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Fundació
Patronat Científic

CONCESIÓN DE BECAS Y PREMIOS 2023

Col·legi de Metges
Illes Balears

Becas de Innovación, Becas *Fundació Banc Sabadell* de rotación externa para MIR, Premios de investigación, Premio *Fundació Mutual Mèdica* al mejor proyecto de tesis doctoral, Premio Camilo José Cela de Humanidades Médicas y Certamen de casos clínicos para MIR.

El jurado calificador de los premios y becas convocados por la *Fundació Patronat Científic* del COMIB, reunido el día 22 de noviembre del presente, acordó la concesión de las siguientes becas y premios:

BECAS DE INNOVACIÓN

Dos becas para estancias en centros sanitarios extranjeros, dotadas cada una con 3.000 euros.

· Lizmar Indira Molina Ochoa, médico general, para realizar una estancia formativa de un mes en el *Sleep Care Clinics* en Leicester, Reino Unido.

· Cristina Merino del Villar, facultativa especialista en Psiquiatría en el Hospital Can Misses, para una estancia de dos meses de duración en el *Douglas Mental Health University Institute* en Montreal, Canadá

Dos becas para estancias en hospitales nacionales, dotadas cada una con 1.500 euros.

1. Cristina Montalvo Ávalos, FEA en Cirugía Pediátrica en el Hospital Universitario Son Espases, para una estancia de un mes en el Servicio de Cirugía Pediátrica y Unidad Plástica del Hospital Universitario "La Paz" en Madrid.

2. Aina Ochogavia Seguí, facultativa especialista en Cirugía General y del Aparato Digestivo en el Hospital Universitario Son Espases, para una estancia de un mes en el Servicio de Cirugía Colorrectal del Hospital Marqués de Valdecilla en Santander.

BECAS FUNDACIÓ BANC SABADELL DE ROTACIÓN EXTERNA PARA MIR

Dos becas para estancias en hospitales internacionales, dotadas cada una con 3.000 euros.

1. Paula Gómez Fernández, residente de la especialidad de Hematología y Hemoterapia en el Hospital Universitario Son Espases, para una estancia de dos meses en el Servicio de Hematología del *St. Michael's Hospital, Unity Health Network-University of Toronto*, Canadá.

* A los pocos días de salir publicado el fallo, nos comunica que, por motivos de organización del Servicio de Hematología del hospital, finalmente no pueden aceptar su estancia, por lo que, en consecuencia, rechaza la beca. A este respecto, el jurado decide adjudicar la misma al siguiente clasificado:
Juan Montes González, residente de la especialidad de Oncología Médica en el Hospital Universitario Son Espases, para una estancia de un mes en el Servicio de Oncología y Cáncer de Mama del *The Royal Marsden, NSH Foundation Trust* de Sutton, Londres.

2. Carla Iglesias i Cels, residente de la especialidad de Neurología en el Hospital Universitario Son Espases, para una estancia de dos meses en el Servicio de Neurología y Unidad de Epilepsia en el *London Health Science Center University (LHSC)-Clinical Neurological Sciences, Western University, London-Ontario*, Canadá.

Dos becas para estancias en hospitales nacionales, dotadas cada una con 1.500 euros.

1. Aitana Bernabeu Follana, residente de la especialidad de Neurología en el Hospital Universitario Son Espases, para una estancia de dos meses en el Servicio de Neurología y Unidad Neuromuscular del Hospital Universitario de Donostia en San Sebastián.

2. María Soledad Parra Carrillo, residente de la especialidad de Medicina Familiar y Comunitaria en el Hospital Can Misses, para una estancia de un mes en el Servicio de Radiodiagnóstico y Urgencias del Hospital General Universitario Morales Meseguer en Murcia.

PREMIOS DE INVESTIGACIÓN

Tres premios de 1.500 euros.

"Premio Mateu Orfila"
Al trabajo científico titulado "Evolución de la parada cardíaca extrahospitalaria en Baleares en la última década", presentado por Laura Asunción Bueno López y María Isabel Ceniceros Rozalén.

"Premio Damià Carbó"
Al trabajo científico titulado "Epidemiología del melanoma cutáneo primario en el sector Migjorn en la isla de Mallorca entre los años 2003-2021", presentado por María Cruz Álvarez-Buylla Puente, Jorge Adsuar Mas, Fernando Terrasa Sagristá, Antoni Nadal Nadal, Cristina Nadal Lladó y Alex Llambrich Mañés.

"Premio Metge Matas"
Al artículo *"Validity and acceptance of self vs conventional sampling for the analysis of human papillomavirus and Pap smear"*, cuyas autoras son Maria Josep Gibert Castanyer y María del Carmen Sánchez-Contador Escudero.

PREMIO FUNDACIÓ MUTUAL MÈDICA AL MEJOR PROYECTO DE TESIS DOCTORAL

Un premio dotado con 2.000 euros al proyecto titulado "Método matemático de reconstrucción 3D para la valoración de infiltración tumoral en el cáncer colorrectal", presentado por Sebastián Jerí McFarlane, FEA en Cirugía General y del Aparato Digestivo en el Hospital Universitario Son Espases y en el Hospital Cruz Roja de Palma.

PREMIO CAMILO JOSÉ CELA DE HUMANIDADES MÉDICAS

Un premio dotado con 1.500 euros concedido este año *ex aequo*, con la misma dotación económica, a los trabajos titulados "Conducta sexual y represión inquisitorial", cuyo autor es el Dr. José Tomás Monserrat, Doctor en Medicina, anterior bibliotecario del COMIB y medalla de Oro al Mérito Colegial de la institución; y al trabajo titulado "Las humanidades médicas aplicadas: el paciente como objetivo fundamental", cuyo firmante es el Dr. Juan Manuel Igea Aznar, Doctor en Medicina y especialista en Alergología colegiado en la provincia de Salamanca.

CERTAMEN DE CASOS CLÍNICOS PARA MIR

Tras la exposición de los cinco casos clínicos seleccionados como finalistas, el jurado, reunido el día 27 de noviembre del presente, acordó conceder:

· **El primer premio, dotado de 1.000 euros,** al caso titulado "Ante una bradiarritmia de nueva aparición, ¡máxima precaución!", cuyas autoras son Natalia Mateos Sánchez, María Martín Talavera, Rebeca Sánchez Salmador y Marta López García.

· **El segundo premio, dotado de 500 euros,** al caso titulado "Ataxia cerebelosa como debut de un cáncer diferenciado de tiroides", cuya autora es Camila Soledad Salomón.

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ORIGINAL

Influence of tobacco consumption on the values of different insulin resistance risk scales and non-alcoholic fatty liver disease and hepatic fibrosis scales in 418,343 spanish people

Influencia del consumo de tabaco en los valores de diferentes escalas de riesgo de resistencia a la insulina y de enfermedad de hígado graso no alcohólico y fibrosis hepática en 418.343 españoles

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Summary

Introduction and objectives: Insulin resistance (IR) and non-alcoholic fatty liver disease (NAFLD) are two very frequent pathologies that are responsible for the appearance of different pathological conditions. A multitude of factors are involved in the genesis of both processes. The aim of this study was to assess the influence of various sociodemographic factors such as age, sex, social class, and tobacco consumption on IR and NAFLD.
Methodology: A descriptive, cross-sectional study carried out in 418343 Spanish workers in which the relationship between sociodemographic variables and tobacco consumption with risk scales for IR, NAFLD, and liver fibrosis was assessed.
Results: All the variables analyzed influence the appearance of IR, NAFLD, and liver fibrosis, especially age and sex. Being male, of advanced age, belonging to social class III, and being a smoker increased the risk of IR, NAFLD, and liver fibrosis.
Conclusions: All the sociodemographic variables analyzed, and tobacco use influence the occurrence of IR, NAFLD, and liver fibrosis.

Key words: Insulin resistance, nonalcoholic fatty liver disease, liver fibrosis, tobacco.

Resumen

Introducción y objetivos: La resistencia a la insulina (RI) y la enfermedad del hígado graso no alcohólico (EHGNA) son dos patologías muy frecuentes que son responsables de la aparición de diferentes cuadros patológicos. En la génesis de ambos procesos intervienen multitud de factores. El objetivo de este estudio es valorar la influencia de diversos factores sociodemográficos como la edad, el sexo o la clase social y el consumo de tabaco en la RI y en la EHGNA.
Metodología: Estudio descriptivo y transversal realizado en 418343 trabajadores españoles en el que se valora la relación entre variables sociodemográficas y consumo de tabaco con escalas de riesgo de RI, EHGNA y fibrosis hepática.
Resultados: Todas las variables analizadas influyen en la aparición de RI, EHGNA y fibrosis hepática, especialmente la edad y el sexo. Ser varón, de edad avanzada, pertenecer a la clase social III y ser fumador incrementan el riesgo de RI, EHGNA y fibrosis hepática.
Conclusiones: Todas las variables sociodemográficas analizadas y el consumo de tabaco influyen en la aparición de RI, EHGNA y fibrosis hepática.

Palabras clave: Resistencia a la insulina, enfermedad del hígado graso no alcohólico, fibrosis hepática, tabaco.

Introduction

When there is excess blood glucose, cells are unable to absorb and utilize blood sugar for energy production, resulting in insulin resistance (IR)[1]. This situation increases the risk of developing prediabetes[2] and ultimately type 2[3] diabetes. Diabetes is less likely to develop and blood glucose will remain within a healthy range if the pancreas can produce enough insulin to overcome the low absorption rate[4].

The liver disease that affects people who drink little or no alcohol is known as non-alcoholic fatty liver disease (NAFLD). As the name implies, the main feature of NAFLD is the excessive accumulation of fat in liver cells.

NAFLD is increasing in frequency worldwide, especially in Western countries[5]. Approximately one-quarter of the U.S. population has this form of chronic liver disease[6].

Some patients with NAFLD may develop non-alcoholic steatohepatitis[7], an aggressive form of fatty liver disease characterized by inflammation of the liver that can progress to advanced scarring (cirrhosis)[8] and liver failure[9]. Excessive alcohol consumption causes the same damage.

The aim of this study was to determine how different sociodemographic variables such as age, sex, socioeconomic level, and tobacco consumption affect the prevalence of insulin resistance, NAFLD, and liver fibrosis in a large group of Spanish workers.

Methods

A descriptive, cross-sectional study was conducted in 418,343 Spanish workers from different regions and productive sectors between January 2017 and December 2019. Individuals were selected from among those who underwent regular health examinations in the different participating companies.

The following were the requirements to participate in the study: being between 18 and 69 years old, working for a company involved in the study, not being temporarily incapacitated, and signing the informed consent to participate in the study and use their data for epidemiological purposes.

Figure 1 shows the flow diagram of the study participants.

Table I shows the characteristics of the population, with all the anthropometric, clinical, and analytical variables showing higher or less favorable values in men. The most frequent age was between 30 and 49 years. Most of the employees belonged to social class III and had only a primary education. Approximately every third person in the study smoked.

Figure 1: Flowchart.

421625 workers started the study

729 were under 18 or over 69 years old

656 did not agree to participate

1897 lacked a variable to calculate CVR

418,343 (246,061 men and 172,282 women) finally entered the study
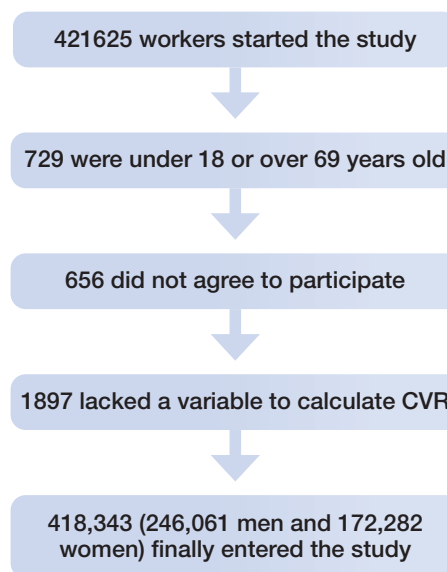
Measurement and data collection

Anthropometric measurements (height, weight, and waist circumference) were taken clinically and analytically by the health professionals of the companies participating in the study after standardization of the measurement techniques.

Weight and height were measured with a SECA model 700 measuring scale. A SECA tape measure was used while the person was standing, feet together, trunk erect, and abdomen relaxed to measure waist circumference. The tape was placed parallel to the floor at the level of the end floating rib.

The person's blood pressure was measured while seated, after a 10-minute rest, with a calibrated OMRON M3 automatic sphygmomanometer. Measurements were taken three times with a period of one minute between them and the mean of the three was recorded. Analytical parameters were obtained after 12 hours of fasting. Total cholesterol, triglycerides, and blood glucose were obtained using automated enzymatic methods. Meanwhile, a precipitation process with dextran sulfate-MgCl2 was used to obtain HDL-c. The Friedewald formula was used to calculate LDL-c indirectly. Each analysis parameter was expressed in milligrams per deciliter.

$$LDL = total\ cholesterol - HDL - triglycerides/5$$

The following insulin resistance risk scales were calculated:
- Triglycerides/HDL-c. A risk ratio greater than 2.4 is considered dangerous[10].
- Triglyceride Glucose Index (TyG). This can be obtained using the following formula: Ln (triglycerides [mg/dL] × glucose [mg/dL]/2). Values above 8.8[11] are considered high.

Derived from the TyG index, there are other indicators that also assess the risk of IR, such as TyG-BMI[12], TyG-waist[13], and TyG-WtHR[14].

- Metabolic score for insulin resistance (METS-IR)[15].
METS-IR = Ln(2 × glucose) + triglycerides × BMI)/(Ln(HDL-c). High values are defined as 50 and above.

The NAFLD risk scales employed in this study were:
- Fatty Liver Index (FLI)[16].

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

Low risk below 30, moderate risk between 30-59, and high risk from 60 onwards.

- Hepatic steatosis index (HSI)[17]
8 × AST/ALT + BMI + 2 if diabetes + 2 if female.
Low risk <30, moderate 30-35.9 and high risk ≥ 36.

- Zhejiang University index (ZJU index)[18]
BMI + Blood glucose (mmol L) + Triglycerides (mmol L) +3 AST/ALT +2 if female.
Low risk < 32, moderate 32-37.9 high risk ≥ 38.

- Fatty liver disease index (FLD)[19]
BMI+ Triglycerides + 3 × (AST/ALT) +2 × Hyperglycemia (present=1; absent=0).
Low risk < 28, moderate 28-36,9 high risk ≥ 37.

- Lipid accumulation product (LAP)[20]
Men: (waist (cm) - 65) x (triglycerides (mMol)).
Women: (waist (cm) - 58) x (triglycerides (mMol)). High risk ≥ 42.7

BARD score[21] is calculated as the liver fibrosis risk scale.

If BMI ≥28 = 1 point, AST/ALT ≥ 0.8 = 2 points, diabetes = 1 point.

BARD score > 2 high risk of liver fibrosis.

Those who had smoked at least one cigarette a day (or its equivalent in other types of consumption) in the previous 30 days or who had quit smoking less than a year before were considered smokers.

The Spanish Society of Epidemiology establishes three categories of social classes according to profession and the proposal of the social determinants group[22]. Directors, managers, sportsmen and artists, university professionals and skilled self-employed workers belong to Class I. Unskilled self-employed workers and intermediate occupations belong to Class II. Unskilled workers make up Class III.

Statistical analysis

The frequency and distribution of categorical variables were calculated, and a descriptive analysis was performed. The mean and standard deviation of quantitative variables are calculated as the variables presented a normal distribution.

For independent samples, the Chi-squared test and Student's t-test were used. When circumstances required it, Fisher's exact statistic was corrected. To perform the multivariate analysis, multinomial logistic regression was used to calculate odds ratios and their 95% confidence intervals. Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) Windows version 28.0 program, which had an accepted statistical significance level of 0.05.

Ethical considerations and/or aspects

The research team always undertook to comply with the standards of research ethics that govern health sciences, established both nationally and internationally in the Declaration of Helsinki, giving special importance to the anonymization of the participants and the confidentiality of the data obtained. The study was approved with indicator IB 4383/20 by the Ethics and Research Committee of the Balearic Islands (CEI-IB). As participation in the study was voluntary, participants gave both oral and written consent after receiving sufficient information regarding the nature of the study. To achieve this, they were given an information sheet with an explanation of the aim of the study, as well as an informed consent form.

The study data were identified using a code, and only the person responsible for the study can connect them to the participants. The identity of the participants will not be disclosed in the results of this study. The researchers will not disclose any information that identifies them. In any event, the research team is committed to complying with Organic Law 3/2018, of December 5, on the protection of personal data and guarantee of digital rights, ensuring that study participants have the right to access, rectify, cancel, and oppose the data collected.

Results

As shown in **table I**, more than 58% of the study participants were men. The average age was 40 years, with most people between 30 and 49 years of age. About 75% of the population belonged to social class III and about 33% smoked. The analytical and clinical variables were more advantageous for women.

Table II shows the mean values of the different risk scales for insulin resistance, NAFLD, and liver fibrosis according to smoking in both sexes. It can be observed that all these mean values were higher in the group of smokers in both men and women, with the differences found being statistically significant. In general, the mean values were higher in men.

Table III shows the prevalence of elevated values for all the risk scales (insulin resistance, NAFLD, and liver fibrosis), revealing the same trend seen for the mean values, i.e., greater prevalence among smokers and in general higher figures in men. All the differences observed were statistically significant.

Table IV shows the results of the multivariate analysis using multinomial logistic regression. The reference variables were female sex, aged under 30 years, social class I, and non-smokers. Odds ratios (OR) with 95% confidence intervals were calculated and it was found that all the sociodemographic variables analyzed, and tobacco consumption increased the risk of presenting high values in the different risk scales, for insulin resistance, NAFLD, and liver fibrosis. The highest OR values were found for age and sex. Tobacco consumption increased the risk, but only slightly.

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
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
Glycemia	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	29.7	27.6	28.4	
40-49 years	29.6	30.0	29.9	
50-59 years	16.8	19.7	18.5	
≥60 years	3.2	3.9	3.6	
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	
Non-smokers	67.2	66.6	66.9	<0.0001
Smokers	32.8	33.4	33.2	

Table II: Mean values of the insulin resistance, non-alcoholic fatty liver disease, and liver fibrosis scales according to smoking by sex.

	Men			Women		
	Non-smokers n=163920 Mean (SD)	Smokers n=82141 Mean (SD)	p-value	Non-smokers n=115727 Mean (SD)	Smokers n=56555 Mean (SD)	p-value
TG/HDL	2.6 (2.1)	2.7 (2.2)	<0.0001	1.6 (1.0)	1.7 (1.0)	0.01
TyG index	8.5 (0.6)	8.7 (0.6)	0.017	8.2 (0.5)	8.4 (0.5)	0.047
METS-IR	39.1 (8.6)	39.3 (8.5)	0.012	35.0 (8.4)	35.5 (8.4)	0.001
FLI	37.6 (27.5)	37.9 (27.5)	0.001	18.1 (21.8)	18.4 (21.8)	0.019
HSI	36.7 (6.9)	36.9 (6.7)	0.013	36.2 (6.8)	36.8(6.9)	0.001
ZJU	37.1 (5.7)	37.5 (5.7)	0.017	36.8 (6.1)	37.4 (6.2)	0.003
FLD	32.0 (5.3)	32.3 (5.4)	0.011	29.9 (5.9)	30.2 (5.9)	0.001
LAP	31.7 (32.9)	32.4 (33.7)	<0.0001	18.0 (18.4)	18.4 (18.2)	0.018
BARD	1.7 (1.1)	1.8 (1.1)	0.027	1.9 (1.0)	2.0 (1.0)	0.038

TG/HDL triglycerides/high density lipoproteins; TyG triglyceride/glucose index; METS-IR metabolic score for insulin resistance; FLI Fatty liver index; HSI hepatic steatosis index; ZJU Zhejiang university index; FLD fatty liver disease; LAP lipid accumulation product.

Table III: Prevalence of high values of insulin resistance and non-alcoholic fatty liver disease scales according to tobacco use by sex.

	Men			Women		
	Non-smokers n=163920 %	Smokers n=82141 %	p-value	Non-smokers n=115727 %	Smokers n=56555 %	p-value
High TG/HDL	25.0	25.3	0.001	17.8	18.2	0.018
High TyG index	27.3	27.6	0.017	12.4	12.7	0.011
High METS-IR	11.3	11.7	0.001	6.2	6.5	0.001
High FLI	24.1	24.5	0.001	7.7	7.9	0.012
High HSI	49.3	49.9	0.001	43.9	45.1	<0.0001
High ZJU	38.2	38.7	0.013	34.8	35.8	<0.0001
High FLD	60.9	61.5	<0.0001	44.5	44.9	0.013
High LAP	36.4	36.8	0.015	24.5	24.9	0.028
High BARD	65.1	65.3	0.010	77.0	77.5	0.001

TG/HDL triglycerides/high density lipoproteins; TyG triglyceride/glucose index; METS-IR metabolic score for insulin resistance; FLI Fatty liver index; HSI hepatic steatosis index; ZJU Zhejiang university index; FLD fatty liver disease; LAP lipid accumulation product.

Table IV: Multinomial logistic regression.

