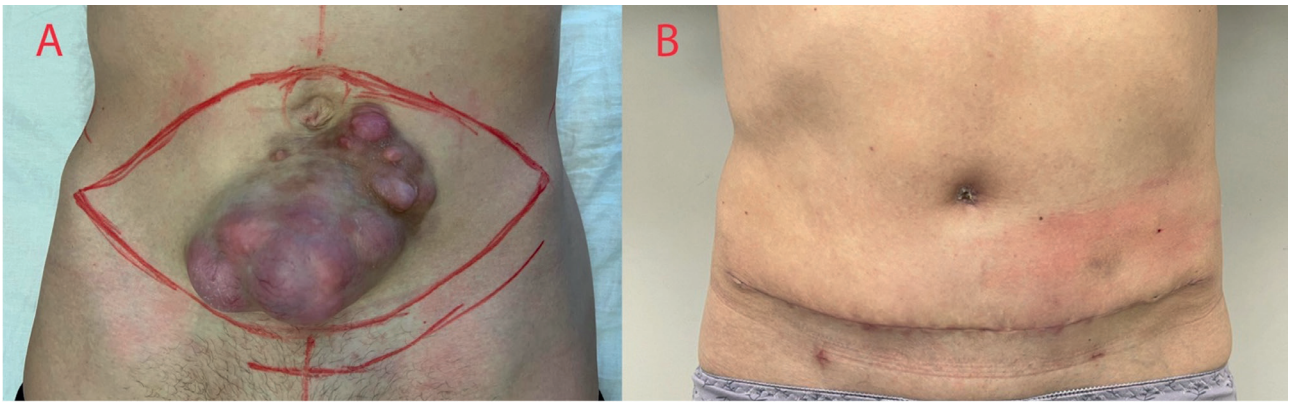


Figure 2: Comparison of preoperative and postoperative picture. A - preoperative marking; C - 14th day after the operation.



Umbilicoplasty was performed using the petal method. The patient received symptomatic therapy with NSAIDs in the postoperative period (ketorolac 30 mg intravenously). On the 2nd day after the operation, the drains were removed. At the control ultrasound examination on the 3rd day after the operation there was soft tissue edema in the area of intervention with no fluid accumulations. The patient was discharged from the hospital on the 3rd day after the operation. Histological examination revealed an infiltrative tumor under the epidermis, completely germinating the subcutaneous fat, consisting of long bundles with elongated, thin, spindle-shaped cells of a homogeneous appearance, subcutaneous areas with minimal signs of cellular atypia, rare mitoses. In the deep areas of the tumor there were noticeable cell atypia with mitoses (about 4 per 10 fields of view). Immunohistochemical examination revealed that tumor cells diffusely expressed vimentin, CD34. Ki67 was 2%, beta-catenin and SMA were negative. According to the results of histological and immunohistochemical studies, the mass was classified as hemangiopericytoma. On the 7th and 14th days after the operation, the patient underwent seroma (60 ml) evacuation under ultrasound guidance (**Figure 2A, B**). During a control ultrasound of the soft tissues of the anterior abdominal wall after 12 months there was no data for recurrence.

Discussions

Hemangiopericytoma is a rare neoplasm of mesenchymal tissue, which is mentioned in the literature mainly in the form of clinical observations. The tumor usually occurs at the age of 20-70 years in the soft tissues of the neck, lower extremities, retroperitoneal space and pelvis. To our knowledge, only 20 cases of hemangiopericytoma of the anterior abdominal wall have been described. According to the literature, most patients were over 50 years old, the average size of the mass was 8 cm (from 1.9 to 16 cm)[1,6,7]. In most cases, patients did not present any complaints, but in some cases they may be bothered by pain or a feeling of pressure in the area of the tumor[1,8]. In the presented clinical observation, the patient was younger and the tumor was 193 x 98 x 42 mm in size. To our knowledge this is the largest tumor reported in the literature.

Two paraneoplasty syndromes occur in patients with hemangiopericytoma: osteoarthropathy and Doege-Potter syndrome. Hypertrophic arthropathy predominantly occurs in 20% of cases in pleural hemangiopericytomas and is manifested by bone pain, finger clubbing, joint stiffness and swelling. Doege-Potter syndrome occurs in approximately 5% of patients, most often with large tumors localized in the pelvis or retroperitoneum, and manifests itself with hypoglycemia, presumably due to the secretion of IGF-2[9,10].

An analysis of 1.243 patients with hemangiopericytoma over 41 years indicates that surgery as the main treatment method significantly increases patient survival. At the same time, according to the results of the study, radiotherapy does not affect survival, and chemotherapy reduces it. The combination of various treatment options with surgery, in general, does not improve the prognosis of the disease[3]. A major difficulty in surgery of tumors of the abdominal wall is the surgical intervention, which often leaves an unpleasant and stigmatizing scar. An alternative to only direct excision is subsequent abdominoplasty, as a means to achieve aesthetic results and improve quality of life, while maintaining the standards of surgical oncology.

Histological verification has a number of difficulties and requires immunohistochemical studies. Cells express CD34 antigens in 78-100% of cases, Bcl-2 in 96%, expression of CD99 and vimentin is common. As a rule, cells do not express cytokeratin, actin, desmin, early membrane antigen, c-kit and S100 protein on the surface[1,8,11].

The question of differential diagnosis of benign and malignant forms of tumors also remains open. To date, there are no precise criteria for malignancy. A presumably high mitosis index, large masses, invasion

into surrounding tissues, the presence of immature cells in the biopsy, necrosis or hemorrhage loci are risk factors for malignancy[3,12].

Surgical excision with reconstruction using local tissues is a common method for giant tumors[13]. However, he cosmetic results of such procedures is often far from ideal. The current case demonstrates that wide surgical excision of a large tumor with subsequent abdominoplasty is a valid alternative to standard wide excision for larger tumors located in the region of the abdominal wall.

Conclusion

Hemangiopericytomas are a group of mesenchymal tumors that are most often asymptomatic and difficult to recognize until they cause compression of adjacent structures. In rare cases they are associated with paraneoplastic syndromes. In the literature, there are only isolated cases of surgical treatment of patients with hemangiopericytomas of the anterior abdominal wall. The combination of wide excision with abdominoplasty leads an optimal cosmetic result while not violating oncological principles.

Disclosures

Ethics Committee Approval: No ethical approval required and the study was performed in accordance with the principles of the declaration of Helsinki.

Conflict of Interest

There is no conflict of interest.

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References

1. Migita K, Watanabe A, Nakagawa K, Ohyama T, Sekigawa S. Solitary fibrous tumor of the abdominal wall. International journal of clinical oncology. 2009;14(6):555-9.

2. Garcia-Bennett J, Olivé CS, Rivas A, Domínguez-Oronoz R, Huguet P. Soft tissue solitary fibrous tumor. Imaging findings in a series of nine cases. Skeletal radiology. 2012;41(11):1427-33.

3. Wang K, Mei F, Wu S, Tan Z. Hemangiopericytoma: Incidence, Treatment, and Prognosis Analysis Based on SEER Database. BioMed research international. 2020;2468320.

4. Bi X, Zhai J, Chun CD. Solitary fibrous tumor of the abdominal wall resurfacing as unilateral pleural effusion and mass: A case report and review of the literature. Respiratory Medicine Case Reports. 2018;23:4-7.

5. Testa DC, Selvaggi F, Andreano T, Mazzola L, Cortellese R. Solitary fibrous tumor of the anterior abdominal wall. A case report and review of the literature. Annali italiani di chirurgia. 2019;13;8.

6. Carnerero Herrera V, Domínguez-Pérez A, González-Martín R, Nacarino-Mejías V, Alcázar Iribarren-Marín M. [Solitary fibrous tumor of the abdomen. A rare neoplasm of vascular origin]. Gastroenterologia y hepatologia. 2010;33(8):578-81.

7. Penel N, Amela EY, Decanter G, Robin YM, Marec-Berard P. Solitary fibrous tumors and so-called hemangiopericytoma. Sarcoma. 2012;2012:690251.

8. Costa M, Oliva A, Velez A, Bento A, Garcia H, et al. (2014) Solitary Fibrous Tumor of the Abdominal Wall. J Clin Case Rep 4: 363.

9. Yuri T, Kanematsu S, Lei YC, Kuwata M, Oishi M, Tsubura A. Solitary fibrous tumor of soft tissue: a case report and immunohistochemical study. Medical molecular morphology. 2010;43(1):60-4.

10. Ouazzani A, Delrée P, De Saint Aubain N, Ceuterick M, Boudaka W. [Malignant solitary fibrous tumor of the abdominal wall in a man]. Annales de chirurgie plastique et esthetique. 2008;53(6):517-20.

11. Park MS, Araujo DM. New insights into the hemangiopericytoma/solitary fibrous tumor spectrum of tumors. Current opinion in oncology. 2009;21(4):327-31.

12. Enzinger FM, Smith BH. Hemangiopericytoma: An analysis of 106 cases. Human Pathology. 1976;7(1):61-82.

13. Shabunin AV, Lebedinsky IN, Dolidze DD, Bagatelia ZA, Covantsev S, Bocharnikov DS, et al. Giant bleeding post-traumatic thoracic sarcoma management: A case report. Front Surg. 2022;8;9:1044077.

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CASE REPORT

Possible benefit of intra- articular ozone in advanced osteonecrosis of the knee: two case reports

Posible beneficio del ozono intraarticular en la osteonecrosis avanzada de la rodilla: informe de dos casos

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Abstract

The knee is the second most common site of osteonecrosis (ON) after the hip. Three different entities are described: a) spontaneous ON; b) secondary ON; c) post-arthroscopy ON. In spontaneous ON the etiology is attributed to subchondral insufficiency fractures and to avascular necrosis due to´ischemic events. Diagnosis is based on clinical and radiological basis (radiography, bone scan scintigraphy and MRI). Koshino´s radiological classification grades severity and guides in the management. Conservative management includes protected weight bearing, drugs (NSAIDs, bisphosphonates, D vitamin, calcium, prostaglandin I-2, corticosteroids, hyaluronic acid), physiotherapy (laser, pulsed electromagnetic fields), and hyperbaric oxygen therapy. Surgical treatment is deserved for advanced stages or if conservative treatment failed. In pre-collapse Stage, joint preserving procedures are expected; on the contrary, in subchondral collapse stages, joint arthroplasty is required. We present for the first time in literature the beneficial effect of intra articular ozone in the management of two cases of advanced ON of the knee.

Keywords: ozone, osteonecrosis of the knee, treatment.

Resumen

La rodilla es la segunda localización más frecuente de la osteonecrosis (ON) después de la cadera. Se describen tres entidades diferentes: a) la ON espontánea; b) la ON secundaria; c) la ON post-artroscopia. En la ON espontánea la etiología se atribuye a las fracturas por insuficiencia subcondral y a la necrosis avascular debida a eventos isquémicos. El diagnóstico se basa en la clínica y la radiología (radiografía, gammagrafía ósea y resonancia magnética). La clasificación radiológica de Koshino califica la gravedad y orienta el tratamiento. El tratamiento conservador incluye la protección del peso, fármacos (AINE, bifosfonatos, vitamina D, calcio, prostaglandina I-2, corticosteroides, ácido hialurónico), fisioterapia (láser, campos electromagnéticos pulsados) y oxigenoterapia hiperbárica. El tratamiento quirúrgico se merece para los estadios avanzados o si ha fracasado el tratamiento conservador. En el estadio precolapso, se esperan procedimientos de preservación articular; por el contrario, en los estadios de colapso subcondral, se requiere una artroplastia articular. Presentamos por primera vez en la literatura el efecto beneficioso del ozono intraarticular en el manejo de dos casos de ON avanzada de rodilla.