	High TG/HDL OR (95% CI)	High TyG OR (95% CI)	High METS-IR OR (95% CI)	High FLI OR (95% CI)	High HSI OR (95% CI)	High ZJU OR (95% CI)	High FLD OR (95% CI)	High LAP OR (95% CI)	High BARD OR (95% CI)
18-29 years	1	1	1	1	1	1	1	1	1
30-39 years	1.26 (1.21-1.30)	1.31 (1.27-1.36)	1.15 (1.10-1.21)	1.08 (1.05-1.12)	1.17 (1.07-1.27)	1.25 (1.15-1.36)	1.18 (1.08-1.29)	1.04 (1.00-1.07)	1.19 (1.08-1.32)
40-49 years	1.84 (1.78-1.91)	2.04 (1.97-2.11)	1.54 (1.47-1.61)	1.20 (1.15-1.26)	1.45 (1.33-1.57)	1.63 (1.50-1.77)	1.33 (1.22-1.45)	1.28 (1.24-1.33)	1.34 (1.21-1.48)
50-59 years	2.93 (2.83-3.04)	3.40 (3.28-3.53)	2.36 (2.25-2.48)	1.85 (1.77-1.93)	1.96 (1.80-2.13)	2.38 (2.18-2.58)	1.72 (1.58-1.88)	1.84 (1.77-1.90)	1.46 (1.33-1.61)
60-69 years	5.60 (5.38-5.83)	6.98 (6.69-7.27)	4.07 (3.86-4.30)	3.41 (3.24-3.58)	3.06 (2.80-3.34)	3.82 (3.49-4.17)	2.49 (2.28-2.73)	3.07 (2.96-3.18)	1.50 (1.36-1.65)
Female	1	1	1	1	1	1	1	1	1
Male	1.47 (1.45-1.50)	2.57 (2.53-2.62)	1.76 (1.72-1.80)	3.70 (3.62-3.78)	1.16 (1.13-1.20)	1.07 (1.03-1.10)	1.94 (1.89-2.00)	1.72 (1.70-1.74)	0.54 (0.53-0.56)
Social class I	1	1	1	1	1	1	1	1	1
Social class II	1.19 (1.17-1.22)	1.22 (1.19-1.24)	1.49 (1.44-1.54)	1.24 (1.19-1.30)	1.11 (1.07-1.16)	1.22 (1.17-1.27)	1.06 (1.03-1.10)	1.11 (1.09-1.13)	1.15 (1.10-1.21)
Social class III	1.39 (1.34-1.44)	1.42 (1.35-1.47)	1.78 (1.68-1.88)	1.26 (1.23-1.29)	1.37 (1.29-1.46)	1.51 (1.42-1.61)	1.07 (1.01-1.13)	1.26 (1.22-1.30)	1.13 (1.08-1.18)
Non-smokers	1	1	1	1	1	1	1	1	1
Smokers	1.03 (1.01-1.05)	1.03 (1.00-1.04)	1.02 (1.00-1.04)	1.06 (1.03-1.09)	1.02 (1.00-1.04)	1.11 (1.08-1.14)	1.07 (1.05-1.11)	1.01 (1.00-1.02)	1.02 (1.00-1.06)

Discussion

Our study shows an increase in the risk of presenting IR, NAFLD, and liver fibrosis in men, with increasing age, especially in people with a low socioeconomic level (social class III). Increased risk was also seen among smokers.

A study based on data from the National Health and Nutrition Examination Survey (NHANES) (2009-2018)[23] conducted in more than 12000 US adults showed that the prevalence of insulin resistance, using TyG for diagnosis, ranged from 13.9% to 22.5%, figures somewhat lower than those obtained in our sample. A meta-analysis performed in Southeast Asia[24] that included 12 studies and 2198 individuals between 2016-2021 estimated the prevalence of insulin resistance in that region at 44.3%, figures well above those obtained by us. Data from Spain[25] estimate that the prevalence of insulin resistance in men is 30%, while in women it is 20% to 22%. This figure is directly related to the increase in abdominal perimeter as an indicator of central obesity, affecting 50% of people with an abdominal perimeter greater than 100 cm. The overall prevalence of insulin resistance in the most developed countries has been estimated at 25-35%[26].

Like us, a systematic review showed a lower prevalence of insulin resistance among women, associating it with the protective effect of estrogens[27]. This protective effect of estrogens has also been related to the lower prevalence of NAFLD in women[28,29].

The relationship found in our investigation between the appearance of insulin resistance and belonging to the most disadvantaged socioeconomic levels was also shown in a Colombian study carried out in children[30]. A study of 1081 Japanese students aged 18 to 22 years[31] found that insulin resistance was more prevalent in women belonging to lower socioeconomic levels. A study conducted in Iran gave similar results[32].

A critical review of the literature conducted in India[33] highlighted the effect of tobacco consumption on insulin resistance indicating that exposure to tobacco initiates immune deterioration related to free radicals, DNA damage, and inflammation, which will favor insulin resistance. Some authors[34,35] even speak of a threat to the health of people living in the homes of smokers, since smoke toxins deposited on surfaces can cause insulin resistance.

A study carried out by our group in 219477 workers[36] that also assessed the variables that influenced the appearance of NAFLD showed that advanced age, male sex, and low socioeconomic status increased the risk of presenting NAFLD and liver fibrosis by applying different scales. Smoking, however, demonstrated no influence.

The results of a systematic review and meta-analysis conducted in 2021[37] that included more than one million people concluded that the worldwide prevalence of NAFLD is considerably higher than previously estimated (overall 37.8%: 39.7% in men and 25.6% in women), and continues to increase at an alarming rate; these prevalence data are lower than those found in our study. That study showed that the incidence and prevalence of NAFLD is significantly higher among men than among women, data that coincide with those presented in this study.

The results of a cross-sectional analysis of the National Health and Nutrition Examination Surveys in the United States[38], 2017-2018, which included 3589 participants revealed that the risk of presenting NAFLD was lower among people with higher educational levels and those belonging to more advantaged socioeconomic groups, data similar to those obtained in our study.

The effect of alcohol consumption on the liver has been extensively studied, although this is not the case with smoking. According to one systematic review[39], smoking is both a risk factor for liver fibrosis and a contributing factor to liver carcinogenesis. Smoking-related fibrosis has been observed in patients with NAFLD and other liver pathologies. Excessive smoking causes systemic inflammation, oxidative stress, insulin resistance, and tissue hypoxia, as well as free radical damage. The more than 4000 chemicals in tobacco – including nitrosamines, aromatic hydrocarbons, nicotine, and other alkaloids – have systemic effects on patients in addition to damaging the liver.

As strengths of the study, it is worth highlighting the enormous sample size, more than 418,000 people, which provides great strength to the results obtained; and the large number of risk scales used to assess insulin resistance as well as NAFLD and liver fibrosis.

The main limitation is that no objective techniques were used to assess insulin resistance, NAFLD, and liver fibrosis.

Conclusion

All sociodemographic variables (age, sex, and social class) influence the increased risk of presenting insulin resistance, NAFLD, and liver fibrosis, especially age and sex.

Tobacco use also increases these risks, although to a lesser extent.

The profile of the person at risk for IR, NAFLD, and liver fibrosis would be an older male belonging to social class III and a smoker.

Conflict of Interest

The authors declared that there is no conflict of interest.

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ORIGINAL

Cardiometabolic risk assessment in 28300 spanish waiters

Valoración del riesgo cardiometabólico en 28300 camareros españoles

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Summary

Introduction and objectives: Cardiometabolic pathologies are highly prevalent and will cause high morbimortality throughout the world. These pathologies are multifactorial and have been related in some cases to sociodemographic factors. The aim of this study is to assess the cardiometabolic risk in a group of workers such as waiters who have been little or not studied at all.
Methods: Descriptive, cross-sectional study of 28300 Spanish waiters in which different scales of cardiometabolic risk such as obesity, insulin resistance, nonalcoholic fatty liver disease, metabolic syndrome, atherogenic indices or cardiovascular risk scales such as SCORE, REGICOR or vascular age were assessed.
Results: There was a high prevalence of high values for the different cardiometabolic risk scales analyzed, especially in men, this being particularly relevant since the mean age of the participants was low, 36 years in men and 33.9 years in women.
Conclusions: The waiters, who belong to the group of manual workers, present a high prevalence of cardiometabolic risk scales such as obesity, insulin resistance, nonalcoholic fatty liver disease or metabolic syndrome.

Key words: Cardiometabolic risk, manual workers, metabolic syndrome, insulin resistance, obesity, nonalcoholic fatty liver disease.

Resumen

Introducción y objetivos. Las patologías cardiometabólicas son altamente prevalentes y van a ocasionar una elevada morbimortalidad en todo el mundo. Este conjunto de patologías son multifactoriales y han sido relacionadas en algunos casos con factores sociodemográficos. El objetivo de este estudio es valorar el riesgo cardiometabólico en un colectivo de trabajadores como son los camareros que han sido poco o nada estudiados.
Material y métodos. Estudio descriptivo y transversal en 28300 camareros españoles en los que se valoran diferentes escalas de riesgo cardiometabólico como obesidad, resistencia a la insulina, hígado graso no alcohólico, síndrome metabólico, índices aterogénicos o escalas de riesgo cardiovascular como SCORE, REGICOR o edad vascular.
Resultados. Existe una alta prevalencia de valores altos de las diferentes escalas de riesgo cardiometabólico analizadas, especialmente en los varones, siendo este dato especialmente relevante ya que la edad media de los participantes era baja, 36 años en los hombres y 33,9 años en las mujeres.
Conclusiones. Los camareros, que pertenecen al grupo de trabajadores manuales presentan una elevada prevalencia de escalas de riesgo cardiometabólico como obesidad, resistencia a la insulina, hígado graso no alcohólico o síndrome metabólico.

Palabras clave: Riesgo cardiometabólico, trabajadores manuales, síndrome metabólico, resistencia a la insulina, obesidad, hígado graso no alcohólico.

Introduction

The World Health Organization (WHO) states that cardiovascular diseases (CVD) are the leading cause of morbidity and mortality worldwide. They accounted for 27.9% of deaths in Spain in 2019[1], making them the leading cause of death in our country. Pathophysiological and biochemical factors, together with environmental factors, contribute to the appearance and development of CVD[2], and its etiology is complex and multifactorial. One of the great challenges for public health is the inequality in health linked to social class among these factors[3]. Thus, members of the most disadvantaged social classes have worse health indicators in terms of lifestyles, morbidity and mortality, and access to medical services[4]. Indicators of socioeconomic position such as income, educational level, employment status and type of employment contribute to these disparities[5]. Non-manual workers who are generally more skilled and manual workers who are generally less skilled have differences in cardiovascular mortality rates. Both men and women who work manually have a higher mortality rate[5].

The occupational diseases of hospitality workers, including waiters, have been studied in depth, most of which belong to the field of musculoskeletal pathologies, among which we would highlight carpal tunnel syndrome[6-8] and epicondylitis[9]. Dermatitis[10] is also very prevalent in this group. However, there are few studies that assess the prevalence of cardiometabolic disorders in hospitality workers and specifically in waiters, and for this reason the aim of this study is to assess the level of cardiometabolic risk in a large group of Spanish waiters by applying a large number of risk scales.

Methods

Between January 2019 and December 2019, a descriptive, cross-sectional study was conducted on 28300 waiters from different regions of Spain (Balearic Islands, Andalusia, Canary Islands, Valencian Community, Catalonia, Madrid, Castilla La Mancha, Castilla Leon and Basque Country). The waiters in the study were chosen from among those who attended medical examinations in the various participating companies.

A series of inclusion criteria were established:

- Age between 18 and 69 years.
- Working in one of the companies participating in the study.
- Agreeing to participate and providing the data to carry out the study.

The flow diagram is shown in **figure 1**.

Figure 1: Flow chart of the study participants.

People start the study
n= 29.285
(14.114 women 15.171 men)

People who were excluded
n= 985
- 97 did not accept to participate
- 888 did not have any variable to calculate cardiometabolic scales

People included in the study
n= 28.300
(13.624 women and 14.676 men)
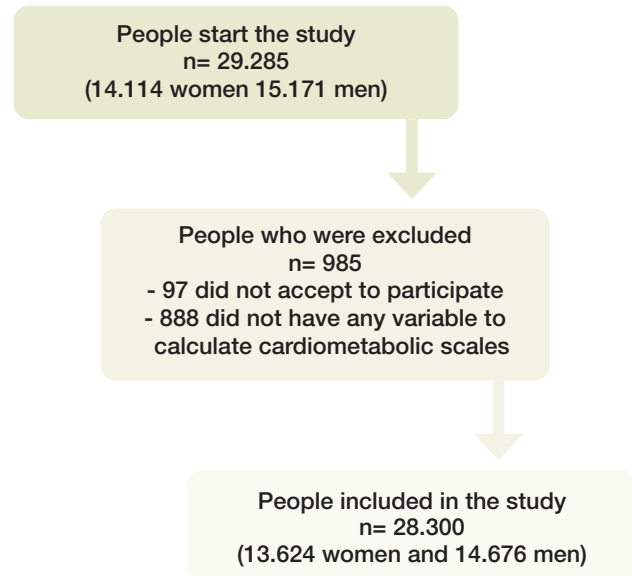
Determination of variables

The anthropometric, analytical and clinical variables required to calculate the various cardiometabolic risk scales were determined by the health professionals of the different participating companies. The measurement techniques were standardized to reduce potential biases in obtaining the variables.

When the person was in an upright position and with the abdomen relaxed. Height and weight were measured using an approved SECA model scale-measuring scale. In this position, the abdominal waist circumference was determined using a tape measure placed parallel to the ground at the level of the last rib.

The OMROM-M3 sphygmomanometer was used to measure blood pressure. Three measurements were taken with an interval of one minute between each and the mean of the three was obtained after ten minutes of rest.

After a fast of no less than twelve hours, different methods were used to determine the analytical variables, including enzymatic techniques for blood glucose, triglycerides and total cholesterol, as well as precipitation techniques for HDL cholesterol. The Friedewald formula was used to calculate LDL-cholesterol, which is valid for triglyceride values up to 400. All analytical parameters were expressed in milligrams per deciliter.

The following were considered altered values: 200 mg/dL cholesterol, 130 mg/dL LDL and 150 mg/dL triglycerides, or if they were under treatment for any of these analytical alterations.

The recommendations of the American Diabetes Association[11] were used to classify blood glucose levels. Patients with a previous diagnosis, those who had a

blood glucose greater than 125 mg/dL or had an HbA1c of at least 6.5% or were receiving treatment to reduce blood glucose were classified as diabetic.

Weight (in kg) was divided by height squared in meters to calculate BMI. Obese was considered obese at 30 kg/m² and above.

Scales for calculating the percentage of body fat:
- CUN BAE (Estimador de Adiposidad Corporal de la Clínica Universitaria de Navarra)[12].

-44.988 + (0.503 × age) + (10.689 × sex) + (3.172 × BMI) - (0.026 × BMI²) + (0.181 × BMI × sex) - (0.02 × BMI × age) - (0.005 × BMI² × sex) + (0.00021 × BMI² × age). Male =0 Female =1.

- ECORE-BF (Equation Córdoba for Estimation of Body Fat)[13]

97.102+0.123 (age) +11.9 (sex) +35.959 (LnBMI) Man =0 Woman =1.

- Palafolls formula[14]

Man =[(BMI/waist) ×10] +BMI.
Woman =[(BMI/waist) ×10] +BMI+10.

- Fórmula Deuremberg[15]

1.2×(BMI) +0.23×(age) −10.8×(sex) −5.4 Man =0 Woman =1.

- Relative fat mass (RFM)[16]

Women: 76- (20 × (height/waist)) Men: 64- (20 × (height /waist)).

Other indicators related to overweight and obesity:
- Visceral adiposity index (VAI)[17]
  It has different formulas for women and men.
  Men: (Waist/(39,68 + (1,88 × BMI)) x (Triglycerides/1,03) x (1,31/HDL)
  Women: (Waist/(36,58 + (1,89 x BMI)) x (Triglycerides/0,81) x (1,52/HDL)

- Body roundness index (BRI)[18]
  BRI=364.2–365.5 × √1-[(waist/ (2π) 2)/(0.5 × height)²].

- Body Surface Index (BSI)[19]. BSA is calculated by applying the DuBois formula, where weight is measured in kg and height in cm.
  BSA = weight^{0,425} x height^{0,725} x 0,0007184
  BSI = weight/√BSA

- Conicity index[20]
  CI = (Waist/0,109) x 1/√ weight/height

- Body shape index (ABSI)[21]
  ABSI = Waist/BMI^{2/3} x height^{1/2}

- Normalized weight-adjusted index (NWAI)[22]
  NWAI = (weight /10) - (10 x height) + 10
  Weight in kg and height in meters.

Other indicators related to cardiovascular risk:
- Triglyceride glucose index[23], Triglyceride glucose index-BMI[24], Triglyceride glucose index-waist[25]

TyGindex = LN (triglycerides [mg/dl] × glycaemia [mg/dl] /2) .
TyGindex – BMI = TyGindex × BMI
TyGindex – waist = TyGindex × waist

- Waist triglyceride index[26]
  waist (cm) × triglycerides(mmol)

- Cardiometabolic index[27].
  Waist/height × triglycerides/HDL

Nonalcoholic fatty liver disease risk scales:
- Fatty liver index[28].

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}) x 100

- Hepatic steatosis index (HSI)[29]
  HSI = 8 × AST/ALT + BMI (+ 2 if 2 diabetes and + 2 if woman)

- Zhejiang University index (ZJU)[30]
  BMI + Glycaemia (mmol L) +Triglycerides(mmol L) +3 AST/ALT +2 if woman

- Fatty liver disease index (FLD)[31]
  BMI+ triglycerides +3 × (AST/ALT) +2 ×Hiperglucemia (presence=1; absence=0)
  If BMI ≥28 = 1 poit, AST/ALT ≥ 0,8 = 2 points, diabetes mellitus type 2 = 1 point. Cutt off high risk 2 points.
- Men= (waist (cm) – 65) × (triglycerides (mMol))
- Women: (waist (cm) – 58) × (triglycerides (mMol))
- Lipid accumulation product (LAP)[32].
  Men= (waist (cm) - 65) × (triglycerides (mMol)).
  Women: (waist (cm) - 58) × (triglycerides (mMol))

Atherogenic indexes[33].
- Total cholesterol/HDL (high values > 5 in men and > 4,5 in women).
- LDL/HDL (high values >3)
- logTriglycerides/HDL (high values >3)
- Total cholesterol -HDL (high values >130)

Metabolic syndrome
- The metabolic syndrome was determined using three models[34]:

(a) NCEP ATP III (National Cholesterol Educational Program Adult Treatment Panel III) considers metabolic syndrome when there are three or more of the following factors: blood pressure greater than 130/85 mmHg; triglycerides greater than 150 mg/dl or specific treatment for this lipid disorder; HDL low and glycaemia ≥ 100 mg/dl or specific treatment for this glycemic disorder.

b) The International Diabetes Federation (IDF) model establishes as essential a waist circumference greater

than 80 centimeters in women and greater than 94 centimeters in men, in addition to two of the other factors mentioned above for ATP III (triglycerides, HDL, blood pressure and glycemia).

c) The JIS (Joint Interim Statement) model, which follows the same criteria as the NCEP ATP III but with waist circumference cut-off points of 80 cm for women and 94 cm for men.

Atherogenic dyslipidemia[35] is characterized by high triglyceride concentrations (>150 mg/dL) and low HDL; if it also presents high LDL values, it is considered a lipid triad[36].

Cardiovascular risk scales:

The REGICOR scale[37], which is an adaptation of the Framingham scale to the Spanish population, evaluates the risk of suffering a cardiovascular event during a 10-year period. It can be used between the ages of 35 and 74 years. The risk is considered to be moderate from 5% and high from 10%.

We calculated the SCORE2[38] (Systematic Coronary Risk Evaluation) scale, which measures the risk of suffering a fatal stroke within 10 years.

ERICE (Spanish Cardiovascular Risk Equation) is based on 7 Spanish population-based cohort studies[39]. It estimates the risk of suffering a fatal or non-fatal cerebrovascular event over a 10-year period. The tables are used in persons between 30 and 80 years of age. To calculate the risk, age, sex, smoking, diabetes, systolic blood pressure, antihypertensive treatment and total cholesterol are assessed. To classify the level of cardiovascular risk with the ERICE tables, the cut-off points recommended by the group responsible for the study were used: moderate risk was considered

moderate if it exceeded 5%, moderate-high if it was between 15%-19%, high if it was between 20% and 39%, and very high if it exceeded 39%.

Using the Framingham model[40] to calculate vascular age. Age, sex, HDL-c, total cholesterol, systolic blood pressure values, antihypertensive treatment, smoking and diabetes are the data we need to calculate it. It can be calculated from the age of 30 years.

The use of the SCORE[41] model to calculate vascular age. Age, sex, systolic blood pressure, smoking and total cholesterol are used to calculate it. It can be calculated in people aged 40 to 65 years, like the scale from which it is derived.

Avoidable years of life lost (ALLY)[42], which can be defined as the difference between vascular and biological age, is an interesting concept that applies to both vascular ages.

Results

Table I shows the characteristics of the sample. The mean age was approximately 35 years, the majority group being between 18 and 39 years of age. More than 34% were smokers (slightly higher in women). All the variables presented more favorable values in women.

Table II shows the mean values of the different cardiometabolic risk scales analyzed, separated by sex. Both the scales that assess overweight-obesity (except those that estimate body fat) and those that determine the risk of insulin resistance, nonalcoholic fatty liver disease, cardiovascular risk or atherogenic risk almost always present significantly higher values in male waiters. In all cases except for the liver fibrosis risk scale (BARD scoring), the differences observed between the sexes were statistically significant.

Table I: Characteristics of the population.

	Men n=14.676	Women n=13.624	
	Mean (SD)	Mean (SD)	p-value
Age (years)	36.0 (12.1)	33.9 (10.5)	<0.0001
Height (cm)	174.7 (6.9)	162.4 (6.3)	<0.0001
Weight (kg)	76.7 (13.1)	62.2 (12.0)	<0.0001
Waist circumference (cm)	83.7 (10.5)	72.7 (8.9)	<0.0001
Systolic blood pressure (mmHg)	125.6 (14.6)	114.7 (14.0)	<0.0001
Diastolic blood pressure (mmHg)	75.4 (10.7)	70.2 (9.7)	<0.0001
Total cholesterol (mg/dl)	183.6 (40.2)	181.3 (34.7)	<0.0001
HDL-cholesterol (mg/dl)	51.5 (7.9)	57.9 (7.4)	<0.0001
LDL-cholesterol (mg/dl)	108.3 (37.1)	107.0 (34.4)	0.003
Triglycerides (mg/dl)	122.1 (94.1)	82.0 (40.2)	<0.0001
Glycaemia (mg/dl)	89.4 (20.1)	84.5 (12.9)	<0.0001
ALT (U/L)	29.0 (22.0)	19.9 (15.7)	<0.0001
AST (U/L)	24.3 (11.4)	17.7 (5.9)	<0.0001
GGT (U/L)	32.1 (34.2)	19.4 (20.2)	<0.0001
Creatinine (mg/dl)	0.9 (0.2)	0.7 (0.1)	<0.0001
	%	%	p-value
18-29 years	36.7	40.7	<0.0001
30-39 years	26.3	31.3	
40-49 years	19.7	17.9	
50-59 years	14.4	8.9	
60-69 years	2.9	1.2	
Non-smokers	66.0	65.1	0.140
Smokers	34.0	34.9	

Table II: Differences in mean values of the scales related with cardiovascular risk by sex using the T-Student test.