Palabras clave: ozono, osteonecrosis de rodilla, tratamiento.

Introduction

Osteonecrosis (ON) of the knee is a progressive disease that leads to subchondral collapse and finally disabling knee osteoarthritis (OA)[1]. It was for the first time described in 1968 by Ahlbäck et al[2]. The knee is the second most affected site after the hip[3].

Knee ON has been recently classified in three entities: 1) spontaneous ON, the most common type with an incidence of 3.4% in people over 50 years and 9.4% in those over 65; 2) secondary ON affects younger patients, in multiple and bilateral joints, and it is related to alcohol

abuse, tobacco, corticosteroids, sickle cell disease and myeloproliferative disorders; 3) post arthroscopy ON, a rare condition affecting 4% of all arthroscopies mainly due to meniscopathies[3].

The etiology of ON of the knee is unknown, although 2 theories are postulated. The vascular insufficiency theory is based on the difference in blood supply between medial and lateral condyles. The traumatic theory states that ON is in reality the result of subchondral insufficiency fractures[4].

Koshino in 1979 classified ON in four stages: Stage I is normal. Stage II shows radiolucent oval area in subchondral region or flattening of medial femoral condyle (MFC). Stage III depicts an sclerotic halo over radiolucent area and "crescent sign" is observed. Stage IV shows collapse of subchondral bone and osteophytes[5].

Prognostic factors for knee ON are based on Koshino´s classification and on size of lesion. Lesions inferior to 3.5 cm^2 tend to regress without surgical intervention. On the contrary, lesions greater than 5 cm^2 will lead to condyle collapse[6]. Lotke states that lesions involving more than 50% of condylar surface will require arthroplasty[7].

Di Caprio has stated an algorithm depending on the size of lesion and where collapse is present or not into three categories: a) Non-operative treatment (protected weight bearing, NSAIDs, bisphosphonates, hyperbaric oxygen therapy, pulsed electromagnetic fields); b) joint preserving techniques at pre-collapse stage (arthroscopic debridement, retrograde or anterograde drilling, core decompression, bone grafting, high tibial osteotomy); c) Replacement at collapse stage (osteochondral autografts or allografts, unicompartimental knee arthroplasty [UKA] or total knee arthroplasty [TKA]). This algorithm also applies for post arthroscopy ON but the decision is made on early or late diagnosis (more than 6 months)[3]. Lair et al also considers Laser, Vitamin D and Calcium, injections of corticosteroids or hyaluronic acid and physiotherapy as conservative treatment[8]. Karim also suggests prostaglandin I_2 as conservative treatment[9].

In the case of ON of the femoral head, there are two case reports (Iliakis et al and Yildizgorem et al)[10,11] and a case series of 71 patients (An et al) treated by intra articular ozone therapy[12]. However, to the best of author's knowledge, there is no report on the use of intra articular ozone in the management of knee ON.

Recently, our study group led by Fernández-Cuadros et al has observed symptomatic and disease modifying effect of ozone in osteoarthritis (OA) of the knee in a case report[13] and in a case series of 115 patients[14], evaluating clinical, biochemical, and radiological variables. Moreover, in another series of 65 knee OA patients, an improvement of anabolic IGF-1 and a decrease of anti-inflammatory cytokine IL-6 were observed after ozone treatment confirming anabolic and anti-inflammatory properties of ozone in knee OA[13].

The objective of the present study is to postulate the possible benefit of intra articular ozone in the management of advanced ON of the knee (Koshino´s Stage III-IV) in two females cases and to report for the first time in literature.

Case report

We present two female cases with ON of the knee Stage III on Koshino´s classification treated successfully by intra articular ozone, evaluated by clinical, biochemical and radiological variables.

Case 1: Case 1 is an 83 years old female with ON of the medial femoral condyle (MFC) of the right knee, Stage III. The patient was previously operated in the left knee 10 months ago (TKA). Symptoms begun as acute onset of pain on the medial aspect of the knee. The patient is independent for activities of daily life and is capable of walking only with the help of a cane. She uses paracetamol on demand as a pain killer. Patient was referred to Rehabilitation Department for conservative treatment because she refused to get a TKA of the right knee.

On anamnesis, the patient referred pain (7/10), rigidity (5/8) and function impairment (55/68) as stated by WOMAC scale (Western Ontario and Mc master Index for OA). We explained the properties of ozone highlighting its symptomatic and disease modifying effects, and patient accepted and signed informed consent. We performed clinical, biochemical and radiological evaluation before and after ozone treatment (evaluations at every cycle of ozone). Ozone treatment consisted on 4 sessions of intra articular ozone, 20 mL of 5% ozone at a 20 µg/mL concentration on the lateral aspect of suprapatellar knee.

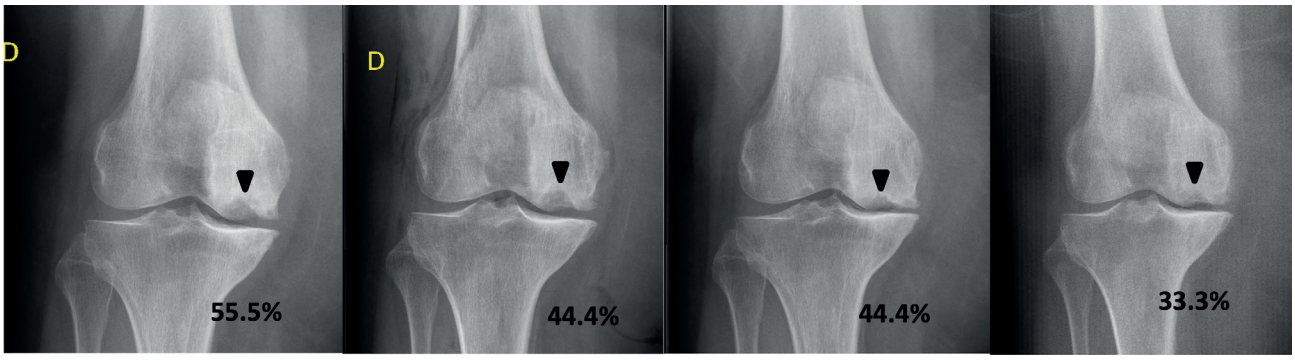
Patient was infiltrated in 6 cycles (4 sessions each cycle), on November 2019, February 2020, October 2020, may 2021, November 2021 and May 2022. We registered clinical and biochemical improvement on the first 4th cycles and radiographies from the beginning to the end of treatment (**Table I** and **figure 1**). There is a clear benefit of ozone treatment in terms of clinical and biochemical variables observed after each cycle; and a radiological improvement from the 1st to 6th cycle after ozone intra articular infiltrations (**Table I** and **Figure 1**). Pain has been reduced in each cycle and function has also improved in the same way.

Tabla I: Clinical, biochemical and radiological improvement before and after ozone therapy from cycle to cycle in both case reports.

Variable	Case 1	Case 2		
	Pre-Ozone	Post-ozone	Pre-Ozone	Post-ozone
Clinical				
VAS 1º (1-10)	7	5	8	4
VAS 2º (1-10)	7	5	3	0
VAS 3º (1-10)	7	3		
VAS 4º (1-10)	5	3		
WOMAC Rigidity 1º (0-8)	5	4	5	3
WOMAC Rigidity 2º (0-8)	5	4	2	0
WOMAC Rigidity 3º (0-8)	5	3		
WOMAC Rigidity 4º (0-8)	4	3		
WOMAC Function 1º (0-68)	55	50	60	40
WOMAC Function 2º (0-68)	55	50	35	20
WOMAC Function 3º (0-68)	55	40		
WOMAC Function 4º (0-68)	40	30		
Biochemical				
CRP 1º (mg/mL)	0.58	0.23	0.5	0.4
CRP 2º (mg/mL)	0.2	0.1	1.82	0.52
CRP 3º (mg/mL)	0.7	0.3		
CRP 4º (mg/mL)	0.15	0.16		
ESR 1º (mL/hour)	17	17	27	13
ESR 2º (mL/hour)	14	13	28	20
ESR 3º (mL/hour)	24	24		
ESR 4º (mL/hour)	15	6		
Uric Acid 1º (mg/dL)	6.2	4.7	6.6	5.4
Uric Acid 2º (mg/dL)	5	4.7	5.4	5.3
Uric Acid 3º (mg/dL)	6.1	5.5		
Uric Acid 4º (mg/dL)	5.2	5.0		
IL-6 1º (pg/mL)	8.41	6.01	1.15	0.83
IL-6 2º (pg/mL)	2.09	2.07		
IL-6 3º (pg/mL)	2.3	2.0		
IGF-1 1º (ng/mL)	114.7	136.4	63.47	102.0
IGF-1 2º (ng/mL)	109.9	138.6		
Radiological				
Surface involvement 1º (%)		55.5		50
Surface involvement 2º (%)		44.4		41.6
Surface involvement 3º (%)		44.4		33.3
Surface involvement 4º (%)		33.3		

VAS, visual analogue scale. WOMAC, Western Ontario and Mc Master Index for Osteoarthritis. ESR, erythrocyte sedimentation rate. IL-6, Interleukin 6. IGF-1, Insulin growing factor 1.

Figure 1: Case 1 after 6 cycles of intra articular ozone infiltrations. Radiographies were performed on October 2019; December 2020; November 2021 and May 2022. On each radiography, surface involvement of osteonecrosis of the medial femoral condyle is expressed in percentage.



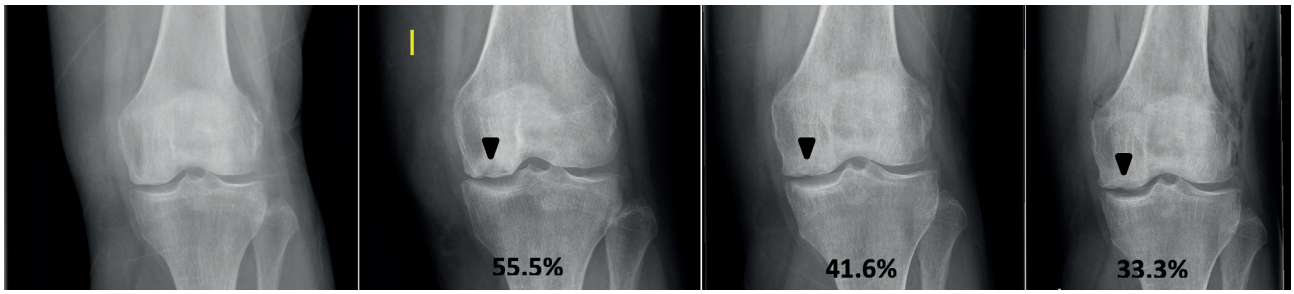
Case 2: Case 2 is a 70 years old female with ON of the MFC of the left knee, Stage III (Koshino´s classification). Patient reported acute onset of pain on medial aspect of the knee and secondary pain on left trochanter because of antalgic walking. Patient was referred to Rehabilitation Department for conservative treatment. At that time, she was candidate for UKA.

At Rehabilitation Department, patient was prescribed pulsed electromagnetic fields (PEMFs) on the left knee and transcutaneous electrical nerve stimulation (TENS) on left trochanter. After 10 sessions (5 sessions/week) and no improvement on pain and gait, she was offered intra articular ozone therapy because of its symptomatic and disease modifying effect on knee OA.

After acceptance and signed informed consent, patient received 2 cycles (4 sessions each) of 20 mL of 5% ozone at a 20 µg/mL concentration. Clinical symptoms (pain, function and rigidity evaluated by WOMAC scale),

biochemical (PCRP, ESR, Uric Acid, IL-6 and IGF-1) and radiological variables were evaluated before and after each cycle (**Table I** and **Figure 2**). Patient was infiltrated on October 2021 (first cycle) and on April 2022 (second cycle). Symptoms and gait improved to the point that a cane as no longer used for walking, and pain disappeared at all.