	Men n=14.676	Women n=13.624	
	Mean (SD)	Mean (SD)	p-value
Waist to height ratio (WtHR)	0.48 (0.06)	0.45 (0.05)	<0.0001
Body mass index (BMI)	25.1 (4.0)	23.6 (4.3)	<0.0001
CUN BAE	22.6 (6.7)	32.0 (6.7)	<0.0001
ECORE-BF	22.8 (6.3)	32.0 (6.6)	<0.0001
Relative fat mass	21.7 (5.1)	30.7 (4.9)	<0.0001
Palafolls formula	28.1 (4.2)	36.8 (4.6)	<0.0001
Deurenberg formula	22.2 (6.4)	30.7 (6.2)	<0.0001
Body fat index	20.5 (7.5)	25.5 (6.5)	<0.0001
Body surface index	55.2 (7.1)	48.0 (7.0)	<0.0001
Normalized weight adjusted index	0.20 (1.2)	-0.02 (1.16)	<0.0001
Body roundness index	3.0 (1.1)	2.5 (0.9)	<0.0001
Body shape index	0.074 (0.006)	0.070 (0.006)	<0.0001
Visceral adiposity index	6.8 (6.2)	2.4 (1.3)	<0.0001
Conicity index	1.2 0.1	1.1 0.1	<0.0001
METS-VF	6.0 (0.8)	5.2 (0.8)	<0.0001
Waist triglyceride index	117.3 94.2	68.0 37.1	<0.0001
Waist weight index	9.6 (0.8)	9.3 (0.7)	<0.0001
nº factors metabolic syndrome NCEP ATPIII	1.0 (1.1)	0.6 (0.9)	<0.0001
nº factors metabolic syndrome JIS	1.4 (1.2)	0.6 (0.9)	<0.0001
Total cholesterol/HDL-c	3.7 (1.1)	3.2 (0.8)	<0.0001
Triglycerides/HDL-c	2.5 (2.2)	1.5 (0.8)	<0.0001
LDL-c/HDL-c	2.2 (0.9)	1.9 (0.7)	<0.0001
Total cholesterol-HDL-c	132.2 (42.3)	123.4 (36.4)	<0.0001
Cardiometabolic index	1.2 (1.1)	0.7 (0.4)	<0.0001
Triglyceride glucose index (TyG index)	8.4 (0.6)	8.0 (0.4)	<0.0001
TyG index-BMI	212.2 (42.4)	190.2 (39.9)	<0.0001
TyG index-waist circumference	705.7 (113.7)	585.6 (85.7)	<0.0001
TyG index-WtHR	4.0 (0.6)	3.6 (0.5)	<0.0001
METS-IR	36.5 (7.6)	32.2 (6.9)	<0.0001
ALLY vascular age SCORE	7.5 (6.8)	3.9 (4.9)	<0.0001
SCORE scale	1.8 (2.2)	0.4 (0.8)	<0.0001
ALLY vascular age Framingham	5.6 (9.9)	-1.0 (10.3)	<0.0001
REGICOR scale	3.3 (2.2)	2.8 (2.2)	<0.0001
ERICE scale	4.2 (5.0)	2.1 (2.7)	<0.0001
Fatty liver index	30.1 (25.2)	12.3 (16.5)	<0.0001
Hepatic steatosis index	35.8 (5.9)	34.5 (5.9)	<0.0001
Zhejiang University index	36.3 (5.1)	34.9 (5.2)	<0.0001
Fatty liver disease	31.2 (4.7)	28.2 (5.0)	<0.0001
BARD scoring	1.6 (1.1)	1.7 (0.9)	0.110
Lipid accumulation product	27.7 (30.2)	14.3 (13.8)	<0.0001

CUN BAE Clinica Universitaria Navarra Body Adiposity Estimator; ECORE-BF Equation Córdoba for Estimation of Body Fat; METS-VF Metabolic score- visceral fat. ALLY Avoidable lost life years. SCORE Systematic COronary Risk Evaluation. REGICOR REgistre GIroni del COR. HDL-c High density lipoprotein cholesterol. LDL Low density lipoprotein cholesterol. METS-IR Metabolic score for Insulin Resistance. TyG Triglyceride glucose index

Table III, which evaluates the prevalence of elevated values of the different cardiometabolic risk scales in both sexes, shows a situation similar to that already mentioned with the mean values, that is, there is a higher prevalence in men. In this case, all the differences observed were statistically significant.

Table IV, which presents the results of the multinomial logistic regression analysis, shows that the variable that most increases the risk of presenting elevated values of the cardiometabolic scales is age, followed by sex (male), whereas smoking does not affect most of the scales. The highest odds ratios were found for SCORE, Deuremberg and diabesity in the case of age and for SCORE, METS-VF and hypertriglyceridemic waist for the male sex.

Discussion

The prevalence of elevated values of cardiometabolic risk scales in waiters can be considered overall as moderate in men and moderate-low in women. We

would highlight the high prevalence of high values of the scales that estimate body fat, dyslipidemia, atherogenic and cardiovascular risk, especially considering that the mean age of the population is low.

We have not found in the literature consulted references to studies analyzing cardiometabolic risk in hospitality workers, nor specifically in waiters, for this reason we are going to compare our results with similar work groups at a socioeconomic level, that is, with people of lower socioeconomic levels.

In a study carried out in 5,370 Spanish farmers (3,695 men and 1,675 women) with an average age of around[41] years, different scales of cardiometabolic risk were analyzed. A high percentage of the farmers were found to have obesity, hypertension, hypertriglyceridemia, hypercholesterolemia, metabolic syndrome, nonalcoholic fatty liver disease, and elevated REGICOR and SCORE values, data similar to those found by us in this group of waiters[43]. This same group conducted a study in 1094 male Bolivian miners and found similar risk levels[44].

Table III: Differences in the prevalence of altered values of different scales related with cardiovascular risk by sex using the chi-square test.

	Men n=14.676	Women n=13.624	
	%	%	p-value
Waist to height ratio > 0.50	33.1	12.3	<0.0001
Body mass index obesity	11.1	8.2	<0.0001
CUN BAE obesity	35.9	29.7	<0.0001
ECORE-BF obesity	36.4	29.2	<0.0001
Relative fat mass obesity	26.6	37.8	<0.0001
Palafolls formula obesity	77.0	59.6	<0.0001
Deuremberg formula obesity	32.7	46.7	<0.0001
METS-VF high	4.4	0.4	<0.0001
Diabesity	1.5	0.6	<0.0001
Hypertension	21.8	7.6	<0.0001
Total cholesterol ≥ 200 mg/dl	31.4	27.1	<0.0001
LDL-c ≥ 130 mg/dl	27.7	23.3	<0.0001
Triglycerides ≥ 150 mg/dl	23.0	5.9	<0.0001
Glycaemia 100-125 mg/dl	12.5	5.9	<0.0001
Glycaemia ≥ 126 mg/dl	2.4	0.6	<0.0001
Metabolic syndrome NCEP ATPIII	10.7	4.2	<0.0001
Metabolic syndrome IDF	7.7	4.2	<0.0001
Metabolic syndrome JIS	19.6	5.0	<0.0001
Atherogenic dyslipidemia	5.4	2.1	<0.0001
Lipid triad	1.6	0.4	<0.0001
Hipertriglyceridemic waist	6.3	0.7	<0.0001
Total cholesterol/HDL-c moderate-high	11.2	6.4	<0.0001
Triglycerides/HDL-c high	23.7	4.6	<0.0001
LDL-c/HDL-c high	18.7	7.9	<0.0001
Total cholesterol-HDL-c high	49.3	39.7	<0.0001
METS-IR high	5.8	2.8	<0.0001
TyG index high	24.3	8.1	<0.0001
LAP high	29.9	15.6	<0.0001
Fatty liver index high risk	15.9	3.6	<0.0001
SCORE scale moderate-high	28.6	3.5	<0.0001
REGICOR scale moderate-high	21.0	16.7	<0.0001
ERICE scale moderate-high	11.7	1.5	<0.0001

CUN BAE Clinica Universitaria Navarra Body Adiposity Estimator; ECORE-BF Equation Córdoba for Estimation of Body Fat; METS-VF Metabolic score- visceral fat. ALLY Avoidable lost life years. SCORE Systematic COronary Risk Evaluation. REGICOR REgistre GIroni del COR. HDL-c High density lipoprotein cholesterol. LDL Low density lipoprotein cholesterol. METS-IR Metabolic score for Insulin Resistance. TyG Triglyceride glucose index. LAP Lipid accumulation product

Different studies carried out by our group in large groups of workers have found a relationship between belonging to the most disadvantaged social classes and presenting high prevalence of different cardiometabolic risk scales such as nonalcoholic fatty liver disease[45], obesity[46], vascular age[47], or metabolic syndrome[48], among others.

A study carried out in Danes aged 18 to 25 years in which the relationship between low socioeconomic status and the prevalence of cardiometabolic risk was assessed concluded that there was an inverse relationship between them, such that the prevalence was higher in people from the lowest socioeconomic stratum[49].

A study carried out in 2650 Chinese adults showed a higher prevalence of cardiometabolic disorders, especially metabolic syndrome, in groups belonging to the poorest socioeconomic groups[50]. This same relationship between metabolic syndrome and low socioeconomic status was observed in another study carried out in a young population in Iran[51].

A study of 15,057 elderly Spanish workers in different occupations, in which different cardiometabolic risk scales were assessed, showed that in addition to male sex and tobacco consumption, one of the factors influencing the prevalence of cardiometabolic disorders such as non-alcoholic fatty liver disease or obesity was belonging to the group of manual workers[52]. An Indonesian study of 137,378 workers found that manual workers were more likely to report symptoms of cardiovascular disease than non-manual workers[53].

Strengths and limitations

Among the strengths of the study, we would highlight the large sample size, in both sexes, and the large number of cardiometabolic risk scales analyzed. It is also one of the first, if not the first article to specifically assess the cardiometabolic level of waiters, so that this study could become a reference for further research in this group of workers.

The main limitation is that most of the cardiometabolic risk parameters were not determined using objective methods but by applying risk scales.

Conclusions

The waiters analyzed in this study, despite their youth, presented higher prevalences of the different cardiometabolic risk scales than expected in persons of this age.

The variables that most increase the risk of presenting high values of all the cardiometabolic risk scales are age followed by sex (male), while smoking does not influence in most cases.

Conflict of Interest
The authors declared that there is no conflict of interest.

Table IV: Multinomial logistic regression.

	≥ 50 years	Male	Smokers
	OR (95% CI)	OR (95% CI)	OR (95% CI)
WtHR < 0.50	1	1	1
WtHR ≥0.50	2.01 (1.87-2.17)	3.38 (3.18-3.60)	ns
BMI non obesity	1	1	1
BMI obesity	2.34 (2.13-2.57)	1.29 (1.19-1.40)	ns
CUN BAE non obesity	1	1	1
CUN BAE obesity	6.83 (6.33-7.36)	1.20 (1.14-1.27)	0.95 (0.90-0.99)
ECORE non obesity	1	1	1
ECORE obesity	6.48 (6.01-6.99)	1.23 (1.16-1.29)	0.94 (0.89-0.99)
RFM non obesity	1	1	1
RFM obesity	1.91 (1.78-2.05)	0.56 (0.54-0.59)	ns
Palafolls formula non obesity	1	1	1
Palafolls formula obesity	3.87 (3.49-4.29)	2.15 (2.04-2.27)	0.93 (0.88-0.99)
Deurenberg formula non obesity	1	1	1
Deurenberg formula obesity	18.23 (16.50-20.15)	0.40 (0.38-0.42)	0.93 (0.88-0.99)
METS-VF normal	1	1	1
METS-VF high	6.70 (5.73-7.83)	10.74 (7.99-14.43)	ns
Non hypertension	1	1	1
Hypertension	5.16 (4.78-5.58)	3.11 (2.88-3.36)	ns
Total cholesterol < 200 mg/dl	1	1	1
Total cholesterol ≥ 200 mg/dl	4.12 (3.84-4.42)	1.10 (1.05-1.16)	ns
LDL-c < 130 mg/dl	1	1	1
LDL-c ≥ 130 mg/dl	4.32 (4.03-4.64)	1.12 (1.06-1.19)	ns
Triglycerides < 150 mg/dl	1	1	1
Triglycerides ≥ 150 mg/dl	2.25 (2.07-2.45)	4.52 (4.17-4.91)	ns
Glycaemia < 126 mg/dl	1	1	1
Glycaemia ≥ 126 mg/dl	9.13 (8.01-10.41)	2.20 (1.90-2.54)	ns
Non metabolic syndrome NCEP ATPIII	1	1	1
Metabolic syndrome NCEP ATPIII	5.53 (5.03-6.08)	2.39 (2.16-2.65)	ns
Non metabolic syndrome IDF	1	1	1
Metabolic syndrome IDF	3.23 (2.90-3.60)	1.72 (1.55-1.91)	ns
Non metabolic syndrome JIS	1	1	1
Metabolic syndrome JIS	5.51 (5.08-5.98)	4.28 (3.91-4.68)	ns
Non atherogenic dyslipidemia	1	1	1
Atherogenic dyslipidemia	3.17 (2.78-3.62)	2.38 (2.07-2.74)	ns
Non lipid triad	1	1	1
Lipid triad	2.69 (2.10-3.44)	3.37 (2.53-1.48)	ns
Non Hipertriglyceridemic waist	1	1	1
Hipertriglyceridemic waist	1.82 (1.57-2.11)	8.50 (6.91-10.45)	ns
Total cholesterol/HDL-c normal	1	1	1
Total cholesterol/HDL-c high	4.88 (4.46-5.34)	1.59 (1.46-1.74)	ns
Triglycerides/HDL-c normal	1	1	1
Triglycerides/HDL-c high	4.56 (4.22-4.94)	2.44 (2.26-2.63)	ns
LDL-c/HDL-c normal	1	1	1
LDL-c/HDL-c high	5.71 (5.26-6.20)	1.34 (1.28-1.41)	ns
SCORE scale low	1	1	1
SCORE scale moderate-high	107.73 (82.21-141.18)	23.14 (18.45-29.02)	7.84 (6.50-9.45)
REGICOR scale low	1	1	1
REGICOR scale moderate-high	1.91 (1.76-2,08)	1.25 (1.15-1.35)	1.20 (1.11-1.30)
Fatty liver index low-moderate risk	1	1	1
Fatty liver index high risk	2.38 (2.15-2.64)	4.80 (4.31-5.35)	ns
LAP low	1	1	1
LAP high	2.21 (2.06-2.38)	2.20 (2.07-2.33)	ns
BARD score low	1	1	1
BARD score high	ns	0.55 (0.45-0.66)	ns
Non diabesity	1	1	1
Diabesity	11.25 (8.84-14.33)	1.77 (1.37-2.28)	0.73 (0.56-0.94)
METS-IR bajo	1	1	1
METS-IR alto	2.60 (2.28-2.95)	1.97 (1.74-2.23)	ns
TyG index low	1	1	1
TyG index high	2.81 (2.60-3.03)	3.41 (3.17-3.66)	ns

WtHR Waist to height ratio. BMI.Body mass index. CUN BAE Clinica Universitaria Navarra Body Adiposity Estimator; ECORE-BF Equation Córdoba for Estimation of Body Fat; METS-VF Metabolic score- visceral fat. ALLY Avoidable lost life years. SCORE Systematic COronary Risk Evaluation. REGICOR REgistre GIroni del COR. HDL-c High density lipoprotein cholesterol. LDL Low density lipoprotein cholesterol. METS-IR Metabolic score for Insulin Resistance. TyG Triglyceride glucose index. LAP Lipid accumulation product

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ORIGINAL

Relación de los Índices de Adiposidad Visceral (VAI) y Adiposidad Disfuncional (DAI) con las escalas de riesgo de resistencia a la insulina y prediabetes

Visceral Adiposity Index (VAI) and Dysfunctional Adiposity Index (DAI). Relationship with insulin resistance and prediabetes risk

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Resumen

Objetivo: Estimar en población laboral española la fortaleza asociativa de los índices de adiposidad visceral (DAI) y adiposidad disfuncional (VAI) con Resistencia a la Insulina (RI) y Riesgo de prediabetes.

Métodos: análisis descriptivo en trabajadores durante la vigilancia de la salud en sus empresas. Se calculó el VAI y El DAI ajustándose a sus ecuaciones, el Riesgo de Resistencia a la Insulina con las escalas TG/HDL, TyG y METS-IR y el riesgo de prediabetes con PRISQ. Se calculan los valores medios de VAI y DAI y, para la valoración de la fortaleza asociativa se usan las curvas ROC: área bajo la curva (AUC), puntos de corte, sensibilidad, especificidad e índice de Youden. Se utilizó el programa estadístico SPSS 27.0, considerando significación estadística p< 0,05.

Resultados: La prevalencia de resistencia a la insulina y el riesgo de prediabetes son más elevados en hombres que en mujeres. Los valores medios de VAI son más elevados que los de DAI y siempre superiores en los hombres (p<0.0001). La RI en mujeres muestra los porcentajes más altos con TG/HDL y en hombres con TyG. Los índices VAI y DAI muestran alta fortaleza asociativa para resistencia a la insulina en ambos sexos y con los métodos tres utilizados (AUC>0,8) y VAI y DAI para PRISQ muestran moderada fortaleza asociativa en ambos sexos (AUC>07-<0,8).

Conclusión: La estimación del riesgo de resistencia a la insulina es diferente en hombres y mujeres y varía en función del método utilizado. VAI Y DAI son estimadores útiles de asociación en Resistencia a la Insulina y moderadamente útiles en prediabetes. Calculada con PRISQ.

Palabras clave: Resistencia a la insulina; Riesgo de Prediabetes, Índice de adiposidad visceral, Índice de adiposidad disfuncional, Salud Laboral.

Abstract

Objective: To estimate the associative relationship of visceral adiposity index (DAI) and dysfunctional adiposity index (VAI) related to insulin resistance and risk of pre-diabetes in the Spanish working population.

Methods: descriptive analysis in workers during health surveillance in their companies. VAI and DAI were calculated according to their equations and the Risk of Insulin Resistance with the scales TG/HDL, TyG and METS-IR, the risk of prediabetes with PRISQ. Mean VAI and DAI values were calculated and, for associative assessment, ROC curves were used: area under the curve, cut-off points, sensitivity, specificity and Youden index. SPSS 27.0 software was used, considering statistical significance p<0.05.

Results: The prevalence of insulin resistance and the risk of prediabetes are higher in men than in women. Mean VAI values are higher than DAI and always higher in men (p<0.0001). The IR in women shows the highest percentages with TG/HDL and in men with TyG. VAI and DAI show high associative relationship for insulin resistance in both sexes and with the three methods used (AUC>0.8) VAI and DAI for PRISQ show moderate associative relationship in both sexes AUC>07-<0.8.

Conclusion: The estimation of insulin resistance is different in men and women and shows variability depending on the method used. VAI and DAI are useful associative method in insulin resistance and moderately useful in prediabetes.

Key words: Insuline Resistance; Prediabetes Risk; Visceral adiposity Índex, Dysfunctional Adiposity Índex; Occupational Health.

Introducción

La definición de síndrome metabólico describe una agrupación de factores de riesgo cardiovascular típicos. También se conoce como síndrome de resistencia a la insulina, ya que una parte sustancial de su fisiopatología está impulsada por la resistencia a los efectos metabólicos de esta sustancia, causada principalmente por un aumento del depósito de lípidos dentro de los tejidos sensibles a la insulina, como: hígado, músculo esquelético y vísceras. Este patrón de depósito de lípidos también se asocia con la infiltración de tejidos intraabdominales y concambios en células del sistema inmunitario, lo que induce una inflamación sistémica de bajo grado en obesos resistentes a la insulina[1].

La resistencia a la insulina (RI) se define clínicamente como la incapacidad de una cantidad conocida de insulina exógena o endógena para aumentar la captación y utilización de glucosa en un individuo tanto como lo hace una población normal. Se produce como parte de un conjunto de anomalías cardiovasculares y metabólicas que puede conducir al desarrollo de diabetes tipo 2, aterosclerosis, hipertensión o síndrome de ovario poliquístico, entre otras enfermedades, dependiendo de los antecedentes genéticos del individuo que desarrolla la RI[2].

Actualmente la prevalencia de RI es alta en todos los grupos de edad aunque varía según poblaciones y estilos de vida. Ejemplo de ello son las cifras en el sudeste asiático donde según resultados de un metaanálisis se cifra su prevalencia en el 44,3 %[3]. En poblaciones europeas comparando húngaros y romaníes la prevalencia de RI es de 42,3% y 40,5 % respectivamente[4].

Es España, en niños y adultos jóvenes, la prevalencia de RI encontrada varía entre el 29% y el 50% según el sistema utilizado en la cuantificación[5].

En una sociedad con una esperanza de vida cada vez más elevada, la evidencia revela alta prevalencia de diabetes en pacientes ancianos frágiles, lo que produce un deterioro adicional del rendimiento físico en personas mayores. La RI parece contribuir a esta manifestación clínica relacionada con el impacto de la diabetes y sus complicaciones. Las intervenciones nutricionales y educativas y el control glucémico aparecen como las estrategias más eficaces para reducir la fragilidad en los ancianos con diabetes o con riesgo elevado de padecerla[6].