Figure 2: Case 2 after 2 cycles of intra articular ozone infiltrations. Radiographies were performed on April 2019; September 2020; May 2021 and April 2022. On each radiography, surface involvement of osteonecrosis of the medial femoral condyle is expressed in percentage.



Discussion

To the best of author's knowledge, these are the first two cases of severe ON of the MFC of the knee treated successfully by intra articular ozone and evaluated by clinical, biochemical and radiological variables.

Ahlbäck in 1968 was the first to describe spontaneous ON of the knee. He described the entity as acute onset of pain typically presented in the MFC, affecting more commonly females and older than 60 years[2]. This is in accordance with our two cases, females of 70 and 83 years with acute onset of pain on the medial aspect of the knee. The presentation is usually in the medial condyle more than lateral one.

In the case of secondary ON of the knee, the presentation is in people younger than 45 years, could be multilateral and is more frequent in hips than in knees[1]. Risk factors include alcohol abuse, coagulopathies, Caisson's disease, chemotherapy, corticosteroids, Cushing's Syndrome, diabetes, familial thrombophilia, Gaucher's disease, gout, hyperthyroidism, irritable bowel disease, liver disease, organ transplantation, pancreatitis, pregnancy, radiation, renal disease, sickle cell disease and other hemoglobinopathies, smoking, systemic lupus erythematous and tumors[3].

Another form is post arthroscopy ON of the knee. This is the rarest form of ON of the knee with a prevalence of 4% of all arthroscopies. Meniscopathy is present in 87% of cases. Onset is usually after 6 weeks of the procedure[3]. None of our cases were treated by arthroscopy procedures before onset of pain.

The etiology of ON is thought to be vascular and is characterized by loss of blood bone circulation[1]. Since ozone is believed to improve rheology of erythrocytes and to favor delivery of oxygen to tissues (by formation of 2,3 DPG which displaces the curve of dissociation of hemoglobin to the right)[15]. This fact would explain the clinical and radiological improvement observed in our cases. Another theory for the explanation of ON presentation is that mechanical factors would lead to subchondral insufficiency fractures[3]. Since we have previously postulated and lately demonstrated that Ozone could stimulate stem cells, chondrocytes and growth factors (TGF-β and IGF-1) in knee OA[13-14], and we have observed improvement in minimal joint space in knee OA patients[14], we believe that these properties have been responsible for the radiological improvement in knee ON. In fact, case 1 reduced surface ON lesion from 55.5% to 33.3% and case 2 ameliorated ON lesion from 50% to 33.3%.

Prognosis of ON of the knee is based on size of the lesion (3.5 cm^2 vs 5 cm^2), surface involvement of lesion (50%) and Kashino´s classification (Stage I-II vs III-IV). Most algorithms state conservative treatment in lesions inferior to 3.5 cm^2, surface involvement lower than 50% or Kashino's Stage I-II. On the contrary, surgical treatment is proposed if lesion is greater than 5 cm^2, superior than 50% surface involvement or Stage III-IV. It depends of pre-collapse to perform arthroscopic procedures or high tibial osteotomy; or collapse Stage to perform osteochondral autografts or UKA or TKA[3].

Intra articular infiltrations of hyaluronic acid, corticosteroids[8], stem cells or platelet-rich plasma[11] are considered as conservative treatment for the management of early Stages (I-II) of knee ON. The importance of the study is that for the first time in literature, we report the benefit of intra articular ozone in the management of advanced knee ON (Stages III-IV) where only surgical procedures are considered and it is supposed that intra articular infiltrations have no place on such advanced stages.

In a very recent article, Spassim et al, in a rat model of knee OA, have demonstrated that 60 daily sessions of intra articular ozone (at 5 and 10 µg/mL concentration) could delay the degeneration of the articular cartilage evidenced clinically, radiologically and histologically[16]. These findings would explain the radiological improvement observed in our two case reports.

There are only three publications on the benefit of intra articular ozone for the management of hip ON. Iliakis et al have stated than in a 43 years old female with ON of the left hip, 7 sessions of intra articular ozone (5 mL at a 40 µµg/mL concentration) improved clinical and radiological status[10]. Yildizgoren reported that in a 45 years old male with bilateral hip ON secondary to corticosteroids use (for treatment of Hodgkin's lymphoma), after 5 sessions (1/week) of intra articular ozone (15 mL at increasing doses of 15, 20 and 25 µg/mL concentration) the patient ameliorated pain (VAS from 7 to 2) and improved walking distance (from 100 to 1000 meters)[11]. An et al, in a series of 71 patients with hip ON, observed that 3 cycles of 10 sessions of intra articular ozone (5 sessions/week) every three months (30 mL at 30 µg/mL concentration) improved pain (VAS scale), Harris Hip Score and bone marrow edema. Ozone also delayed total hip arthroplasty at a 30-months follow-up period[2].

Conclusion

Based on two case reports, intra articular ozone could improve clinical, biochemical and radiological variables in patients with advanced ON of the knee. It is necessary to perform a study with a greater sample to confirm the promising benefit observed in this report.

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Conflicts of interest
The authors declare no conflict of interest.

Ethics approval
The case report has been approved by the Ethical Committee of the Hospital.

Consent to participate
For the application of this treatment, patients signed an informed consent.

Consent for publication
For case report publication, patients signed an informed consent.

References

1. Mont MA, Marker DR, Zywiel MG, Carrino JA. Osteonecrosis of the knee and related conditions. J Am Acad Orthop Surg. 2011 Aug;19(8):482-94. doi: 10.5435/00124635-201108000-00004.

2. Ahlbäck S, Bauer GC, Bohne WH. Spontaneous osteonecrosis of the knee. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology 1968; 11(6):705-33.

3. Di Caprio F, Meringolo R, Navarra MA, Mosca M, Ponziani L. Postarthroscopy Osteonecrosis of the Knee: Current Concepts. Joints. 2017 Nov 6;5(4):229-236. doi: 10.1055/s-0037-1608666.

4. Alexa, O., Cionca, D., Albetar, S., & Veliceasa, B. (2015). Spontaneous Osteonecrosis of the Medial Femoral Condyle: Case Report. chirurgie, 10(4), 291-3.

5. Koshino T, Okamoto R, Takamura K, Tsuchiya K. Arthroscopy in spontaneous osteonecrosis of the knee. The Orthopedic Clinics of North America 1979; 10(3):609-18.

6. Sibilska A, Góralczyk A, Hermanowicz K, Malinowski K. Spontaneous osteonecrosis of the knee: what do we know so far? A literature review. Int Orthop. 2020 Jun;44(6):1063-1069. doi: 10.1007/s00264-020-04536-7.

7. Lotke PA, Abend JA, Ecker ML. The treatment of osteonecrosis of the medial femoral condyle. Clinical Orthopaedics and Related Research 1982;171:109-16.

8. Lair J, Fink C, Csapo R. Spontaneous Osteonecrosis of the Knee: a Systematic Review of Conservative Treatment Approaches. Research Square, 2021. DOI: 10.21203/rs.3.rs-239294/v1.

9. Karim AR, Cherian JJ, Jauregui JJ, Pierce T, Mont MA. Osteonecrosis of the knee: review. Ann Transl Med. 2015 Jan;3(1):6. doi: 10.3978/j.issn.2305-5839.2014.11.13.

10. Iliakis E, Bonetti M, Iliakis A. Osteonecrosis of the femoral head: Could oxygen-ozone therapy became a treatment option?. Journal of Ozone Therapy 2015; 1(1):3-7.

11. Yildizgören MT, OĞUZ H. Ultrasound-Guided Intra-Articular Ozone Injection as a Therapeutic Option for Hip Osteonecrosis. Journal of Physical Medicine & Rehabilitation Sciences/Fiziksel Tup ve Rehabilitasyon Bilimleri Dergisi 2020; 23(3).

12. An JX, Wu GP, Niu K, Wei YP, Liu H, Gao XY, Wu JP, Wang Y, Renz H, Williams JP. Treatment of Femoral Head Osteonecrosis with Ozone Therapy: Pilot Trial of a New Therapeutic Approach. Pain Physician. 2022 Jan;25(1):E43-E54.

13. Fernández-Cuadros ME, Pérez-Moro OS, Albaladejo-Florín MJ, Álava-Rabasa S. Symptomatic (Pain and Inflammation) and Disease-Modifying Effect (Minimal Joint Space) of Intra-articular Ozone (O2-O3) in Osteoarthritis of the Knee: a Clinical Case. SN Comprehensive Clinical Medicine 2019;1(10):817-21.

14. Fernández-Cuadros ME, Pérez-Moro O, Albaladejo-Florín MJ, Álava-Rabasa S. El ozono intra-articular modula la inflamación, mejora el dolor, la rigidez, la función y tiene un efecto anabólico sobre la artrosis de rodilla: estudio cuasi-experimental prospectivo tipo antes-después, 115 pacientes. Revista de la Sociedad Española del Dolor 2020; 27(2):78-88.

15. Fernández-Cuadros ME, Albaladejo-Florín MJ, Peña-Lora D, Álava-Rabasa S, Pérez-Moro OS. Ozone (O3) and SARS-CoV-2: physiological bases and their therapeutic possibilities according to COVID-19 evolutionary stage. SN Comprehensive Clinical Medicine 2020; 2(8):1094-102.

16. Spassim MR, Dos Santos RT, Rossato-Grando LG, Cardoso L, da Silva JS, de Souza SO, et al. Intra-articular ozone slows down the process of degeneration of articular cartilage in the knees of rats with osteoarthritis. The Knee 2022; 35: 114-23.

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CASE REPORT

Drug-Induced Stevens Johnson's Syndrome; 4 case Series in Tertiary Hospital in Somalia

Síndrome de Stevens Johnson inducido por fármacos; serie de 4 casos en un hospital terciario de Somalia

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Abstract

Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is a well-known severe cutaneous adverse reaction (SCAR) that belongs to type IV hypersensitivity and is mediated by an immunological effect.

Here, we report 4 cases of SJS presented to a tertiary hospital in Mogadishu, Somalia. Stevens-Johnson syndrome has a significant relationship to various drugs. Stevens-Johnson syndrome is a potential therapeutic complication, especially in Somalia, where antibiotics are used irrationally. Steroids are controversially used as treatment. SJS is more common in Somalia and other parts of Africa because antibiotics are available without a prescription. It's difficult to detect and manage; most patients die before a firm diagnosis is obtained.

Keywords: Stevens Johnson syndrome, Type IV Hypersensitivity, toxic epidermal necrolysis.

Resumen

Una conocida reacción adversa cutánea grave (RAC) de tipo IV, mediada por un impacto inmunitario, es el síndrome de Stevens-Johnson/necrolisis epidérmica tóxica (SJS/TEN).

En este artículo se presentan 4 casos de SJS en un hospital de tercer nivel de Mogadiscio (Somalia). El síndrome de Stevens-Johnson tiene una importante relación con diversos fármacos. El síndrome de Stevens-Johnson es una complicación terapéutica potencial, especialmente en Somalia, donde los antibióticos se utilizan de forma irracional. Los esteroides se utilizan de forma controvertida como tratamiento. El síndrome de Stevens-Johnson es más común en Somalia y otras partes de África porque los antibióticos están disponibles sin receta. Es difícil de detectar y manejar; la mayoría de los pacientes mueren antes de obtener un diagnóstico firme.

Palabras clave: Síndrome Stevens Johnson, hipersensibilidad de tipo IV, necrolisis epidérmica tóxica.