De otro lado, la prediabetes (PD) o hiperglucemia intermedia es un estado de alto riesgo para diabetes. Se define por variables glucémicas que son más altas de lo normal, pero más bajas que los umbrales de la diabetes. Entre un 5-10% de las personas con PD progresarán a diabetes. Su prevalencia está aumentando en todo el mundo y los expertos han estimado que más de 470 millones de personas tendrán PD en 2030. La PD está asociada con la presencia simultánea de RI y anomalías de disfunción de las células β que comienzan antes de que los cambios en la glucosa sean detectables. Entre sus complicaciones asociadas se encuentran: formas tempranas de nefropatía, enfermedad renal crónica, neuropatía de fibras pequeñas, retinopatía diabética y mayor riesgo de enfermedad macrovascular. La actividad preventiva y su detección precoz/temprana pueden reducir hasta en un 40-70% el riesgo de PD y de RI y evitar las complicaciones multisistémicas derivadas[7,8].

Se parte de la base de considerar la resistencia a la insulina, no como un defecto primario sino que su desarrollo es secundario al aumento de masa grasa[9], y que la expansión del tejido adiposo se comunica con otros tejidos para regular el metabolismo sistémico, tanto a nivel central como periférico creando una red de señalización robusta y multidimensional que es necesaria para la homeostasis metabólica[10],

Se viene asumiendo que, la adiposidad visceral supone un aumento en los niveles circulantes de ácidos grasos libres. El hígado y el músculo esquelético tienen reducida su capacidad para metabolizar estos ácidos grasos, por lo que éstos se acumulan como intermediarios del metabolismo lipídico favoreciendo la aparición de resistencia a la insulina en lo que se denomina lipotoxicidad[11]. Del mismo modo, se considera que la adiposidad visceral está fuertemente asociada con resistencia a la insulina, sin embargo factores genéticos y ambientales también predisponen al desarrollo de esta condición[12].

El Índice de Adiposidad Visceral (VAI) El índice de adiposidad disfuncional (DAI) se consideran marcadores tempranos de anomalías cardiometabólicas basándose en alteraciones morfofuncionales de los adipocitos y se calculan en base a modelos matemáticos utilizando parámetros antropométricos y de laboratorio.

Es objetivo de este trabajo estimar la prevalencia de RI (con el cociente TG/HDL, índice TG y la fórmula de METS-IR) y la de PD con la escala PRISQ, y estimar la fortaleza asociativa del índice de adiposidad visceral (VAI) y del índice de adiposidad disfuncional (DAI) con RI y PD en la población laboral objeto de estudio.

Método

Estudio transversal realizado en 418.343 trabajadores de diferentes comunidades autónomas de España (Baleares, Andalucía, Canarias, Comunidad Valenciana, Cataluña, Madrid, Castilla La Mancha, Castilla León, País Vasco) y con diversas ocupaciones laborales (hostelería, construcción, comercio, sanidad, administración pública, transporte, educación, industria y limpieza), durante el periodo comprendido entre enero de 2019

hasta septiembre de 2021. La población de estudio se obtuvo de la base de datos anonimizada de trabajadores depositada en el repositorio de la escuela universitaria ADEMA-UIB (Universidad de las Islas Baleares). Esta base de datos procede de los reconocimientos médicos laborales realizados en los últimos 5 años en diversos servicios de prevención de riesgos laborales de toda España[13]. El sistema de anonimización de ADEMA no permite a los investigadores conocer la identidad de los trabajadores. Son criterios de inclusión: edad entre 18 y 67 años, ser trabajador en activo y aceptación voluntaria de participación en el estudio.

Las medidas antropométricas de talla y peso, clínicas y analíticas, fueron realizadas por el personal sanitario de las diferentes unidades de salud laboral participantes en el estudio, previa homogeneización de las técnicas de medición.

Para el cálculo de Resistencia a la Insulina se han utilizado tres escalas:

Triglicéridos/HDL que calcula la relación TGL/HDL atendiendo a la siguiente fórmula: triglicéridos en ayunas (mg/dl)/colesterol-HDL (mg/dl). El diagnóstico de diabetes se ha basado atendiendo a los niveles de glucosa plasmática 2 horas post-sobrecarga ≥ 200 mg/dl[14].

Triglicéridos e índice de glucosa (TyG) calculado siguiendo la fórmula: Ln (TG [mg/dL]×glucosa [mg/dL]/2). El punto de corte para el índice TyG se ha establecido en 8,8 en hombres y 8,7 en mujeres[15].

Metabolic Score for Insulin Resistance (METS-IR), se obtiene utilizando el inverso de la suma de los logaritmos de la insulina en ayunas y la glucosa en ayunas: 1 / (log(insulina en ayunas µU/mL) + log(glucosa en ayunas mg/dL[16]

Para el cálculo del riesgo de prediabetes se ha utilizado Prediabetes Risk Score in Qatar (PRISQ)[17,18] basado en: edad, sexo, perímetro de cintura, peso, talla (IMC) y presión arterial.

Se han utilizado las siguientes fórmulas para el cálculo de VAI y DAI[19,20]:

VAI = (cintura(cm)/(39.68+(1.88*IMC)))*(TG/1.03)*(1.31/HDL) para hombres y VAI = (cintura(cm)/(36.58+(1.89*IMC)))*(TG/0.81)*(1.52/HDL) para mujeres.

DAI=[cintura/[22.79+[2.68*IMC]]]*[triglicéridos (TG, mmol/L)/1.37] * [1.19/lipoproteína-colesterol de alta densidad (HDL-C, mmol/L)] para hombres y [cintura/[24.02+[2.37*IMC]]]*[TG(mmol/L)/1.32]*[1.43/HDL-C(mmol/L)] para mujeres.

Análisis estadístico:

Para el estudio estadístico se realizó un análisis descriptivo de las variables categóricas, calculando la frecuencia y la distribución de las respuestas en cada variable. En el caso de las variables cuantitativas, se calcularon la media y la desviación típica. Para evaluar la normalidad de la muestra se aplicó la prueba de Kolmogorov-Smirnov. Para valorar la utilidad de los diferentes métodos en la predicción del síndrome metabólico, se realizaron curvas ROC y se determinó el área bajo la curva (AUC), así como los puntos de corte con su sensibilidad, especificidad e índice de Youden. El análisis estadístico se realizó con el programa SPSS 27.0, siendo el nivel de significación estadística aceptado de $p<0,05$.

El estudio fue aprobado por el Comité Ético de Investigación Clínica del Área de Salud de Baleares (IB 4383/20).

Resultados

Los resultados de prevalencia de resistencia a la insulina y de riesgo de prediabetes son más elevados en los hombres que en las mujeres ($p<0.0001$). En RI entre las mujeres los porcentajes más altos de valores elevados se obtienen con TG/HDL (17,80%) y en los hombres con TyG (37,33%). PRISQ presenta valores moderados (22,7 vs 39, 59) y altos (6,663 vs14, 43) más elevados en los hombres ($p<0.0001$) (**Tabla I**).

Los valores medios más elevados de VAI son siempre mayores que los de DAI y superiores en los hombres ($p<0.0001$). Los valores más altos de VAI y DAI en RI y mujeres se obtienen con el índice TyG (VAI 5,61 (dt2,

Tabla I: Prevalencia de Resistencia a la Insulina y Riesgo de prediabetes según método utilizado y sexo.

Método		Mujeres				Hombres				p
		Normal		Alto		Normal		Alto		
		n	%	n	%	n	%	n	%	
Resistencia Insulina	TG/HDL	141617	82,20	30665	**17,80**	184437	74,96	61624	25,04	<0.0001
	TyG	150798	87,53	21484	12,47	178806	72,67	67255	37,33	<0.0001
	METS-IR	161225	93,58	11057	6,42	218013	88,60	28048	11,40	<0.0001
		Normal		Moderado		Alto		Normal		Moderado		Alto		p
		n	%	n	%	n	%	n	%	n	%	n	%	
Riesgo Prediabetes	PRISQ	121643	70,61	39209	22,76	11430	6,63	113130	45,98	97423	39,59	35508	14,43	<0.0001

Triglicéridos/colesterol HDL (TG/HDL), Triglicéridos-Glucosa (TyG), Valoración metabólica de resistencia a la insulina (METS-IR), Estimación de Riesgo de prediabetes. Qatar (PRISQ), Se considera significativo p<0,005.

63)-DAI 1,41 (dt 0,65). En hombres en relación con RI el VAI y DAI más alto se obtiene con METS-IR (VAI 16,26 (dt 11,40)-DAI 1,70 (dt1, 26).

En cuanto a detección de riesgo de prediabetes con PRISQ, los valores medios de VAI son más altos que los de DAI y siempre más elevados en hombres que en mujeres (p<0.0001) (**Tabla II**).

En el análisis ROC del área bajo la curva (AUC) de los índices VAI y DAI para RI con los 3 métodos empleados (TG/HDL, TyG, METS-IR) se observa que, atendiendo al AUC, VAI y DAI muestran fortaleza asociativa, tanto en hombres como en mujeres con AUC>0,8 en todos los casos y con valores próximos a la unidad en algunos de ellos: Para METS-IR en mujeres VAI 0,824 (IC95% 0,820-0,827) y DAI 0,798 (IC95% 0,794-0,802); en

hombres VAI 0,888 (IC95% 0,886-0,890) y en DAI 0,822 (IC95% 0,820-0,825). Para TG/HDL en mujeres VAI 0,994 (IC95% 0,993-0,994) y DAI0,992 (IC95% 0,992-0,993); en hombres VAI 0,992 (IC95% 0,992-0,992)y DAI 0,995 (IC95% 0,995-0,995); y para TyG en mujeres VAI 0,966 (IC95% 0,965-0,967) y DAI 0,965 (IC95% 0,964-0,966); en hombres VAI 0,958 (IC95% 0,957-0,958) y DAI 0,962 (IC95% 0,961-0,963).

En relación con el riesgo de prediabetes calculado con PRISQ la utilidad de VAI y DAI como valor de asociación es moderada con AUC>0,7 pero<0,8 tanto en hombres VAI 0,765 (IC95% 0,762-0,767) y DAI 0,719 (IC95% 0,716-0,721 como en mujeres VAI 0,738 (IC95% 0,734-0,743) y DAI 0,725 (IC95% 0,720-0,730) (**Figuras 1, 2** y **tabla III**).

Tabla II: Valores medios de VAI y DAI por sexo según escalas de riesgo de resistencia a la insulina (Triglicéridos/HDL, TyG índice y METS-IR) y de Prediabetes (PRISQ).

Método de Valoración		Mujeres					Hombres				
		n	VAI		DAI		n	VAI		DAI	
			media (dt)	p	media (dt)	p		media (dt)	p	media (dt)	p
Resistencia a la Insulina	TG/HDL normal TG/HDL alto	141617 30665	2,16 (0,70) 5,25 (2,28)	<0.0001	0,55 (0,18) 1,32 (0,57)	<0.0001	184437 61624	4,80 (1,93) 15,17 (8,71)	<0.0001	0,62 (0,22) 1,79 (0,98)	<0.0001
	TyG índice normal TyG índice alto	150798 21484	2,29 (0,87) 5,61 (2,63)	<0.0001	0,59 (0,22) 1,41 (0,65)	<0.0001	178806 67255	4,85 (2,17) 14,17 (8,83)	<0.0001	0,62 (0,24) 1,68 (0,99)	<0.0001
	METS-IR normal METS-IR alto	161225 11057	2,56 (1,39) 4,79 (3,10)	<0.0001	0,66 (0,35) 1,16 (0,76)	<0.0001	218013 28048	6,25 (4,39) 16,26 (11,40)	<0.0001	0,81 (0,55) 1,70 (1,26)	<0.0001
Riesgo de Prediabetes	PRISQ bajo PRISQ moderado PRISQ alto	121643 39209 11430	2,39 (1,31) 3,30 (1,97) 4,03 (2,36)	<0.0001	0,62 (0,33) 0,83 (0,49) 1,00 (0,58)	<0.0001	113130 97423 35508	5,16 (3,89) 8,28 (6,50) 12,07 (9,32)	<0.0001	0,70 (0,50) 1,01 (0,76) 1,32 (0,99)	<0.0001

dt= desviación típica. Índice de adiposidad visceral (VAI) Índice de adiposidad disfuncional (DAI).Se considera significativo p<0,05. Triglicéridos/colesterol HDL (TG/HDL), Triglicéridos-Glucosa (TyG), Valoración metabólica de resistencia a la insulina (METS-IR), Estimación de Riesgo de prediabetes. Qatar (PRISQ).

Figura 1: Áreas debajo de la curva de VAI y DAI para predecir valores altos de las diferentes escalas de riesgo de resistencia a la insulina en mujeres.
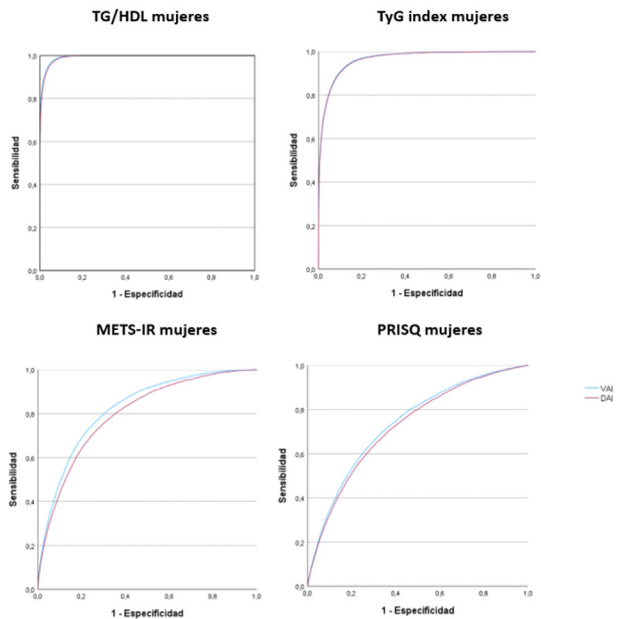
Figura 2: Áreas debajo de la curva de VAI y DAI para predecir valores altos de las diferentes escalas de riesgo de resistencia a la insulina en hombres.
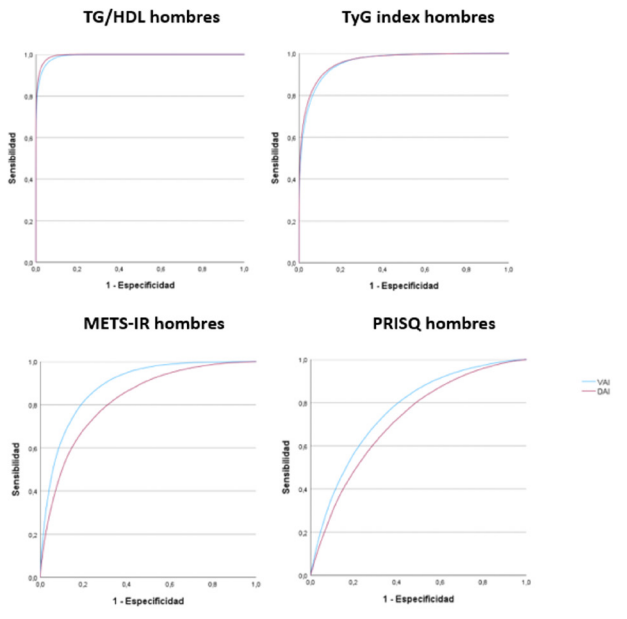
Tabla III: Áreas debajo de la curva, puntos de corte con su sensibilidad, especificidad e índice Youden de VAI y DAI para predecir valores altos de las diferentes escalas de riesgo de resistencia a la insulina en mujeres y hombres.

	VAI mujeres	DAI mujeres	VAI hombres	DAI hombres
	AUC (IC 95%)	AUC (IC 95%)	AUC (IC 95%)	AUC (IC 95%)
TG/HDL alto	0,994 (0,993-0,995)	0,992 (0,992-0,993)	0,992 (0,992-0,992)	0,995 (0,995-0,995)
TyG index alto	0,966 (0,965-0,967)	0,965 (0,964-0,966)	0,958 (0,957-0,958)	0,962 (0,961-0,963)
METS-IR alto	0,824 (0,820-0,827)	0,798 (0,794-0,802)	0,888 (0,886-0,890)	0,822 (0,820-0,825)
PRISQ alto	0,738 (0,734-0,743)	0,725 (0,720-0,730)	0,765 (0,762-0,767)	0,719 (0,716-0,721)
	Pcorte-sens-especif- Youden	Pcorte-sens-especif- Youden	Pcorte-sens-especif- Youden	Pcorte-sens-especif- Youden
TG/HDL alto	3,45-95,7-95,7-0,914	0,87-95,7-95,2-0,909	8,31-95,1-95,0-0,901	1,02-96,8-94,5-0,918
TyG index alto	3,50-90,5-90,2-0,807	0,88-90,7-89,1-0,798	7,48-88,7-88,5-0,772	0,93-89,7-88,8-0,785
METS-IR alto	3,00-75,1-74,8-0,499	0,75-73,3-72,3-0,456	8,50-80,9-80,5-0,614	0,95-75,2-75,0-0,502
PRISQ alto	2,78-68,0-67,8-0,356	0,70-67,1-66,3-0,334	7,00-70,0-69,6-0,396	0,84-66,8-65,4-0,322

Discusión

La resistencia a la insulina se postula como un factor de riesgo para el desarrollo de enfermedad coronaria, pero actualmente no hay datos suficientes sobre la asociación con los índices de RI basados en la relación TG/HDL-C, el índice TyG y METS-IR21. Nuestro estudio comparativo en trabajadores sanos y con edades entre 18-66 años muestra datos muy similares en todos ellos, pero se obtienen porcentajes más altos con TG/HDL-C y con el índice TyG que con METS-IR. Estudios de otros autores destacan que todos ellos son predictores valiosos de la presencia y gravedad de la enfermedad coronaria pero que el METS-IR tiene la mayor fortaleza asociativa frente a los otros índices IR no basados en insulina.

El índice de triglicéridos-glucosa (TyG) se ha identificado como un biomarcador alternativo confiable de RI, asociado con el desarrollo y pronóstico de la enfermedad cardiovascular. Sin embargo, la aplicación del índice TyG como marcador de ECV no ha sido evaluada sistémicamente, ni se ha descrito información sobre los mecanismos subyacentes asociados a la ECV[22]. La bibliografía muestra que el índice TyG y la relación TG/HDL-C están significativamente asociados con la progresión de la rigidez arterial en la población hipertensa, pero no así en la población prehipertensa[23].

Estos indicadores se correlacionan con el riego de diabetes tipo 2 (T2D) combinada con hipertensión y, con ello con el riego de desarrollar ECV. En algunos trabajos de ha investigado la relación de estos indicadores de RI (TyG, TG/HDL y Mets-IR) con el riesgo de desarrollar T2D combinado con hipertensión con resultados de asociaciones positivas. Además, el aumento del IMC hacia el sobrepeso y especialmente hacia la obesidad puede preceder al cambio del índice TyG, de este modo, el índice TyG juega un papel mediador en la DT2 combinada con hipertensión inducida por el IMC. En nuestro trabajo el riesgo de prediabetes calculado con PRISQ ha dado resultados moderados/altos y siempre superiores en hombres.

Es clara la relación de RI, riesgo de prediabetes y obesidad y algunos estudios han demostrado que VAI

puede estar asociada con el desarrollo de resistencia a la insulina en adultos estadounidenses, donde se ha demostrado una fuerte asociación positiva entre el nivel de VAI y la resistencia a la insulina y se sugiere que este índice se puede utilizar como un indicador con fortaleza en su asociación respecto a RI[24]. Coincide con nuestros resultados que, con los tres métodos empleados de RI muestran una alta fortaleza asociativa del VAI. Esta asociación positiva también se ha obtenido con otros métodos de estimación de RI como el HOMA-IR, que describe una alta sensibilidad y especificidad de los puntos de corte facilitando la aplicación de VAI en la práctica clínica común[25]. DAI ha mostrado en nuestro trabajo una alta fortaleza asociativa para RI con los tres métodos, tanto en hombres como en mujeres y coincide con lo observado por otros autores respecto al DAI concluyendo en ellos que puede usarse como herramientas de utilidad en fortaleza asociativa para detección temprana de síndrome metabólico y RI[26].

En cuanto al riesgo de prediabetes existe una mayor incertidumbre en la literatura en los resultados obtenidos. Algunos estudios epidemiológicos sugieren que la asociación entre el VAI y el riesgo de prediabetes es inconsistente y no está claro si el VAI es un parámetro de utilidad en su asociación con prediabetes. En un metanálisis de 2021 se sintetizó la evidencia epidemiológica observacional disponible para identificar la asociación entre VAI y riesgo de prediabetes que apoya la hipótesis de que el VAI es un índice antropométrico combinado de lípidos y puede ser un factor de alto riesgo para la prediabetes sin embargo se asume un sesgo de publicación y heterogeneidad en los resultados[27]. En nuestro trabajo, en relación con la estimación de prediabetes realizada con PRISQ se observa una moderada fortaleza asociativa tanto con VAI como con DAI y en ambos sexos, pero son necesarios más trabajos que confirmen con este u otros indicadores de prediabetes su fortaleza asociativa.

Sin embargo, aun en el momento actual siguen existiendo dudas sobre si la distribución de la grasa corporal está asociada con un mayor riesgo de desarrollar

resistencia a la insulina, diabetes, síndrome metabólico y enfermedades cardiovasculares. Uno de los depósitos de grasa que se sabe que está asociado con un mayor riesgo de resistencia a la insulina y síndrome metabólico es la adiposidad visceral, pero aunque es un factor importante, no explica únicamente el desarrollo de la resistencia a la insulina, por lo que se plantéa que quizás los depósitos de grasa corporal distintos de la grasa visceral también puedan estar relacionados con la resistencia a la insulina. A pesar de las discrepancias entre diferentes estudios, establecer un vínculo entre la adiposidad y su disposición corporal y los factores de riesgo metabólicos, independientemente del IMC, puede ser útil para identificar a las personas en riesgo y prevenir enfermedades cardiometabólicas destacando la diabetes y el síndrome metabólico entre ellas[28]. Este trabajo se ha basado en aportar información que permita establecer asociación de utilidad entre estos índices y el riesgo de desarrollar estas enfermedades.