Introduction

Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is a well-known severe cutaneous adverse reaction (SCAR) that belongs to type IV hypersensitivity and is mediated by an immunological effect[1]. It has been determined that this hypersensitivity reaction is a dysregulation of cellular immunity[2] brought on by the production of cytotoxic signals such as granulysin[3], perforin/granzyme B, and Fas/Fas ligand[4], which were triggered by cytotoxic T lymphocytes and natural killer cells. SJS/TEN is a spectrum disorder characterized by widespread epidermal detachment and mucocutaneous involvement[5]. Stevens-Johnson syndrome (SJS), SJS/TEN overlap (SJS-TEN), and toxic epidermal necrolysis (TEN) are represented by different total body surface areas (TBSA) of detached or detachable skin lesions as 10%, 10%-30%, and >30%[6]. SJS, SJS-TEN, and TEN mortality rates were 5-10%, 30%, and 50%, respectively[2-5].

In this case series, we report 4 cases of SJS presented to a tertiary hospital in Mogadishu, Somalia.

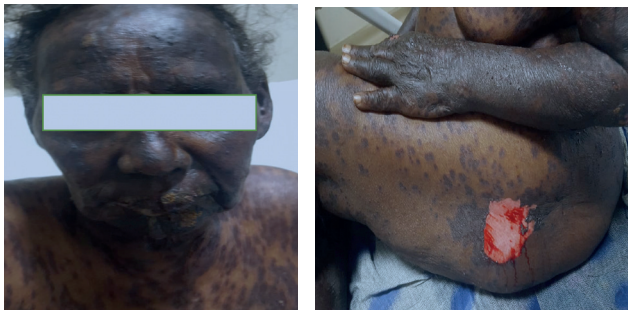
Case Report

We present four cases of Steven John's Syndrome admitted in our ward.

Case 1

71 years of female patient with no history of any chronic disease presented in our emergency department with complain of macular rash extending from the trunk toward the extremities, worsening lip swelling, mouth sores, she gives a history of UTI for which she was treated with Ciprofloxacin for her general practitioner. On examination, she was ill looking old lady with rashes over all her body, the mouth had stomatitis, with ulcers involving lips, tongue, and buccal mucosa and Nikolisky sign was positive.

Figure 1: 71 years old with rashes all over her body, and some ruptured bullous. Consent was taken from the patient to use this photo.

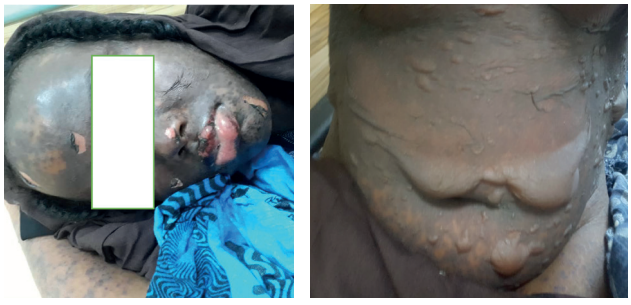


Laboratory investigation showed wbc 6 x1000mm^3 Hg 10.7g/dl Plt 101x1000mm^3, Glucose 147mg/dl Urea 75mg/dl Creatinine 1.59mg/dl Sodium 131mEq/l K 4.76mEq/L CRP 92.5mg/l. She was admitted in the ward, treated with IV fluids, methylprednisolone 90mg for 5 days, daily dressing with normal saline and Bepanthen cream, Oral hygiene care. And patient is discharged after 10 days with good recovery.

Case 2

18 years old female patient presented to our emergency department with complain of bullous formation all over her body for 4 days, initially it started with itching and suddenly the bullous started becomes bigger and rupturing easily. She was treated Co-trimoxazole for tonsillitis few days ago. On examination, tense bullous that contain clear fluids was noted in her torso, and ruptured bullous all over her body. Oral and eye lesions were less pronounced. Nikolisky sign was positive.

Figure 2: 18 years old female, bullous formation and some ruptured bullous on face and lips.

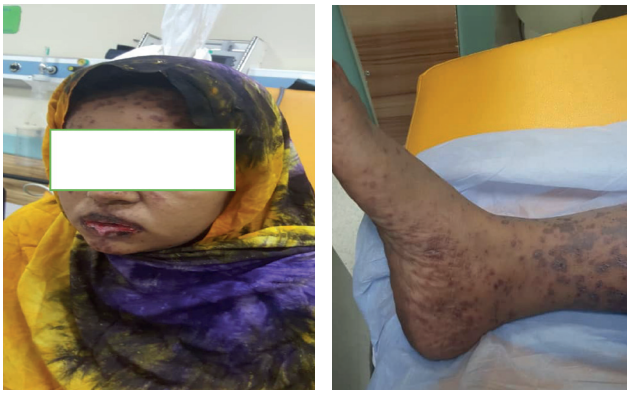


Laboratory research showed wbc 6.15 x1000mm^3 Hg 13.1g/dl Plt 291x1000mm^3, Glucose 112mg/dl Urea 20mg/dl Creatinine 0.58mg/dl Sodium 140mEq/l K 4.25mEq/L CRP 96mg/l.

Case 3

30 years female patient presented to our emergency with rash around her forehead, nose, chest and also lower extremity, and oral ulcers for 5 days. Patient reported she was well before 10 days ago, then she developed generalized body ache, fever, and headache. Then she visited her local doctor and he prescribed Acyclovir tablet, Ciprofloxacin, Artemether injection and Diclofenac tablet. She developed itching and rash after starting these medications. On examination she had hyperpigmented skin, minute blisters around both the eyes and lips, all over the body.

Figure 3: 30 years female presented with rash and oral ulcers.



Laboratory research showed wbc 14.78 x1000mm^3 Hg 9.8g/dl Plt 473x1000mm^3, Glucose 78mg/dl Urea 27mg/dl Creatinine 1.91mg/dl Sodium 144mEq/l K 3.4mEq/L CRP 131.1mg/l.