Se considera fortaleza de este trabajo su tamaño muestral, el uso de índices específicos de adiposidad como el VAI y el DAI en la estimación de fortaleza de asociación con Resistencia a la Insulina y prediabetes y la comparativa realizada con los distintos métodos y parámetros utilizados. La mayor debilidad es no tener un comparativo por sectores laborales en esta muestra de población tan extensa, ser un estudio transversal y las dudas en la generalización de los resultados.

Conflicto de intereses

No existen conflictos de intereses.

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ORIGINAL

Evaluation of 10-year anesthesia management in patients diagnosed with placenta accreata spectrum and placenta previa: A comparative study

Evaluación del manejo anestésico a 10 años en pacientes diagnosticadas de placenta accreata spectrum y placenta previa: Un estudio comparativo

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Summary

Objective: In this study, we aimed to evaluate anesthesia management of placenta accreta spectrum disorder and placenta previa who had undergone cesarean section.

Materials and methods: The patients were allocated into 2 groups: group 1: general anesthesia, and group 2: spinal anesthesia. Age, gestational age, gravida, parity, previous cesarean section number, anesthesia method applied, preoperative hemoglobin, platelet counts, and postoperative hemoglobin values were recorded. Transfusion applications (erythrocyte suspension, fresh frozen plasma), use of colloid, tranexamic acid, and fibrinogen concentrate were recorded.

Results: The mean age of the patients was 32.53±5.35 years. However, the mean number of gravida was 5.20±2.33 and the mean parity number was 3.50±1.92. The preoperative mean hemoglobin value of the pregnant women was 11.28±1.62 g/dL, and the mean postoperative hemoglobin value was 9.62±1.43 g/dL. The mean number of previous cesarean sections of the pregnant women was found to be 2.31±1.03. Patients who underwent spinal anesthesia required less erythrocyte suspension transfusion (80.2% vs 38.9%) (p<0.001). While the rate of hysterectomy in group 2 was 3.7%, hysterectomy had to be performed in 20.6% of the patients in group 1 (p<0.001). There was no statistical difference between the groups in terms of DIC development and acute renal failure (p>0.05). Intraoperative total complications were found to be lower in the spinal anesthesia group (OR: 5.7) (p<0.001). The need for tertiary intensive care was found to be lower in the spinal anesthesia group (p<0.001). No statistically significant difference in terms of mortality.

Conclusions: Regardless of which anesthesia technique is used in pregnant women with placenta previa or placenta accreta spectrum diagnosis, it should be kept in mind that serious bleeding may occur during or after cesarean section and that a team should be able to reach the necessary blood and blood products for this.

Key words: Spectrum Disorder of Placenta Accreta, Placenta Previa, Anesthesia management, Transfusion of blood products, Need for intensive care.

Resumen

Objetivo: En este estudio, nos propusimos evaluar el manejo anestésico del trastorno del espectro de la placenta acreta y la placenta previa sometidas a cesárea.

Materiales y métodos: Las pacientes fueron asignadas a 2 grupos: grupo 1: anestesia general, y grupo 2: anestesia raquídea. Se registraron la edad, la edad gestacional, la gravidez, la paridad, el número de cesáreas previas, el método de anestesia aplicado, la hemoglobina preoperatoria, el recuento de plaquetas y los valores de hemoglobina postoperatoria. Se registraron las aplicaciones de transfusiones (suspensión eritrocitaria, plasma fresco congelado), el uso de coloide, ácido tranexámico y concentrado de fibrinógeno.

Resultados: La edad media de las pacientes fue de 32,53±5,35 años. Sin embargo, el número medio de grávidas fue de 5,20±2,33 y el número medio de partos fue de 3,50±1,92. El valor medio de hemoglobina preoperatoria de las embarazadas fue de 11,28±1,62 g/dL, y el valor medio de hemoglobina postoperatoria fue de 9,62±1,43 g/dL. El número medio de cesáreas previas de las embarazadas fue de 2,31±1,03. Las pacientes sometidas a anestesia raquídea necesitaron menos transfusiones de suspensión eritrocitaria (80,2% frente a 38,9%) (p<0,001). Mientras que la tasa de histerectomía en el grupo 2 fue del 3,7%, hubo que realizar una histerectomía en el 20,6% de las pacientes del grupo 1 (p<0,001). No hubo diferencias estadísticas entre los grupos en cuanto al desarrollo de CID e insuficiencia renal aguda (p>0,05). Las complicaciones intraoperatorias totales fueron menores en el grupo de anestesia raquídea (OR: 5,7) (p<0,001). La necesidad de cuidados intensivos terciarios fue menor en el grupo de anestesia raquídea (p<0,001). No hubo diferencias estadísticamente significativas en términos de mortalidad.

Conclusiones: Independientemente de la técnica anestésica que se utilice en gestantes con diagnóstico de placenta previa o placenta accreta spectrum, debe tenerse en cuenta que puede producirse una hemorragia grave durante o después de la cesárea y que un equipo debe ser capaz de alcanzar la sangre y hemoderivados necesarios para ello.

Palabras clave: Trastorno del espectro de la placenta acreta, Placenta previa, Manejo anestésico, Transfusión de hemoderivados, Necesidad de cuidados intensivos.

Introduction

According to the quantity of prior cesarean sections, the prevalence of placental adhesion and localization anomalies rose in subsequent pregnancies. Previously uncommon, this pathological condition is now seen frequently by obstetricians and gynecologists. The proper clinical management, medical, and particularly surgical treatment approaches for placental adhesion and location anomalies that raise maternal and fetal morbidity and mortality are crucial to know[1,2].

Anesthesia management of patients with placental invasion anomalies is specific. Prolonged surgical time due to placental anomaly, surgical complications, and deterioration of hemodynamic balance as a result of massive bleeding bring anesthesia management to the fore. Placenta previa is defined as the placement of the placenta in the lower segment of the uterus. As we mentioned above, the prevalence of placenta previa has increased in parallel with the recent increase in cesarean section surgery and constitutes approximately 0.5% of all pregnancies. Placental invasion anomalies can occur in three ways[3].

In their subsequent pregnancies, women who have previously delivered by cesarean section (C/S) should be evaluated for placenta previa and placenta attachment anomalies. It is crucial that women who have suspected placentation anomalies give birth in facilities where obstetric hemorrhage can be properly managed and under the care of clinicians who are knowledgeable about the surgical treatment options for obstetric hemorrhage[4].

In this study, we aimed to retrospectively evaluate the anesthesia management of cases diagnosed with preoperative or intraoperative placenta previa and placenta accreta spectrum (PAS) disorder anomaly, who had undergone cesarean section in our hospital.

Materials and methods

Study design
This study was designed retrospectively. Ethical approval was obtained from Dicle University. A total of 631 patients with a prediagnosis of placenta previa totalis and placenta accreta spectrum disorder in elective or emergency cesarean sections performed in the operating room of Dicle University Medical Faculty Hospital between January 2010 and December 2020 were included in our study. Patients who underwent general anesthesia were Group 1 (n=253); patients who underwent spinal anesthesia were defined as Group 2 (378). Observation files and electronic data of the patients were scanned retrospectively through the hospital computer system.

The patients' age, gravida, parity, gestational age, number of previous cesarean sections, the anesthesia method applied, and whether they were emergency/ elective were reported. Preoperative hemoglobin, platelet, and postoperative hemoglobin values of the patients were recorded. The amount of erythrocyte suspension and fresh frozen plasma (FFP) used was recorded. In addition, the use of colloid, tranexamic acid, and fibrinogen applications were reported. Complications that developed in the perioperative period, length of stay in the tertiary intensive care unit, and whether mortality developed or not were determined. The mean weight and mean week of the birth of the babies were recorded.

Inclusion criteria
Patients who were diagnosed with previa/accreta, aged 16-55, delivered by cesarean section, and had a single or twin pregnancy were included in the study.

Exclusion criteria
Patients with a lack of data in their observation files or hospital information system were excluded from the study.

Statistical analysis
SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) program was used for statistical analysis, and type I error level was accepted as 5% in statistical analysis. The conformity of continuous variables to the normal distribution was examined using the Shapiro-Wilk test. Continuous variables using mean ± standard deviation (min - max) values; Categorical variables were expressed as n (%). In comparisons between groups according to the results of the normality test; Normally distributed data were analyzed using Student's t-test and non-normally distributed data were analyzed using Mann Whitney U test. Categorical variables were analyzed using the chi-square test and Fisher's exact chi-square test. The relationship between the number of cesarean sections and blood transfusion was examined by correlation analysis, and the Spearman correlation coefficient was calculated.

Results

The mean age of the patients was 32.53±5.35 years. However, the mean number of gravida was 5.20±2.33 and the mean parity number was 3.50±1.92 in the patients included in our study. The mean weight of the babies born was 2566.65±658.65 g and the mean week of delivery was 34.85±3.12. The preoperative mean hemoglobin value of the pregnant women was 11.28±1.62 g/dL, and the mean postoperative hemoglobin value was 9.62±1.43 g/dL. The mean number of previous cesarean sections of the pregnant women was found to be 2.31±1.03. It is seen that 55.50% of 631 patients received a blood transfusion. It was determined that fibrinogen concentrate was used in 5.90% of the patients included in the study, and tranexamic acid was used in 5.10%.

Among 631 patients diagnosed with placenta previa and accreta spectrum disorder, 28 patients in need of 3rd-level intensive care were seen, and the average intensive care unit stay of these patients was 4.5 days. When examined in terms of hysterectomy, it was seen that 10.50% of the patients had hysterectomies. In terms of complications, 4.80% had bladder rupture, 0.30% hypogastric artery injury, 0.30% bladder and ureter injury, 0.20% bladder, and bowel injury, and Ureteral injury was observed in 0.20%. It was determined that 4.40% of the patients needed tertiary intensive care. It was observed that 0.80% of the patients participating in the study had DIC and 0.50% had ARF 26. In addition, the incidence of DIC was 3.20% and the rate of ARF was 1.10% in patients with 4 or more blood transfusions (**Table I**).

Patients who underwent spinal anesthesia required less erythrocyte suspension transfusion (80.2% vs 38.9%) (p<0.001). While the rate of hysterectomy in group 2 was 3.7%, hysterectomy had to be performed in 20.6% of the patients in group 1 (p<0.001). There was no statistical difference between the groups in terms of DIC development and acute renal failure (p>0.05). Intraoperative total complications were found to be lower in the spinal anesthesia group (OR: 5.7) (p<0.001). The need for tertiary intensive care was found to be lower in the spinal anesthesia group (p<0.001). No statistically significant difference in terms of mortality. The relevant data was summarized in **table II**.

Discussion

This study was carried out by retrospectively screening 631 patients with a prediagnosis of placenta previa and placenta accreta spectrum disorder as the elective or emergency cesarean section between 2010 and 2020. Demographic data of patients, cesarean section numbers, gestational age, parity, gravida, anesthesia method applied, preoperative/postoperative hemoglobin and preoperative platelet values, transfusion applications (erythrocyte suspension, fresh frozen plasma), fluid management, tranexamic acid, fibrinogen concentrate applications, the length of stay in the intensive care unit and the complications that developed in the perioperative period were investigated.

In the literature, studies on placenta previa and placenta accreta spectrum disorders indicate that age is an important risk factor. In the study of Karapınar et al, the mean age of patients with placenta previa was found to be 31.4±5.3[5]. Taşgöz et al. found the mean age of

Table I: Patients characteristics.

	n=631 (%)
Age (year)	32,5±5,3 (16-49)
Gravida	5,2±2,3 (1-6)
Parity	3,5±1,9 (0-12)
Preoperative hemoglobin (g/dl)	11,2±1,62 (5,5-15,3)
Postoperative hemoglobin (g/dl)	9,6±1,4 (7-21,40)
Number of Cesarian section	2,3±1,0 (0-6)
Cesarian history	628 (99.5%)
Cesarian status	
Emergency	311 (49.3%)
Elective	320 (50.7%)
Birth weight (gram)	2566,6±658,6 (200-4110)
Birth week	34,8±3,1 (19-40)
Blood transfused patients	350 (55,5)
Those given fibrinogen concentrate	37 (5,9)
Those given tranexamic acid	32 (5,1)
Blood transfusion (unite)	1,6±2,0 (0-12)
Colloid	0,5±0,8 (0-5)
Fresh frozen plasma	0,7±1,6 (0-11)
Hysterectomy	66 (10,5)
Complications	
Bladder rupture	30 (4,8)
Hypogastric artery injury	2 (0,3)
Bladder and ureter injury	2 (0,3)
Bladder and bowel injury	1 (0,2)
Ureteral injury	1 (0,2)
DIC	5 (0,8)
Acute renal failure (ARF)	3 (0,5)
Need for intensive care (n)	28 (4,4)
Number of intensive care hospitalization days	6,9±5,9 (2-24)

** The data was given n(%) or mean±SD (range)

patients diagnosed with placenta previa as 31.7±5.34 in another study[6]. Seyhan et al. found the mean age of the patients as 32.5±4.20 in their study[7]. In our study, the mean age was found to be 32.5±5.3. The data in our study support previous studies.

Placenta previa and placenta accreta spectrum (PAS) disorder are the most important causes of massive obstetric hemorrhage, maternal and fetal mortality, and morbidity; It is seen at a rate of 0.48% and is fatal at a rate of 0.03%[8]. No mortality was detected in our study. It is stated that the incidence of placental adhesion anomaly increases in pregnant women with a history of previous cesarean section and diagnosed with placenta previa. In this study, it was determined that 628 (99.5%) of 631 women with a diagnosis of placenta previa and invasion had undergone previous cesarean sections.

In a study by Panigrahi et al; 89% of pregnant women with PAS disorder and placenta previa had a postpartum hysterectomy[9]. In our study, a hysterectomy (10.5%) was performed in 66 of 631 patients with a prediagnosis of PAS disorder and placenta previa. The low rate of hysterectomy was attributed to the surgical team's preference for fertility-preserving surgery and the experience of the team.

In the study by Panigrahi et al., 62 (46%) of 136 women were given erythrocyte suspension and 23 fresh frozen plasma among patients with placenta accreta spectrum disorder and placenta previa[9]. In another study by Seyhan et al. including 61 patients, erythrocyte suspension was given to 13 patients[7]. Erythrocyte suspension and 173 fresh frozen plasma were given to 350 patients (50.5%) out of 631 patients included in our study. The proportional blood donation rate is in line with the literature.

In a study by Binici et al., the incidence of erythrocyte transfusion and administration of tranexamic acid and human fibrinogen concentrate in patients who underwent general anesthesia was found to be significantly higher than in other patients[10]. In our study, it was observed that more erythrocyte suspension and more fibrinogen concentrate were given to patients who were administered general anesthesia compared to regional anesthesia.

Tranexamic acid has been shown to be effective in reducing the incidence of blood loss greater than 1000 ml in 1534 women who have had a previous cesarean section. The authors of the Cochrane review on the use of tranexamic acid in the prevention of postpartum hemorrhage concluded that further studies are needed to investigate the risk of serious adverse events. One study concluded that high-dose tranexamic acid may reduce blood loss, decrease Hgb, and the need for blood transfusion[11]. Ducloy et al. conducted the first study showing that the use of tranexamic acid reduces post-partum bleeding[12]. In our study, it was observed that the use of tranexamic acid did not reduce blood transfusion. This was attributed to the use of tranexamic acid after blood replacement.

Table II: Comparison of the groups.

	Group 1 (n=253)	Group 2 (n=378)	P-value
Age (year)	32,3±5,3 (17-49)	32,6±5,3 (16-45)	0,343
Gravida	5,2±2,1 (1-14)	5,14±2,41 (1-16)	0.053
Parity	3,5±1,8 (0-9)	3,49±1,96 (0-12)	0.421
Preoperative hemoglobin (g/dl)	10,8±1,7 (5,5-15,1)	11,57±1,49 (7-15,3)	**<0.001**
Postoperative hemoglobin (g/dl)	9,3±1,4 (7-21,4)	9,7±1,3 (7-14,1)	**<0.001**
Number of Cesarian section	2,3±1,1 (0-5)	2,2±0.9 (0-6)	0.472

Cesarian status
    Emergency
    Elective
	149 (58,9)
	104 (41,1)
		162 (42,9)
		216 (57,10)
			<0.001

Birth weight (gram)	2464±737 (200-4110)	2634±591 (400-3900)	**0.006**
Birth week	34,2±3,6 (19-40)	35,2±2,6 (20-40)	**<0.001**
Blood transfused patients	203 (80,2)	147 (38,9)	**<0.001**
Those given fibrinogen concentrate	28 (11,1)	9 (2,4)	**<0.001**
Those given tranexamic acid	11 (4,3)	21 (5,6)	0.498
Blood transfusion (unite)	2,6±2,1 (0-12)	0,9±1,5 (0-12)	**<0.001**
Colloid	0,5±0,9 (0-5)	0,4±0,7 (0-4)	0.602
Fresh frozen plasma	1,3±1,8 (0-9)	0,4±1,3 (0-11)	**<0.001**
Hysterectomy	52 (20,6)	14 (3,7)	**<0.001**
Complications	28 (11,1)	8 (2,1)	**<0.001**
DIC	4 (1,6)	1 (0,3)	0.163
Acute renal failure (ARF)	4 (1,6)	0	0.064
Need for intensive care (n)	25 (9,9)	3 (0,8)	**<0.001**
Number of intensive care hospitalization days	6 (2-24)	3 (3-5)	0.391
Mortalite	0	0	1.000

** The data was given n(%) or mean±SD (range)

Ömer Oygen et al.

Evaluation of 10-year anesthesia management in patients diagnosed with placenta accreata spectrum and placenta previa: A comparative study

In the anesthesia management of pregnant with placenta previa and placenta accreta spectrum disorder, including 92 patients, Binici et al. 61 (66%) of 92 patients were administered general anesthesia and 31 (34%) spinal anesthesia[10]. In our study, placenta previa and placenta accreta spectrum disorder were administered. General anesthesia was applied to 253 (40.1%) patients and spinal anesthesia was applied to 378 (59.9%) patients under anesthesia management. However, regional techniques are being used more and more[13,14]. However, patients undergoing regional anesthesia should be warned that it may require a transition to general anesthesia depending on the severity of bleeding and the course of the operation in the intraoperative period[15,16].

The literature shows that regional anesthesia may be a better option than general anesthesia, as inhaled anesthetics used in the induction of general anesthesia in patients undergoing surgery for placenta previa cause relaxation in the uterus, thus causing more blood loss and the need for more blood and blood products[17-19]. In the study conducted by Binici et al., they found that intraoperative blood loss, the need for hospitalization in the postoperative intensive care unit, and the length of stay in the postoperative intensive care unit were significantly higher in patients who underwent general anesthesia compared to those who received other regional anesthesia[10]. In another study, a total of 122 patients with placental invasion and localization anomalies were evaluated retrospectively over a period of 18 years, and it was suggested that regional block could be successfully applied in these patients[20]. In our study, it was found that patients who underwent spinal anesthesia had less use of blood products. Additionally, we found fewer complications in the spinal anesthesia group.

Conclusions

Better outcomes were found in the spinal anesthesia group. Regardless of which anesthesia technique is used in pregnant women with placenta previa or placenta accreta spectrum diagnosis, it should be kept in mind that serious bleeding may occur during or after cesarean section and that a team should be able to reach the necessary blood and blood products for this.

Conflict of Interest

The authors declared that there is no conflict of interest.

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ORIGINAL

Knowledge, acceptability and willingness to receive HPV vaccine among women in Owerri municipal Imo state

Conocimiento, aceptabilidad y voluntad de recibir la vacuna contra el VPH entre las mujeres del municipio de Owerri, estado de Imo

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Abstract

Background: Regrettably, levels of HPV awareness among the general population are poor throughout the world. The aim of the study was to determine the Knowledge, acceptability and willingness to receive HPV Vaccine among women in Owerri Municipal Imo State.

Methods: A descriptive cross sectional study design was adopted for this study. A multi stage sampling method was using in recruiting 424 women for the study and the Statistical Package for Sciences the Social (SPSS) version 20.0 was used in the analysis of the study. Data was obtained using an interviewer based semi structured questionnaire.

Results: The study showed that majority of the women (participants) were of Igbo origin 65.8% (280) and for the knowledge of HPV Vaccine, 78.9% (335) of the respondents agreed they had heard about HPV vaccine, while 21.0% (89) denied. Majority of the respondents affirmed they would accept HPV vaccine if offered a chance (85.9%). Based on the association between Socio demographic Characteristics and willingness to receive HPV Vaccine among women, Marital status (P = 0.0042) and educational level (P = 0.0015) had a statistically significant relationship with willingness to receive HPV Vaccine among women.

Conclusion: This study established that even though a number of women showed considerable knowledge of HPV vaccine, several others are deficient of relevant information and this finding is evident in the willingness to receive HPV vaccines among respondents. Counseling of women on the safety and efficacy of HPV vaccine to improve their willingness to receive the vaccine.

Key words: Knowledge, Willingness, Acceptability, Vaccine, Human Papilloma Virus.

Resumen

Antecedentes: Lamentablemente, los niveles de concienciación sobre el VPH entre la población general son bajos en todo el mundo. El objetivo del estudio era determinar los conocimientos, la aceptabilidad y la disposición a recibir la vacuna contra el VPH entre las mujeres del municipio de Owerri, en el estado de Imo.

Métodos: Se adoptó un diseño de estudio descriptivo transversal. Se utilizó un método de muestreo en varias etapas para reclutar a 424 mujeres para el estudio y se utilizó el paquete estadístico Statistical Package for Sciences the Social (SPSS) versión 20.0 para el análisis del estudio. Los datos se obtuvieron mediante un cuestionario semiestructurado basado en entrevistas.