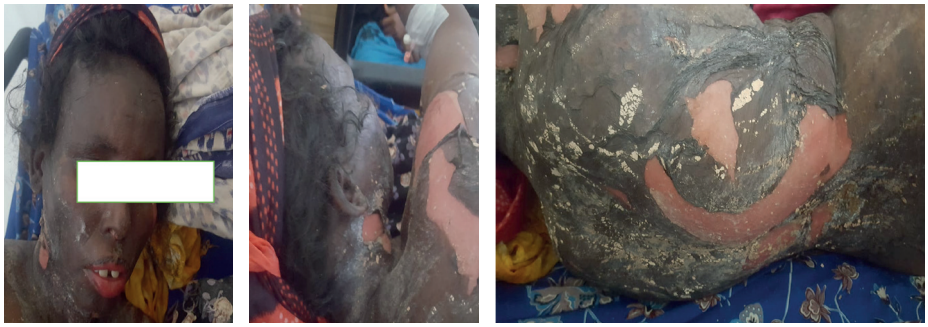
Case 4

40 years old female patient presented to our emergency with widespread erythema, necrosis, and bullous detachment of the epidermis and mucous membranes for 8 days, which she developed her body after 3 days of Ceftriaxone use, which her GP prescribed for urinary tract infection. On examination, she was disoriented, looked dehydrated with sunken eyes, and also had bullous detachment of almost all of her body, Nikolisky sign was positive.

Laboratory investigation showed wbc 1.54 x1000mm^3 Hg 13.3g/dl Plt 546x1000mm^3, Glucose 68mg/dl Urea 73mg/dl Creatinine 1.17mg/dl Sodium 158mEq/l K 4.05mEq/L CRP 295.6mg/l. Ph 6.99 pCO2 44.8 pO2 69 cNa 160 cK4.99 cHCO 7.6

We admitted two of the patients in ICU and the other two in Medical Ward, we used plenty of IV fluids, Steroids 90mg for 5 days, parenteral nutrition, oral hygiene care, dressing with normal saline, and covered with wet sterile gauze, we also used Dexpanthenol cream for open wounds in the evening.

Figure 4: patient presented with severe ruptured bullous all over her body.



One of our two patients admitted in ICU who presented late to the hospital died due to sepsis and multiorgan failure.

We didn't use antibiotics during the patients stay in the hospital and took extra care of the sterilization. After the lesions has improved, we discharged patients with oral steroids and trapped off during their outpatient clinic visits.

Discussion

In this case series, we enrolled 4 cases diagnosed with SJS-TEN overlap, presented to a tertiary hospital in Mogadishu, Somalia. All patients had drug relationship, and major contribution was antibiotics and antivirals. According to Li and Ma, antibiotics and anticonvulsants are the most commonly used single drugs in SJS and traditional Chinese medicines in TEN[7]. Allopurinol, aromatic anticonvulsants, sulfonamide antibiotics, oxicam NSAIDs, and nevirapine have been linked to an increased risk of induced severe cutaneous adverse reaction (SCARs)[5].

SJS begins with a viral-like prodrome lasting one to two weeks, followed by an acute onset of a widespread erythematous, macular rash with blisters or flat typical target lesions on the face, trunk, extremities, oral conjunctiva, and anogenital mucous membranes. The epidermis eventually becomes necrotic and can separate from the dermis, a positive Nikolsky sign[8]. Drugs and infections, most notably trimethoprim-sulfamethoxazole and Mycoplasma, are frequently cited as causes of SJS in both adults and children[8].

In Somalia, a country where there is indiscriminate prescription of antibiotics is available, there is limited reports in the literature for SJS, this, as far as we know, is the only documented case series reported from Somalia.

Conclusion

Stevens-Johnson syndrome is a potentially fatal multiorgan disease with a strong etiologic link to some medications. Physicians must therefore consider Stevens-Johnson syndrome as a potential complication of treatment, especially in a country like Somalia where there is discriminate antibiotic use. Steroids were mostly used as treatment although its controversial yet. SJS is much higher in Somalia and other part of Africa due to availability of Antibiotics without prescription and it's difficult to diagnose and manage, usually patients die before a definite diagnosis is made.

Consent

Written and informed consent was taken from the patient for possible publication of the cases.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Roujeau JC. Immune mechanisms in drug allergy. Allergol Int [Internet]. 2006;55(1):27-33. Available from: http://dx.doi.org/10.2332/allergolint.55.27

2. Su SC, Mockenhaupt M, Wolkenstein P, Dunant A, Le Gouvello S, Chen CB, et al. Interleukin-15 Is Associated with Severity and Mortality in Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis. J Invest Dermatol [Internet]. 2017;137(5):1065-73. Available from: http://dx.doi.org/10.1016/j.jid.2016.11.034

3. Chung WH, Hung SI, Yang JY, Su SC, Huang SP, Wei CY, et al. Granulysin is a key mediator for disseminated keratinocyte death in Stevens-Johnson syndrome and toxic epidermal necrolysis. Nat Med. 2008;14(12):1343-50.

4. Posadas SJ, Padial A, Torres MJ, Mayorga C, Leyva L, Sanchez E, et al. Delayed reactions to drugs show levels of perforin, granzyme B, and Fas-L to be related to disease severity. J Allergy Clin Immunol. 2002;109(1):155-61.

5. Su SC, Hung SI, Fan WL, Dao RL, Chung WH. Severe cutaneous adverse reactions: The pharmacogenomics from research to clinical implementation. Vol. 17, International Journal of Molecular Sciences. 2016.

6. Jean Claude Roujeau RSS. Severe Adverse Cutaneous Reactions to Drugs. N Engl J Med. 1994;332(14):959-60.

7. Li LF, Ma C. Epidemiological study of severe cutaneous adverse drug reactions in a city district of China. Clin Exp Dermatol. 2006;31(5):642-7.

8. Peters J. Toxic epidermal necrolysis. Nurs Times. 2000;96(36):43-4.

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