Resultados: El estudio mostró que la mayoría de las mujeres (participantes) eran de origen Igbo 65,8% (280) y para el conocimiento de la vacuna contra el VPH, el 78,9% (335) de las encuestadas estaban de acuerdo en que habían oído hablar de la vacuna contra el VPH, mientras que el 21,0% (89) lo negaron. La mayoría de los encuestados afirmaron que aceptarían la vacuna contra el VPH si se les ofreciera la oportunidad (85,9%). Según la asociación entre las características sociodemográficas y la disposición a recibir la vacuna contra el VPH entre las mujeres, el estado civil (p = 0,0042) y el nivel educativo (p = 0,0015) tenían una relación estadísticamente significativa con la disposición a recibir la vacuna contra el VPH entre las mujeres.

Conclusiones: Este estudio estableció que aunque un número de mujeres mostró un conocimiento considerable de la vacuna contra el VPH, varias otras carecen de información relevante y este hallazgo es evidente en la disposición a recibir vacunas contra el VPH entre las encuestadas. Es necesario asesorar a las mujeres sobre la seguridad y eficacia de la vacuna contra el VPH para mejorar su disposición a recibirla.

Palabras clave: Conocimiento, Disposición, Aceptabilidad, Vacuna, Virus del Papiloma Humano.

Introduction

Human papillomavirus (HPV) vaccinations are shots that protect against contracting specific strains of the virus (HPV). There are HPV vaccinations that can defend against two, four, or nine different forms of HPV[1]. The HPV types 16 and 18 that are most likely to cause cervical cancer are at least partially protected by all HPV vaccinations. HPV vaccinations may prevent 70% of cervical cancer, according to estimates[1]. The high prevalence, mode of transmission, association with cervical cancer and availability of effective vaccines all have made Human Papillomavirus (HPV) a significant virus and of public health importance[2]. Cervical cancer is the second most common type of cancer occurring in women worldwide, it has caused the death of about 275,000 women with about 529,000 new cases yearly[1,3,4,5]. Some studies reported that more than 80% of these deaths occur in developing countries, where cervical cancer is the leading cause of death in adult females[6,7,8,9,10,11,12].

In Nigeria, cervical cancer is the most common genital tract malignancy among women[13]. Most of which are caused by HPV. Cancer is usually preceded by a premalignant stage which can be prevented by HPV immunization when appropriate and can be cured if detected early by regular screening[7]. Follow up of abnormal test results have also been recommended[2]. An estimate of 40.43 million women are at risk of developing cervical cancer and the number of women estimated to harbor cervical Human Papillomavirus (HPV) infection is about 23.7% with over 90% of invasive cervical cancer attributed to HPV subtypes 16 or 18, current estimates also indicates that 14,089 women are diagnosed and 8,240 die from cervical cancer[13]. HPV 16 and HPV 18 are responsible for 70% of cervical cancer and most non-cervical HPV associated cancers[14,15]. While HPV infection is the most important risk factor for cervical cancer, other predisposing factors include: early age of sexual activities, early marriage (below 20 years of age), multiple sexual partners, unprotected sex, long term use of hormonal contraceptives, increased number of pregnancies, smoking, and unhygienic practices[16,17].

HPV is one of the common sexually transmitted infections implicated in 5% of cancers globally including most cervical cancer cases [18]. In Sub Saharan Africa, HPV vaccine has been offered routinely to girls aged 11-13 years and cervical cancer screening to women aged 25-64 years since 2008[18]. Several reports have posited that HPV vaccination offers a unique opportunity for primary prevention of cervical cancer. Two HPV vaccines (Gardasil and Cervarix) protect against the two strains of HPV types 16 and 18, the vaccine is approved and recommended for use in females between 9-26 years of age, and the Advisory Committee on Immunization Practices (ACIP) recommends 'catch up vaccination' for females between 13-26 years of age.

A significant impact has been made on the health and well-being of the world through the different types of life-saving vaccines[7,9,19]. There is however the need for a robust public health and primary care partnership in order to continuously achieve national immunization coverage targets and low incidence of vaccine-preventable diseases. Some publications have revealed that primary care providers detect infectious disease among patients and report same to state or local health departments[1,3,4,5]. This information usually drives public health response. Public health usually works with primary care providers to ensure adequate access to vaccines and provision of healthcare services to individuals, families and the community as a whole. This collaboration and integration of public health and primary care influences and reinforces the capabilities of each entity to deliver critical services[4,5]. Primary care benefits from public health's role in policy, population health, health equity and education, while public health benefits from primary care's ability to provide individual patient assessment, disease management, care coordination, and quality improvement[1]. Most parents follow the advice of their primary health care providers and conform to the national immunization requirements[13,16,17].

According to some recent reports, HPV has remained prevalent with the presence of a safe and effective vaccine with highest risk period in the late adolescence and early adulthood[8,11]. Therefore, college students have been the target for HPV prevention and vaccination promotion particularly in regions with low vaccination rates.

Cervical cancer is the fourth most common cancer among women worldwide, with an estimated 528, 000 new cases and 266, 000 deaths in 2010[7,9,14,15,20,21]. Despite the fact that the Pap smear test is well integrated into the Nigerian healthcare system and widely accepted by women. HPV vaccine is recommended for female aged 20-45,[13]. The acceptance of HPV vaccination will be expected to depend on factors such as knowledge of HPV infection and its link to cervical cancer.

Regrettably, levels of HPV awareness among the general population are poor throughout the world[20,21]. Among the general population of Nigerian women, 24% have heard of HPV. In a cross-sectional survey on parents in Northern Nigeria, 22.63% have heard of HPV, 40.8% parents are willing to accept HPV vaccination for children[13]. Only 10% of high school students have heard of HPV, and only 19% know that HPV infection can lead to cervical cancer (Markowitz et al., 2017). It is unclear how much knowledge the general population in Nigeria has about HPV, such as how the virus is transmitted, how infection can be detected, and whether it is linked to cervical cancer. Therefore, it is due to this burden that this research aims to investigate the Knowledge, acceptability and willingness to receive HPV Vaccine among women in Owerri Municipal Imo State.

Methods

Study Design and Settings

A descriptive Cross-sectional Research design was adopted for this study on the Knowledge, acceptability and willingness to receive HPV Vaccine among women in Owerri Municipal Imo State.

This study included only women aged 18 years and above in Owerri Municipal LGA who were available and gave in their consent for the study. Women in Owerri Municipal LGA, who were sick, physically disabled and who refused to give in their consent were excluded from the study.

Sampling Size

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 (20,201)
e is margin of error (0.05)

Therefore,

$$n = \frac{N}{1+Ne^2}$$

$$\frac{20201}{1+20201 * (0.05)^2}$$

n = 392.23242718

Furthermore, to account for Non Response Rate, the sample size was increased by 10% = 0.10 = 392 x 0.10 = 39.2 ≈40
n =392+40 = 432.

Sampling Techniques

A Probability based Multi stage sampling method was adopted for the study on Knowledge, acceptability and willingness to receive HPV Vaccine among women in Owerri Municipal Imo State.

First stage: Selection of Wards /Communities
A total of six (6) communities were selected through simple random sampling via balloting which gave every ward an equal chance of being selected. And a total of 72 (i.e 432/6). questionnaires were allocated for each of the community.

Second stage: Selection of households
A systematic probability sampling method was used to select each household in the selected streets which gave each household an equal chance of selection.

Third stage: Selection of Respondents
The researcher purposefully selected residents present at the time of study. They were selected until the minimum sample size was reached to ensure that the appropriate number respondents were obtained from each of the communities namely Umuororonjo, Amawom, Umuonyeche, Umuodu and Umuoyima proportionately.

Data Collection

The instrument for data collection was a semi-structured questionnaire aimed to obtain relevant information on the Knowledge, acceptability and willingness to receive HPV Vaccine among women in Owerri Municipal Imo State. The Data tool (Questionnaire) consisted of Five (5) sections as follows:

Section A: Consisted of information on the socio demographic characteristics of respondents.
Section B: Consisted of questions on the level of knowledge of respondents towards HPV Vaccine.
Section C: Consisted of Questions on the acceptability of HPV vaccine among the respondents.
Section D: Consisted of questions on the willingness towards HPV vaccine among respondents in Owerri Municipal L.G.A Imo State.
Section E: Consisted of questions on the factors affecting the acceptability towards HPV vaccine among respondents in Owerri Municipal L.G.A Imo State.

Reliability of the instrument was determined using test retest method. 40 copies of the questionnaire were given to some respondents outside the area of study by the researcher. This area for reliability testing was Ihiagwa community in Owerri west LGA. This area shared similar characteristics with the Owerri Municipal LGA that was used for the study. Chrombach alpha test was used to test for the reliability of the questionnaire.

Data was obtained with the aid of Two (2) field assistants who were hired and trained to aid the researcher in the data collection process.

Data Analysis

The Statistical Package for the Social Sciences (SPSS) version 20 were used in the analysis of the data gotten from the study. Results were expressed in percentages, frequencies, tables and charts (Descriptive Statistics).

Ethical Consideration

A letter of introduction and ethical clearance were obtained from the Department of Public Health Ethical clearance committee in Federal University of Technology Owerri (FUTO) before the research was conducted. The purpose of the research was explained to each respondent and verbal informed consent obtained from them before inclusion into the study. Also, anonymity of the respondents was assured and ensured. The confidentiality of the information they gave was maintained.

Results

Socio-demographic Factors of the women

Table I revealed that 27.8% (118) of the women represented age groups between 25-34 and 45-49, 19.9% (85) of the women were 35-44 years of age, 13.8% (59) were aged 50 years and above, and 10.8% (46) aged 18-24 years. 65.8% (280) of the women were of Igbo origin, 19.1% (81) reported 'others', 11.8% (50) Yoruba, and 3.4% (14) Hausa/Fulani. 65.1% (276) of the respondents were Christians, 21.9% (93) listed religions not included in the options but label 'others', 11.3% (48) Muslims and 1.8% (8) Traditional.

Table I: Socio-demographic Factors of the women.

Characteristics	Frequency (n=424)	Percentage (%)
Age		
18-24	46	10.8
25-34	118	27.8
35-44	85	19.9
45-49	118	27.8
50 and Above	59	13.8
Total	**424**	**100**
Ethnicity		
Igbo	280	65.8
Hausa/Fulani	14	3.4
Yoruba	50	11.8
Others	81	19.1
Total	**424**	**100**
Religion		
Christianity	276	65.1
Muslim	48	11.3
Traditional	8	1.8
Others	93	21.9
Total	**424**	**100**
Marital Status		
Married	180	42.5
Single	118	27.8
Separated	82	19.3
Widowed	44	10.4
Total	**424**	**100**
Educational Level		
No formal education	29	6.7
Primary	38	8.8
Secondary	88	20.8
Tertiary	270	63.6
Total	**424**	**100**
Occupation		
Artisan e.g. Carpenter, Hairdresser, Tailor, Driver	41	9.7
Civil servant e.g. Teacher	202	47.6
Self-employed e.g. Trader, Photographer	36	8.4
Unemployed	15	3.4
Professionals e.g. Doctor, Nurse, Lawyer, Accountant	60	14.2
Total	**424**	**100**
What is your Level of Income		
1-1,000	16	3.6
2,000-10,000	27	6.4
11,000-30,000	47	11.1
31,000-60,000	86	20.1
61,000-100,000	79	18.6
Above 100,000	109	25.6
Others	60	14.1
Total	**424**	**100**
Are you satisfied with your monthly income?		
Yes	110	25.9
No	142	33.4
Somehow	172	40.7
Total	**424**	**100**
Number of Children (Parity)		
None	13	3.1
1	175	41.3
2	136	32.2
3 and above	99	23.5
Total	**424**	**100**
Do you have a Health plan/insurance at any healthcare		
Yes	145	34.1
No	279	65.8
Total	**424**	**100**

41.3% (175) of the women had a child, 32.2% (136) had two children, 23.5% (99) had 3 children and above, and 3.1% (13) had no children. Concerning the educational level of the respondents, 63.6% (270) were tertiary education level certificate holders, 20.8% (88) secondary, 8.8% (38) primary education, and 6.7% (29) of the women had no formal education. 47.6% (202) of the respondents were civil servants, 14.2% (60) professionals, 9.7% (41) were artisans, 8.4% (36) were self-employed, and 3.4% (15) were unemployed. On the monthly income level of the respondents, 25.6% (109) earned above 100,000, 20.1% (86) earned between 31,000-60,000, 18.6% (79) 61,000-100,000, 14.1% (60) earned figures not mentioned but label 'others', 11.1% (47) earned 11,000-30,000, 6.4% (27) from 2,000-10,000, and 3.6% (16) of the women earned a meagerly 1-1000 monthly. 40.7% (172) were not sure concerning monthly income satisfaction, 33.4% (142) were not satisfied, and 25.9% (110) of the women said "Yes". 42.5% (180) of the respondents were married, 27.8% (118) single, 19.3% (82) separated, and 10.4% (44) widowed. 65.8% (279) of the respondents did not have a health plan/insurance at any healthcare facility, while 34.1% (145) affirmed they did.

Knowledge of HPV Vaccine among Women

From **table II** below, 78.9% (335) of the respondents had heard about HPV vaccine, while 21.0% (89) denied. For example, sources include (**Figure 1**); 28.5% (95) health practitioners, 25.7% (86) social media, 23.5% (79)

school, 8.7% (29) each for Tv/radio programs and 'others' respectively, 3.1% (10) for newspapers/magazines, and 1.7% (6) from parents/family. Majority of the respondents replied "yes" when asked if 'Human papillomavirus (HPV) vaccines are vaccines that prevent infection by certain types of human papillomavirus' (97.4%), while 2.5% (9) replied "no". Also, 88.2% (296) of the women accepted that HPV vaccines prevent 70% of cervical cancer, 80% of anal cancer, 60% of vaginal cancer, 40% of vulvar cancer, and show more than 90% efficacy in preventing HPV-positive oropharyngeal cancers, while 11.7% (39) disagreed. Over 90% of the respondents also confirmed that HPV vaccines were safe (91.0%), while 8.9% (30) reported otherwise. 49.2% (165) of the women reported that cervical cancer screening is still required following HPV vaccination, while 50.7% (170) disagreed.

Figure 1: Sources of Information on HPV Vaccines among women.
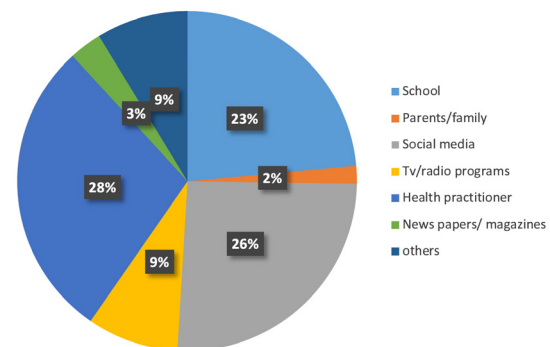
Table II: Knowledge of HPV Vaccine among Women.

Variables	Frequency (n=424)	Percentage (%)
Have you heard about HPV Vaccine?		
Yes	335	78.9
No	89	21.0
Total	**424**	**100**
What is your source of information?		
School	79	23.5
Parents/family	6	1.7
Social media	86	25.7
Tv/radio programs	29	8.7
Health practitioner	95	28.5
Newspapers/ magazines	10	3.1
Others	29	8.7
Total	**335**	**100**
Human papillomavirus (HPV) vaccines are vaccines that prevent infection by certain types of human papillomavirus?		
Yes	326	97.4
No	9	2.5
Total	**335**	**100**
HPV vaccines prevent 70% of cervical cancer, 80% of anal cancer, 60% of vaginal cancer, 40% of vulvar cancer, and show more than 90% efficacy in preventing HPV-positiveoropharyngeal cancers?		
Yes	296	88.2
No	39	11.7
Total	**335**	**100**
HPV vaccines are very safe		
Yes	305	91.0
No	30	8.9
Total	**335**	**100**
Cervical cancer screening is still required following HPV vaccination		
Yes	165	49.2
No	170	50.7
Total	**335**	**100**

Acceptability of HPV Vaccine among Women

Table III below illustrated the acceptability of HPV vaccine among the women in this survey. Majority of the respondents affirmed they would accept HPV vaccine if offered a chance (85.9%), while 14.1% (60) reported otherwise. 63.5% (269) of the respondents affirmed they had been advised to receive HPV vaccine by a physician, 35.2% (149) reported 'no', while 1.2% (5) said they could not remember. 69.8% (296) of the women denied receiving vaccination against cervical cancer and related, 8.9% (38) said 'yes', and 21.2% (90) could not remember. 29.3% (11) of the women who affirmed said 6-12 months ago, 21.3% (8) reported 2 years or more, 17.3% (7) reported more than a year but less than two years, and 1.3% (1) said "3 months ago". 'Less than a month' was reported by 30.6% (12). The reason for vaccination as reported by the women were 'just decided to go for the examination' 31.5% (12), 29.7% (11) cancer cases in the family, 16.2% (6) reported reasons not listed but mention 'others', 12.6% (5) said "for prevention", and 9.9% (4) reported they were presented with symptoms.

Willingness to receive HPV Vaccine among Women

From **table IV** below, 41.2% (175) of the women, agreed that they would accept HPV vaccination only if they were assured of its safety, 19.0% (81) strongly agreed, 6.1% (26) were undecided, 9.6% (41) disagreed, and 24.0% (102) strongly disagreed. 35.1% (149) of the respondents agreed that it was right to go for HPV vaccination irrespective of symptoms, 36.5% (155) were undecided, 9.4% (40) disagreed, 15.1% (64) strongly disagreed, and 4.0% (17) of the women strongly agreed. 28.2% (120) of the women strongly agreed that women should go for vaccination when it is appropriate, 21.4% (91) agreed, 17.8% (76) disagreed, 26.9% (114) strongly disagreed, and 5.7% (24) were undecided. 30.3% (128) strongly agreed that they would accept HPV vaccine because it increases the chances of living a healthier life, 26.4% (112) agreed, 0.6% (3) strongly disagreed, 18.8% (80) disagreed, and 23.9% (101) were undecided. Over half (54.0%) of the respondents 'strongly agreed' that they would accept the HPV Vaccination because the benefits of HPV vaccination outweighs any difficulty one might have going through in treatment, 23.8% (101) agreed, 5.8% (25) remained undecided, 10.1% (43) disagreed, and 6.2% (26) strongly disagreed. When the women were asked if they sought the consent of their family before going for HPV vaccination, 28.5% (121) agreed, 27.4% (116) undecided, 17.1% (73) strongly disagreed, 14.4% (61) disagreed, and 12.6% (53) strongly agreed.

Factors Influencing Willingness to receive HPV Vaccine among Women

From **table V** below, factors influencing willingness to receive HPV vaccine among employees include 41.5% (176) who listed lack of information, 18.2% (77) lack of time, 15.2% (65) financial constraints, 11.9% (51) cultural factors, and 5.1% (22) of the participants chose religious norms.

Association between Socio demographic Characteristics and willingness to receive HPV Vaccine among women

Table VI below shows the results for the test of a statistically significant association Socio demographic

Table III: Acceptability of HPV Vaccine among Women.

Variable	Frequency (n=424)	Percentage (%)
Would you accept HPV vaccine if offered a chance?		
Yes	364	85.9
No	60	14.1
Total	**424**	**100**
Has any physician advised you to receive HPV vaccination?		
Yes	269	63.5
No	149	35.2
Can't remember	5	1.2
Total	**424**	**100**
Have you vaccinated cervical cancer and related?		
Yes	38	8.9
No	296	69.8
Can't remember	90	21.2
Total	**424**	**100**
If YES, when was that?		
Less than a month	12	30.6
3 months ago	1	1.3
6-12 months ago	11	29.3
More than a year but less than two years	7	17.3
2 years or more	8	21.3
Total	**38**	**100**
What was your reason for the Vaccination?		
Presented with symptoms	4	9.9
Cancer cases in the family	11	29.7
For prevention	5	12.6
Just decided to go for the examination	12	31.5
Others	6	16.2
Total	**38**	**100**

characteristics and willingness to receive HPV vaccine among women. The table below shows that age was not significantly associated with willingness to receive HPV vaccine among women (P=0.735). Marital status was found to be significantly associated with willingness to receive HPV vaccine among women (P = 0.0042).

Also, educational level is significantly associated with willingness to receive HPV vaccine among the women (P = 0.0015). Moving further, the table reveals that level of income of the participants was not significantly associated with the willingness to receive HPV vaccine among women (P = 0.784).

Table IV: Attitude of the women towards the Uptake of Routine HPV vaccine.

Variable	Frequency (n=424)	Percentage (%)
I would accept HPV Vaccination only if I am assured of safety		
Strongly agree	81	19.0
Agree	175	41.2
Undecided	26	6.1
Strongly disagree	102	24.0
Disagree	41	9.6
Total	**424**	**100**
It is right to go for HPV Vaccination irrespective of symptoms		
Strongly agree	17	4.0
Agree	149	35.1
Undecided	155	36.5
Strongly disagree	64	15.1
Disagree	40	9.4
Total	**424**	**100**
A woman should go for Vaccination when it is appropriate		
Strongly agree	120	28.2
Agree	91	21.4
Undecided	24	5.7
Strongly disagree	114	26.9
Disagree	76	17.8
Total	**424**	**100**
I will accept HPV vaccine because it increases the chances of living a healthier life		
Strongly agree	128	30.3
Agree	112	26.4
Undecided	101	23.9
Strongly disagree	3	0.6
Disagree	80	18.8
Total	**424**	**100**
I will accept HPV Vaccination because the benefits of HPV vaccination outweighs the any difficulty one might have going through in treatment	Strongly agree	22954.0
Agree	101	23.8
Undecided	25	5.8
Strongly disagree	26	6.2
Disagree	43	10.1
Total	**424**	**100**
Before I accept HPV Vaccination I must seek the consent of my family before going for HPV vaccination		
Strongly agree	53	12.6
Agree	121	28.5
Undecided	116	27.4
Strongly disagree	73	17.1
Disagree	61	14.4
Total	**424**	**100**

Table V: Factors Influencing Willingness to receive HPV Vaccine among Women

Variable	Frequency (n=424)	Percentage (%)
Which of the factors influences your willingness to receive HPV vaccine?		
Lack of Information (Ignorance)	176	41.5
Financial Constraints	65	15.2
Distance to the Facility	33	7.8
Cultural Factors	51	11.9
Religious norms	22	5.1
Lack of time	77	18.2

Table VI: Association between Socio demographic Characteristics and willingness to receive HPV Vaccine among women.

Socio-demographics	X^2	D.F	P value	Decision
Age	6.411	36	0.735	NS
Marital Status	3.340	13	0.0042	S
Educational Level	4.008	24	0.0015	S
Level of Income	0.124	7	0.784	NS

NS: not significant   S: significant

Discussion

According to the findings of this study on the socio demographic characteristics of the respondents, 27.8% of the women were between the ages of 25 and 34. This data supports a statement in a publication by Ferlay et al.[10] that women in a similar HPV study done among women in ABSUTH had an average age of 30 years. The bulk of the respondents (65.1%) were Christians of Igbo descent, according to the study's findings (65.8%). This could be owing to the fact that the study was done in a region of Nigeria where Igbo and Christian people prevail. According to the findings, 65.8% of respondents did not have a health plan or insurance at any healthcare facility as seen in another study by[9].

This study found that about 78.9% of the respondents had heard about HPV vaccine. The high knowledge of HPV vaccine is also found in studies according to Chauke-Moagi & Mumba[8], (83.5%) and Levine et al.[1], (79.2%), and thus corroborates this finding. The women mentioned 'health practitioners' (28.5%) as the commonest source of information on the HPV vaccine, followed by 25.7% who reported 'social media'. Another study however mentioned 'school' (23.5%), and Tv/radio (22.1%), and hence disagrees with the findings of this study[6]. A similar study by Ozawa et al. (2011) corroborates this finding and suggested that 26.1% of the women affirmed they obtained information on HPV vaccine from health practitioners. Several other studies have mentioned 'health practitioners, social media, and school as principal sources of information on HPV vaccination[6]. 97.4% of the women correctly agreed with the study definition of Human papilloma-virus (HPV) vaccines with about 88.2% of the women also affirming the potency of HPV vaccines in preventing 70% of cervical cancer, 80% of anal cancer, 60% of vaginal cancer, 40% of vulvar cancer, and more than 90% efficacy in preventing HPV-positive oropharyngeal cancers. Some studies have shown poor knowledge of the efficacy of HPV vaccines among participants, while others have illustrated very good knowledge of the use of HPV vaccines[3,11,12]. 91.0% of the study population rightly confirmed that HPV vaccines were safe. This further confirms the perceived good knowledge of HPV vaccines among the respondents.

In concordance with recent studies based on the acceptability of HPV vaccine among the women, over three quarters of the women (85.9%) would accept HPV vaccine if offered a chance[4]. 63.5% of the respondents affirmed they had been advised to receive HPV vaccine by a physician. This is in consistence with statements in a publication by Saville,[20] that 65% of the women in an ABSUTH study affirmed they had been advised to receive the HPV vaccine. 35.2% reported otherwise. Whereas 45.1% of the respondents in another study denied being well-advised to receive the HPV vaccine by any medical personnel[5]. Only 8.9% of the women had received vaccination against cervical cancer and 31.5% of them 'just decided to go for the examination. A few others mentioned 'cancer cases in the family' (29.7%). A similar study has demonstrated cancer cases in the family (23.5%) and the need to go for an examination (25.6%) as reasons for cervical cancer vaccination[20].

Concerning the willingness of women to receive the HPV vaccine, study showed that 41.2% of the women 'agreed' that they would receive the HPV vaccine if assured of its safety. The next common response included 19.0% of the women who 'strongly agreed'. Similar findings on willingness of women to receive HPV vaccine in Delta suggested that over half of the respondents 'agreed' to the importance of HPV vaccines. Additionally, a study by Gakidou et al.[15] conducted in an Illorin medical facility revealed that 29.5% of the nurses in that survey emphasized the advantages associated with receiving HPV vaccine. The women were undecided concerning if it was right to go for HPV vaccination irrespective of symptoms, (36.5%). A statement in a recent publication by Ozawa et al.[7], goes against this finding that 37.2% of the respondents 'agreed' but supports another observation[14]. Over half of the respondents (54.0%) 'strongly agreed' that they would accept the HPV vaccination because the benefits of HPV vaccination outweighs any difficulty one might have going through in treatment. Several other studies have suggested willingness of the women to receive HPV vaccines if they were thoroughly informed of the process[14]. This shows a lack of information on the advantages of receiving HPV vaccines among the women of Owerri municipal. The most recurrent factor influencing the willingness to receive HPV vaccine among the women was lack of appropriate information (41.5%). This is similar to a finding by Alrum & Jamal,[21] that 43.4% of the women opined that they lacked adequate information and this influenced uptake of HPV vaccine. Another study by Sitas et al.,[19] corresponds to this finding that 46.6% of women who did not receive HPV vaccines reported reasons such as 'Ignorance'. Findings concerning the test of a statistically significant association between socio demographic characteristics and willingness to receive HPV vaccine among women, marital status (P = 0.0042) and educational level (P = 0.0015) were found to be significantly associated with willingness to receive HPV vaccine among women. The possibility that spouse and/or children of the women influenced their decisions to receive HPV vaccine. This study also observed the willingness of educated groups to receive the HPV vaccine compared to women who had attained primary education and respondents with no formal education at all. Other studies have also illustrated the association of education and willingness to receive vaccines among respondents (p = 0.0012, p = 0.102, and p = 0.043)[7]. A similar study demonstrated the influence of family members and decisions to receive vaccines[9].

Conclusion and recommendation

Observation from this study establish that even though a number of women showed considerable knowledge of HPV vaccine, several others are deficient of relevant information and this finding is evident in the willingness to receive HPV vaccines among respondents. Factors such as 'lack of information' and 'time' also evidently affected uptake of HPV vaccines among the women in Owerri municipal. The study also recommends the following:

1. Counselling of women on the safety and efficacy of HPV vaccine.
2. Awareness campaigns must provide accurate information especially on the misconceptions regarding the HPV vaccines so that the women and their families can make informed choices.
3. Emphasis must be made on the types of HPV vaccine that will be beneficial to the women.
4. Accessibility to HPV vaccine must be considered and policies should be established for easy and wide administration.
5. Factors such as 'time', and financial 'constraints' must be considered to promote the process for women.

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ORIGINAL

Trastuzumab Response in Iraqi Women with Her2 Positive Breast Cancer: The Role of PIK3CA Oncogene Mutations at E542k and E545k

Respuesta al trastuzumab en mujeres iraquíes con cáncer de mama Her2 positivo: El papel de las mutaciones del oncogén PIK3CA en E542k y E545k

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Abstract

Introduction: Breast cancer (BC) frequently carries PIK3CA mutations. These frequently include the helical domains and exon 10 of the protein kinase, which can activate it. In addition to being expensive, trastuzumab, a human epidermal growth factor receptor 2 antagonist, is ineffective in 20% to 25% of patients with related Her2-positive BC. The response to treatment is significantly influenced by genetic differences. The study's goal was to determine whether the presence of PIK3CA polymorphism at sites on E542k and E545k would affect Iraqi patients with Her2-positive breast cancer's propensity to respond to trastuzumab (TRS) or not. in addition to cardiac toxicity.

Method: The Department of Oncology/Diwaniya University Hospital recruited 60 Her2-positive Iraqi BC women who had been receiving TRS for at least 1 year. Patients were divided into non-responders and responders using the Response Evaluation Criteria in Solid Tumors (RECIST). After DNA amplification by polymerase chain reaction, the DNA was sequenced using the Sanger method to detect polymorphisms at positions E542k and E545k.

Result: Data analysis revealed that there was no statistically significant association between Her2 promoter region E542k and E545k polymorphism and the propensity to respond positively to TRS. Reactive and unresponsive females had a very significant difference in the frequency of the combination of mutations.

Key words: Breast cancer, Her2 positive, Trastuzumab, Genetic polymorphism.

Resumen

Introducción: El cáncer de mama (CM) es frecuentemente portador de mutaciones en PIK3CA. Éstas suelen incluir los dominios helicoidales y el exón 10 de la proteína cinasa, que pueden activarla. Además de ser caro, el trastuzumab, un antagonista del receptor 2 del factor de crecimiento epidérmico humano, es ineficaz en el 20% al 25% de las pacientes con CB Her2-positivo relacionado. Las diferencias genéticas influyen significativamente en la respuesta al tratamiento. El objetivo del estudio era determinar si la presencia del polimorfismo PIK3CA en los sitios E542k y E545k afectaría a la propensión de las pacientes iraquíes con cáncer de mama Her2-positivo a responder o no al trastuzumab (TRS), además de a la toxicidad cardiaca.

Metodología: El Departamento de Oncología del Hospital Universitario de Diwaniya reclutó a 60 mujeres iraquíes con cáncer de mama Her2 positivo que habían estado recibiendo TRS durante al menos 1 año. Las pacientes se dividieron en no respondedoras y respondedoras utilizando los Criterios de Evaluación de la Respuesta en Tumores Sólidos (RECIST). Tras la amplificación del ADN mediante la reacción en cadena de la polimerasa, se secuenció el ADN con el método Sanger para detectar polimorfismos en las posiciones E542k y E545k.

Resultados: El análisis de los datos reveló que no existía una asociación estadísticamente significativa entre el polimorfismo E542k y E545k de la región promotora de Her2 y la propensión a responder positivamente al TRS. Las hembras reactivas y no reactivas presentaron una diferencia muy significativa en la frecuencia de la combinación de mutaciones.

Palabras clave: Cáncer de mama, Her2 positivo, Trastuzumab, Polimorfismo genético.

Introduction

Women in Iraq are most commonly diagnosed with breast cancer (BC)[1]. Breast cancer is believed to be the leading cause of cancer death in women[2-3] and is responsible for approximately 25% of all new cancer cases in women worldwide[1-2]. Breast cancer, which can affect one or both breasts, is known as breast cancer. Fat, ducts and glands make up the breast. Breastfeeding gives birth to babies and produces milk to breastfeed them. Both secondary (metastatic) or primary BC are possible[4]. The major health problem, cancer, tends to develop drug resistance, increasing efforts to develop new protocols for cancer treatment[5]. The HER2 ECD transmembrane protein is targeted by humanized antibodies known as TRS. This was initially approved for the treatment of HER2-positive breast cancer. The extracellular domain of the HER2 receptor can be attacked to produce ADCC or to antagonize HER2 receptors, which have an anti-tumor effect. The method of anti-HER2 therapy has been shown to involve blocking upstream signaling pathways and vasculature, activating cell cycle arrest or death, and impairing genome repair[6].

TRS is used independently or in conjunction with other treatments. The HER2 protein, present on the surface of certain cancer cells, is a target of this drug[7]. This could improve the immune system's ability to fight cancer cells. TRS is a monoclonal substance and a potent HER2 inhibitor, also known as Herzuma[8-9]. Researchers are currently evaluating available PI3K antagonists; investigate their potential relevance in HER2+ breast cancer; and in this article provide an additional comprehensive article on current studies of PI3K inhibitors in HER2+ disease. Researchers are also evaluating the status of screening for somatic PIK3CA mutations and looking for information gaps that could prevent the successful use of PI3K drugs in chemotherapy for HER2+ prostate cancer. The PI3K signaling pathway is necessary for tumor development, replication, or survival[10]. PI3K is used to transmit signals from oncogenesis receptor tyrosine kinases (RTKs), which include insulin-like growth receptor 1, platelet-derived neurotrophic receptor, and female epidermal proliferation regulatory receptors 2 (HER2). Its serine-threonine kinase AKT is attracted to membranes through this phosphorylation of (PIP2) (PIP3), which is achieved by activation of 3-kinase. AKT and mTOR (mammalian target of rapamycin) complexes are stimulated by RTK-based signaling. AKT inhibits apoptosis while promoting growth, epithelial-mesenchymal transformation, infiltration, metastasis, or vasculature. The absence of heterozygosity, inhibitory mutations and epigenetic inactivation is often thought to enhance the effect of PI3K stimulation[11]. The catalytic subunit (PI3K) is encoded by the PIK3CA oncogene. The PI3K/AKT/mTOR signaling pathway is more frequently activated in cancers with PIK3CA gene mutations, including breast cancer[12].

Among the mutations found in the PIK3CA gene are the E542k and E545k mutations. At positions 545 and 542 of the protein sequence it causes lysine (k) to replace glutamic acid (E). In breast cancer, this mutation causes an increase in PI3K activity, which in turn triggers the activation of downstream signaling pathways[13].

HER2-positive breast cancer is often treated with targeted therapy, such as TRS. Although it has demonstrated great effectiveness, cardiac side effects may occur. Decreased left ventricular ejection fraction (LVEF) is the main symptom of cardiac toxicity associated with TrRS. During treatment, cardiac biomarkers such as B-type natriuretic peptide (BNP) and troponin I can be used to monitor cardiac function[14].

Since it takes 12 months for a patient's response to TRS treatment to become apparent, this is a long period of time to determine whether or not the patient is responding. During this period, in addition to the expensive but clinically ineffective treatment, the patient may also be exposed to risky side effects. Therefore, to avoid exposing patients to the toxicity of this drug without any clinical benefit, we should study this allele as a determinant marker of response in the future for those receiving TRS treatment. The aim of the present study was to determine whether the presence of single nucleotide polymorphisms in the pik3ca gene at positions E542k and E545k can influence the propensity of Iraqi patients to become non-responders or responders. Previous studies have examined the influence of single nucleotide polymorphisms in PIK3CA on the propensity to become positive in TRS non-responders.

Patients and methods

This article was part of a research project that ran from December 10, 2021 to August 8, 2022. Sixty patients with BC who tested positive for Her2 were included in the study and classified according to the revised version 2010 (ACO)/ (RECIST). Standard BC modifications[15]. The patients were from the Iraqi Oncology Department of Diwaniya Teaching Hospital. This department provides services to a wide variety of Iraqi communities, including urban, rural and inner-city areas of various provinces. The ethical clearance number (RECAUBCP7102021A) was agreed on July 10, 2021 by the Scientific and Ethics Committee of the Baghdad P-University School of Pharmacy and the Medical Department of Rheumatology of Baghdad University Hospital. Additionally, each participant provided written informed consent.

Patients' selection
Sixty-nine patients with Her2-positive breast cancer who met the following inclusion criteria received trastuzumab alone as sole therapy during the study. However, only sixty-three patients agreed to participate in the study, and only sixty of them met all the requirements.

The inclusion criteria:

- Women under 18 years of age with a history of HER2-positive breast cancer determined by biopsy.
- After the full twelve-month period, patients received TRS.
- Before starting treatment with TRS, normal cardiac, renal and hepatic function should be monitored in all patients[16].
- Disease evaluation: clinical, radiological or endoscopic using radiographs, plain films, computed tomography (CT), ultrasound (US) and magnetic resonance imaging (MRI). Patients were also asked to complete the TRS. the first dose was administered as an intravenous infusion of 8 mg/kg over 90 minutes. After a continuous 12-month period of intravenous infusion of 6 mg/kg over 30-90 minutes every three weeks with no history of missed doses.

The exclusion criteria:

- People with breast cancer and other concomitant neoplastic disease.
- Less than a year has passed since treatment with TRS.
- Has already undergone radiotherapy.
- Infections such as those caused by bacteria, HIV and tuberculosis.
- History of heart disease.

Patients' classification:

After 12 continuous months of TRS treatment, patients were divided into non-responders and responders according to (RECIST) criteria[14], as shown in **figure 1**. Stable disease is one in which no new lesions appear. appears. No lesion changes in size by more than 20% and no new lesions appear. All visible or radiographic tumors must disappear completely to be considered a complete response. If the maximum radius of metastatic lesions decreases by 30% or less without the appearance of new lesions, this is considered a partial response. Response was defined as stable disease, complete response, or partial response within 12 months (clinical benefit = stable disease + complete response + partial response). People who met the criteria for disease progression, defined as the appearance of new lesions or an increase in the size of existing lesions at a rate of at least 20%, were classified as "non-responders", while those who met the criteria the criteria for responding were classified as "responders". Patients were divided into two groups based on their responses. Thirty BC patients who did not respond to TRS formed the first group (group A). 30 BC patients who responded well to TRS formed the second group (group B).

Data collection

Simple patient interviews using an information sheet specially designed for this study allowed information on disease duration, age and weight to be collected. By dividing the weight in kilograms by the square of the height in meters, the body mass index (BMI) can be calculated[17].

Sample collection and preparation

Collect a venous blood sample (5 ml) from the patient's forearm. Then, deoxyribonucleic acid was extracted from blood (2 ml) using an ethylenediaminetetraacetic acid tube. After centrifugation for 10 min, the remaining blood (3 ml) was poured into a gel tube. The remaining serum was collected and stored in an Eppendorf tube at -20°C until all samples were obtained. Creatine kinase-MB, cardiac

Figure 1: Flow diagram for the study participants.
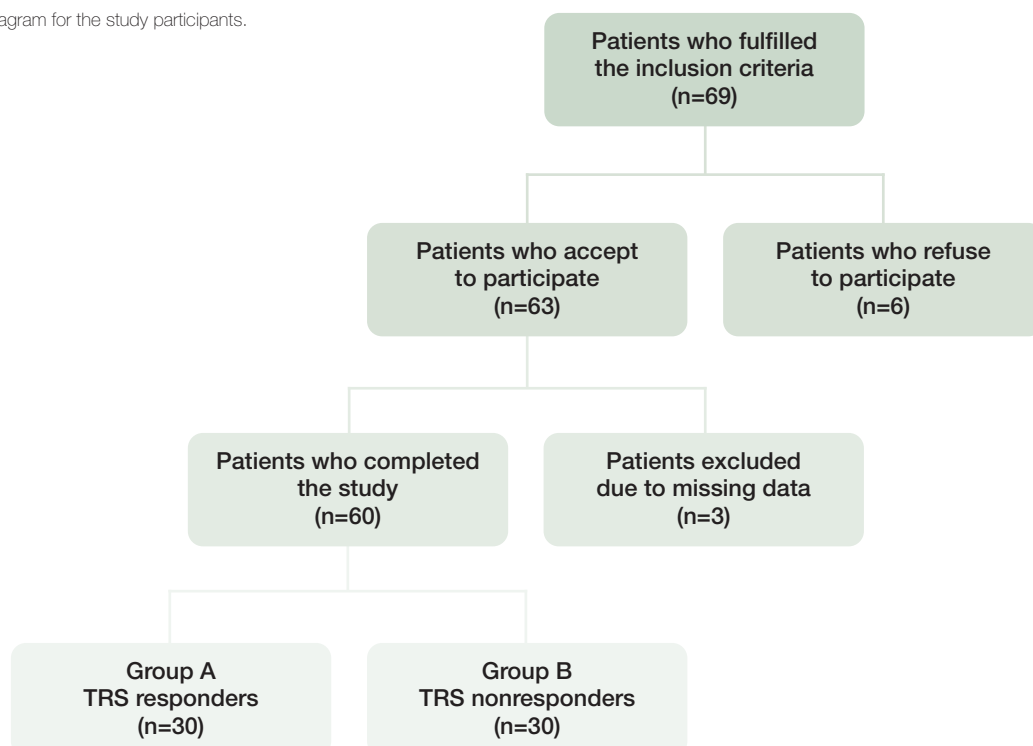
troponin I, and cardiac troponin T were measured using an enzyme immunoassay. One China; Cat. The device was used to measure and identify cardiac troponin I, troponin T, and creatine kinase-MB levels. NO. (fitted ELIZA kit) CSB-SL0536hu, CSB-Sl1747hu and CSB-Sl1746hu. ELIZA[18] is used in this test. Direct DNA purification is offered by the \"Promega ReliaPrepTM Blood gDNA Miniprep System\" for DNA extraction. A hybrid thermal cycler and polymerase chain reaction were used for enlargement[19].

Statistical analysis

The data was verified using the SPSS program for Windows 26.0. Constant fluctuations are called the standard error of the mean or mean value. Alleles and genotypes are described using frequencies and percentages[18]. There is a possibility that more than 0.05 is considered statistically significant. The Shapiro-Wilk test was used to verify the normality of the results[19]. The t test is used for distributed data to determine when there is a significant difference in parameters and statistical characteristics between the responding group and the non-responding group. To examine the change in the mean between more than two groups, the analysis of variance test is used. And if an important difference between the three sample means or a significant difference between the three-sample means was detected through the analysis of variance, a post hoc analysis was used. To determine the extent to which the percentages of the test groups varied, Fisher or chi-square tests were used. If any of the expected values in a 2 x 2 comparison are greater than 5, the Fisher test is used. Phi correlation is used to quantify the probability of non-response and the relationship between genotypes.

Results

Demographics and clinical characteristics of the study groups.

Table I summarizes the statistical characteristics of the study groups. Patients in the present study consented. Additionally, there were differences in smoking levels between non-respondents and respondents (P). After twelve months of Herceptin administration, non-responders and responders showed differences in creatine kinase MB, TN I and T (value 0.04).

DNA concentration

The extracted DNA concentration ranged from 20 to 30 µg/ml across all samples.

PCR amplification Result

Figure 2 shows the PIK3CA magnification of the samples. PIK3CA is a magnification of samples divided by electrophoresis on 1% agarose gel and stained with ethidium bromide.

Figure 2: Enlargement of the human PIK3CA gene was obtained by 1% agarose gel electrophoresis and ethidium bromide staining. Conductive marker M:100bp. the 522 bp PCR products in lanes 39 to 57.

Analysis of Sanger sequence data

A study of the single nucleotide polymorphism of PIK3CA. The PCR products were directly sequenced. There were homozygous wild-type and heterozygous mutant genotypes of the E542K mutation.

Figure 3: Sequence analysis of the leading strand of the E542K mutation. The lower sequence represents the heterozygous mutant genotype, while the upper sequence represents the homozygous wild type.

Table I: Demographics and clinical characteristics of the study groups.

Variables		Responder group (N=30)	Non-Responder group (N=30)	p-value
Age (yrs.)		51.86 ±8.148	48.76 ±8.601	0.1[a]
BMI (Kg/m²)		63.37 ±8.277	63.20 ±9.297	0.1[a]
Smoking status (N%)	Non smoker	5(16.7%)	12(40.0%)	0.04*[c]
	Smoker	25(83.3%)	18(60.0%)	
CK_-MB ng/ml	Baseline	10.912 ±2.404	10.989 ±2.370	0.9
	After 12 months	12.012 ±2.419	11.458 ±2.075	0.3
Tn T Pg/ml	Baseline	158.696 ±185.82	134.652 ±26.429	0.4
	After 12 months	130.55 ±32.381	149.590 ±38.88	0.04*
Tn I Pg/ml	Baseline	626.66 ±169.029	732.489 ±195.09	0.183
	After 12 months	671.177 ±151.33	1008.93 ±150.66	0.0001*

Results are reported as means ±SD or frequency (percentage).CK_MB Creatine kinase MB. Tn-troponin a: 2-sample independent t-test. b: chi-square test. C: Fisher's exact test.

Figure 4: Sequence analysis of the leading strand of the E545K mutation. The lower sequence represents the heterozygous mutant genotype, while the upper sequence represents the homozygous wild type.
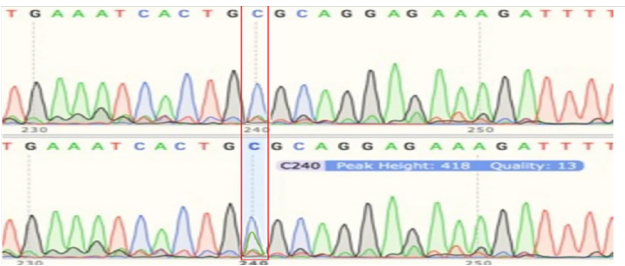
According to mutation analysis, 20% of unresponsive women had the E542K mutation, compared to only 33% of responders, with no apparent difference. Non-responding women (23 points, 33 percent) and responsive women (33 points, 33 percent) had almost identical distributions of the E545K mutation, but there was a significant difference (OR = 8 points 83, CI to 95 percent = 1 point 0-76). points). 96, p= 0 point 049). **Table II** shows that the combination of mutations was significantly more common in unresponsive women (40%) than in responsive women (6.67%) (OR = 9.33, 95% CI = 1.87 to 46, 68, p = 0.007).

Discussion

Breast cancer, currently the most common form of cancer worldwide, continues to increase in incidence every year. 2.3 million new cases are expected in 2020. Human epidermal growth factor receptor 2 (HER-2) plays an important role in breast cancer and serves as a diagnostic marker and target for genetic engineering[20-21].

The demographic information and clinical characteristics of the study group are shown in **table I**. That is, a non-responder group (N=30) and a responder group (N=30). The table contains several variables with corresponding p-values, which indicate the statistical significance of the differences observed between the two groups. The first two variables, age and BMI, showed no statistically significant differences between the non-responder and responder groups, as indicated by the p-value of 0.1. In terms of clinical characteristics, baseline values of creatine kinase-MB (CK-MB), troponin T (TnT) and Tn

I showed no significant differences between the two groups, as demonstrated by the p-value of 0.9, 0, 4 and 0.183. Everything is fine. However, troponin I (TnI) levels at 12 months showed a significant difference between groups with a p-value of 0.0001. Due to higher doses of anthracyclines (mainly in combination with trastuzumab), non-responders at 12 months had higher mean baseline TnI values (1,008.93 pg/ml) than responders (671.177 pg/ml) in previous study.: Elevated cTn levels have also been shown to be a predictor of cardiac toxicity in breast cancer patients[22]. T and I cTn isotypes are very important for the assessment and diagnosis of ACS risk as well as other causes such as chemotherapy. It is a sensitive and specific indicator of myocardial damage[23]. Cardiac biomarkers such as NT-pro BNP, CK-MB or myoglobin have no proven value in predicting the course of cardiovascular events. The challenge is to effectively treat JK while minimizing toxicity[24]. In the present study, the presence of E542K and E545K mutations was significantly associated with trastuzumab resistance (OR = 9.33, 95% CI = 1.87 to 46.68, p = 0.007). This means that carriers of this mutation have a 9.33 times greater risk of not responding to trastuzumab compared to wild-type carriers. These findings are consistent with many previous studies conducted around the world.

Cizkova and colleagues[25] reported that the prevalence of PIK3CA gene mutations in patients with HER2-positive breast cancer is relatively high and has prognostic implications, and that these mutations lead to resistance to trastuzumab. Vasan et al.[26] showed that the presence of a double PIK3CA mutation in the same allele led to increased PI3K activity and enhanced downstream signaling, cell proliferation and tumor growth. Huang et al.[27] showed that most human gain-of-function mutations of p110α and p85 occur at the interface between them or at residues located between the p110α kinase domain and other domains of the catalytic subunit. These mutations increase Her2 activity and contribute to resistance to trastuzumab. Additionally, Burns et al. [28] showed a significantly worse response to trastuzumab in a cohort of 55 breast cancer patients with low PTEN levels and the presence of oncogenic PIK3CA mutations. In contrast, many other studies have reported no association. In this context, Loi et al. [29], evaluating PIK3CA gene mutations in 705 HER2-positive breast cancer samples, reported that PIK3CA gene mutations

Table II: Mutational profile of E542K and E545K in responsive and non-responsive women with her-2 new breast cancer for trastuzumab.

Mutation	Non-responsive (n=30)	Responsive (n=30)	p-value	OR (95%CI)
E542K Wild type Mutant	24 (80%) 6 (20%)	29 (96.67%) 1 (3.33%)	0.076	1.0 7.25 (0.81-64.46)
E545K Wild type Mutant	23 (76.67%) 7(23.33%)	29 (96.67%) 1 (3.33%)	0.049	1.0 8.83 (1.0-76.96)
E542K/E545K Wild type Mutant	18 (60%) 12 (40%)	28 (93.33%) 2 (6.67%)	0.007	1.0 9.33 (1.87-46.68)

were not significantly associated with trastuzumab resistance. In a meta-analysis study, Wang et al. [30] also concluded that in patients with HER2-positive BC, PIK3CA mutation was not associated with response to trastuzumab-based therapy. Finally, an Italian study showed that there was no association between mutations in the PIK3CA gene and resistance to trastuzumab[31].

Interestingly, there might even be a link between PIK3CA mutation and response to trastuzumab. A systematic review of breast cancer clinical trials including 2,587 breast cancer cases from 12 independent studies found that patients with tumors harboring a PIK3CA mutation have better clinical outcomes than those with a wild-type PIK3CA gene[32].

These conflicting results strongly suggest that trastuzumab resistance is multifactorial and that the impact of PIK3CA mutations on the clinical course of breast cancer appears to vary depending on the background of other genomic alterations such as HER2 status. hormonal status and other genetic and epigenetic influences.

The possible fundamental component of increased resistance to trastuzumab in women with E542K and E545K alterations is suggested by the work of the PIK3 protein. It has been well established that the p110α catalytic subunit of PI3K is encoded by the quality PIK3CA, which phosphorylates phosphatidylinositol 4,5-biphosphate (PIP2) at the third position of the inositol ring, producing PIP3, after inscription into the cellular film

by part of the receptor -mediated activation. In this way, Akt is phosphorylated, stimulating a signaling cascade involving the mammalian target of rapamycin (mTOR) and downstream effectors[33]. Hotspot transformations within helical or kinase spaces hyperactivate the PI3K/Akt pathway downstream of the ErbB family[34]. among which H1047R, E545K and E542K are the most common transformation sites, accounting for approximately 63% of all PIK3CA modifications[35]. In vitro information informed that the unusual execution of the PI3K/Akt pathway through the effect of PIK3CA changes was involved in resistance to anti-HER2 targeted trastuzumab[36].

Conclusion

After 12 months of treatment with trastuzumab, both troponin I and T increased significantly in non-responders compared to responders, whereas CK-MD had no such association with response to trastuzumab. Troponins I and T are cardiotoxic markers, but also have excellent predictive value for trastuzumab resistance in Her-2-positive breast cancer. Resistance to trastuzumab is significantly related to the E545K mutation, either present alone or in combination with the E542K mutation.

Competing interests

Authors have declared that they have no competing interests.

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ORIGINAL

Five Finger Hypnosis Therapy for Anxiety: A Case Study

Terapia de hipnosis con cinco dedos para la ansiedad: un estudio de caso

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Abstract

Introduction: Student anxiety can affect personal well-being and academic performance. Nursing care intervention should be given to cope with anxiety. The purpose of the study was to report the effect of five-finger hypnotic therapy in reducing anxiety in college students.

Methods: A case study was conducted in West Java, Indonesia. The implementation uses the nursing process, the Roy adaptation model and instruments to measure anxiety. Participants were selected by purposive sampling. Eight participants were selected for nursing care with an intervention focus on five-finger hypnosis therapy.

Results: Subjective evaluation of participants stated a decrease in anxiety, and the results of pre- and post-administration of five-finger hypnotic therapy using the Beck Anxiety Inventory (BAI) showed a significant decrease in anxiety.

Conclusions: Five-finger hypnotic therapy is influential in reducing anxiety experienced by students. It can be done alone by students. The therapy can be one of the skills trained in college students to reduce anxiety independently.

Key words: Anxiety, student, case study, hypnosis.

Resumen

Introducción: La ansiedad de los estudiantes puede afectar el bienestar personal y el rendimiento académico. Se debe realizar una intervención de cuidados de enfermería para afrontar la ansiedad. El propósito del estudio fue informar el efecto de la terapia hipnótica con cinco dedos para reducir la ansiedad en estudiantes universitarios.

Metodología: Se llevó a cabo un estudio de casos en Java Occidental, Indonesia. La implementación utiliza el proceso de enfermería, el modelo de adaptación de Roy e instrumentos para medir la ansiedad. Los participantes fueron seleccionados mediante muestreo intencional. Se seleccionaron ocho participantes para recibir atención de enfermería con una intervención centrada en la terapia de hipnosis con cinco dedos.

Resultados: La evaluación subjetiva de los participantes indicó una disminución de la ansiedad, y los resultados de la administración previa y posterior de la terapia hipnótica con cinco dedos utilizando el Inventario de Ansiedad de Beck (BAI) mostraron una disminución significativa de la ansiedad.

Conclusiones: La terapia hipnótica con cinco dedos influye en la reducción de la ansiedad que experimentan los estudiantes. Los estudiantes pueden hacerlo solos. La terapia puede ser una de las habilidades entrenadas en estudiantes universitarios para reducir la ansiedad de forma independiente.

Palabras clave: Ansiedad, estudiante, estudio de caso, hipnosis.

Introduction

Students entering university education experience a period of developmental crisis. These developments include biological, psychological, and social. This results from the creation of new relationships, new identities and increased autonomy and responsibility[1,2]. Students are at risk of stress, anxiety and depression. This condition can have an impact on academic performance[3,4]. Study results estimate that 12-50% of college students worldwide have at least one diagnostic criterion for one or more mental health problems[5,4]. The most common mental health problems are anxiety and depression[6]. Mental health problems can be experienced in life as a student.

Causes of psychological problems during campus life include academic pressure (such as exams and college load), lack of free time, competition, worries about not being able to meet parental expectations, establishing new personal relationships and studying in a foreign place[7,4]; biological factors such as age and gender, predominantly female[8,4]; and financial burden[9,4]. Many factors that trigger psychological problems in students.

The systematic review results suggest that mental health problems among students have become a global concern. The prevalence of anxiety and depression in health students is also reported to be higher than the general population in low-income and middle-income countries[10]. Another study found that 7.04% of students in Asia had anxiety disorders and one-fifth of students in China experienced stress, depression and anxiety[11,12]. The anxiety experienced can have an impact on various aspects of student life.

Anxiety is one of the mental health problems in college students.The anxieties faced by students include facing new changes and challenges. When students deal with anxiety, they will succeed in their study careers. The anxiety thye initially met motivated their success[13]. Anxiety experienced by students will adversely affect academic performance, quality of life, decreased empathy, academic dishonesty, have contributed to alcohol and drug abuse[14,5,15]. Despite the adverse effects of anxiety on students, the study's results stated that most students did not receive or seek treatment[16,17]. Only one-fifth of students in high-income countries seek health help to cope with anxiety[18,19,17]. The anxiety experienced by students needs to be addressed.

Psychotherapy underwent an evolution, with different modalities and evolved as a branch of the existing approach. Changes have occurred in response to theories, research evidence and attempts to understand individual vulnerability, psychopathology and psychiatric disorders[20].Psychotherapeutic interventions that have been given and proven to overcome anxiety in students are yoga and meditation[21], meditation and *Cognitive Behavioral Therapy*[22], Mildfullness[23]. Anxiety in students can be overcome with psychotherapy.

Handling anxiety in the campus environment through practical psychotherapy interventions is essential to help students who are identified as experiencing anxiety. Finding cases and managing anxiety early can prevent worsening anxiety experienced by students. The psychotherapeutic intervention given by mental health nurses is five-finger hypnosis. Five-finger hypnosis refers to the theory of hypnosis carried out by mental health nurses to focus, relax, concentrate and suggest through words to relaxation and lower symptoms. Five-finger hypnosis is also self-hypnotic so that after being trained by a mental health nurse, the client can perform independently[24]. The study focused on the use of five-finger hypnosis on college students with anxiety. In-depth case analysis is performed using a case study design.

Methods

Purpose
Describes the effect of five-finger hypnosis as a nursing intervention on nursing anxiety diagnosis. The theoretical framework used in nursing care draws on Roy's adaptation model.

Ethical aspects
The study was conducted on eight participants. Participants have received an explanation and filled out an approval form related to research and publication of case data. The institution's research ethics committee has approved the research activities numbered 031/USTB/Ethics/Results/VI/2023. Participants have read, understood the case report's contents and signed an agreement to publish the data submitted to the researcher.

Type of study
Descriptive research involving eight cases. Research is developed according to CARE guidelines (CaseReport) which aims to create, disseminate and implement adequately according to the standards that case studies do, transparently inform results and guide clinical practice[25,26].

Methodological procedures
This case study describes nursing care provided from June 19-25, 2023, to eight participants who experienced anxiety. Nursing care is carried out based on the nursing process. The assessment was conducted by nursing students and psychiatric nursing specialist nurses who are experienced in their fields. Determination of diagnoses, interventions and outcomes refers to NANDA International Nursing Diagnoses: Definitions and Classification[27], Nursing Intervention Classification (NIC)[28] and Nursing Outcomes Classification (NOC)[29].

Study site

The study site was a university in West Bandung District, Indonesia.

Data collection and organization

An instrument used to measure anxiety before and after nursing intervention: Beck Anxiety Inventory (BAI). BAI is an instrument measuring anxiety level consisting of 21 questions. Participants answered according to each symptom felt by choosing 0 (not at all), 1 (little/mild), 2 (sufficient/moderate), and 3 (very disturbing/severe). Total 0-21 (mild anxiety), 22-35 (moderate anxiety) and 36-63 (severe anxiety)[21,26].

Data analysis

Quantitative data (**Table IV**) were obtained from BAI instruments, measured and analyzed using descriptive statistics to assess the outcome of five-finger hypnotic therapy. Nursing care activities are made in a systematic report guided by the stage of the nursing process. Roy's adaptation model is used as a theoretical foundation for predicting and assessing behavior as an adaptation process.

Results

Case Overview

Eight students from one of the West Java universities were willing to participate in this study. The results of the nursing assessment obtained 2 participants were male and 6 participants were female. All participants were 21 years old and expressed worry caused by coursework that had to be completed. The worry experienced has a physical impact in the form of dizziness, uncomplicated diarrhoea and difficulty sleeping. Participants also expressed difficulty concentrating and always thinking about worries (**Table I**).

Assessments related to medical history were carried out with a focus on focal, contextual and residual stimuli by Roy's adaptation model (**Table II**).

Nursing diagnosis and intervention

Based on the study's results, eight participants obtained behavioral and emotional characteristics: crying, expressing fear / worry, expressing distress and unable to sleep. The physiological characteristics found are uncomplicated diarrhoea, no appetite and dizziness. Found cognitive characteristics: difficulty concentrating and always thinking about problems.

Table I: Results of nursing assessment.

Participans	Age (years)	Gender	Results
P1	21	Man	Worry about the final project. Things that are felt are not calm, dizziness, there is a feeling of fear, uncomplicated diarrhoea, difficulty sleeping, and always thinking about what is worrying. I tried to reduce the anxiety experienced by praying and telling others, but I failed.
P2	21	Man	Worry about lectures in the last semester. Things that are felt are often not calm, dizziness, a feeling of fear, and always thinking about what is worrying so it is challenging to concentrate. Trying to reduce anxiety experienced by praying but has not succeeded.
P3	21	Girl	Worry about the tasks that need to be completed. Things that are felt are often not calm; there is a feeling of fear, no appetite, always thinking about what is worrying.
P4	21	Girl	Worry about being at the final level with many heavy tasks. Things that are felt are often not calm, crying, difficulty sleeping, fear, and always thinking about what is worrying, so it is not easy to concentrate.
P5	21	Girl	Worry about a lot of tasks. Things that are felt are often not calm, difficulty sleeping, a feeling of fear, always thinking about what is worrying so it is difficult to concentrate.
P6	21	Girl	There is a fear of not being able to complete learning well. Things that are felt are often not calm, difficulty sleeping, a feeling of fear, always thinking about what is worrying, so it is difficult to concentrate.
P7	21	Girl	The task is increasing, afraid to do well or not, often not calm, difficulty sleeping, a feeling of fear, and always thinking about what is worrying, make it difficult to concentrate.
P8	21	Girl	I was confused about what kind of final project I did, often not calm, having difficulty sleeping, a fear of being unable to finish, and always thinking about what was worrying so it was not easy to concentrate.

Table II: Focal, contextual and residual stimuli studied based on Roy adaptation model.

Participants	Focal	Contextual	Residual
P1	Tasks of scientific work at the final level	Having parents, academic supervisors, and friends but not yet providing comfort (fear of telling parents or supervisors, feeling friends also have the same problem)	Fear of failure and not completing tasks well
P2			Fear of a prolonged study period
P3			Fear of not finishing on time
P4			Fear of the study period lengthening and becoming a burden on parents
P5			Fear of not being able to complete the final task
P6			Fear of failure and disappointing parents
P7			Fear of lower achievements
P8			Fear of not being able to finish well

Behavioral and emotional, physiological and cognitive characteristics, according to NANDA 2021 refer to nursing diagnoses: anxiety (Herdman et al., 2021). Nursing intervention refers to the NIC (Bulecheck et al., 2013) with implementation as per **table III** and focused on five-finger hypnotic therapy.

The stages of five-finger hypnotic therapy include:

1. Set a comfortable position.

2. Take a deep breath for one minute while closing the eyes.

3. Insist in my heart that "I intend to enter physical and mental relaxation".

4. Give gratitude and deeply enjoy the breath that relaxes the body and mind.

5. Feel the present time the body becomes really relaxed, comfortable, and very light.

6. Counting down from ten to one will help to enter more profound relaxation.

7. Impart and feel how grateful you are when you find out about your circumstances, bring up your feelings of pleasure, happiness and pleasure for your current condition (while touching your thumb with your index finger).

8. Imagine and feel that your friends, family, relatives, and relatives are always present and supporting you during this time. Friends who accompany you and help during lectures bring encouragement, courage and positive thinking at all times (while touching the thumb with the middle finger).

9. Imagine and feel when getting great happiness, feel when getting the most beautiful gift that until now can not be forgotten, and feel that getting happiness, achievements and praise as something to wait for (while touching the thumb with the ring finger).

10. Imaginate and feel the present moment life becomes colorful with the presence of a significant person, affection, and a warm hug from a very loved one and feel very happy with their presence (while touching the thumb with the little finger).

11. After 5-10 minutes, end the relaxation. Count one to five and will slowly wake up again in a very fresh, healthy, and favourable condition. First, take a deep breath and exhale freely; second, move your fingers, and present yourself enterely in this place; third, you can really be aware of the surroundings completely and clearly; fourth, straighten your body, and prepare to open your eyes; Fifth, please open your eyes and feel a fresh, fit, healthy, and very positive body condition.

12. Feel the condition of the body after relaxing the five fingers.

Nursing intervention five-finger hypnosis therapy was carried out for seven days for 25-30 minutes each time the intervention showed a decrease in anxiety score before and after the intervention (**Table IV**).

Table III: Nursing interventions and activities.

Nursing Intervention (NIC)	Nursing activities
Reduction of anxiety	Help clients identify situations that trigger anxiety.
	Use an instrument to measure anxiety levels. Teach breath exercises to promote relaxation. Teach five-finger hypnotic therapy.
Counseling	Educate about anxiety and train clients to replace thoughts that can increase anxiety with positive thoughts.
Distraction	Encourage clients to choose distraction techniques such as listening to music, deep breathing exercises and positive affirmations.

Table IV: Results of participants' anxiety levels based on Beck Anxiety Inventory (BAI) instruments before and after nursing interventions.

Participans	Before Intervention		After Intervention	
	Score	Interpretation	Score	Interpretation
I	14	Mild anxiety	5	Mild anxiety
II	36	Severe anxiety	12	Mild anxiety
III	17	Mild anxiety	6	Mild anxiety
IV	25	Moderate anxiety	7	Mild anxiety
V	21	Mild anxiety	8	Mild anxiety
VI	27	Moderate anxiety	9	Mild anxiety
VII	30	Moderate anxiety	9	Mild anxiety
VIII	23	Moderate anxiety	7	Mild anxiety

Discussion

The results of previous studies stated that 22.2% of students experienced mild anxiety, 1.8% moderate anxiety and 0.7% severe anxiety. Anxiety is more experienced by female students who have a higher educational background[30]. The anxiety experienced by students can affect individual functioning. Anxiety is a mental health problem that students often experience, so prevention programs are needed to reduce the prevalence of anxiety. The results showed that cognitive behavior therapy and mindfulness can be done well among students[31]. The current results, before the intervention, anxiety was in the mild-severe range after five-finger hypnotic therapy changed to mild anxiety.

Five-finger hypnosis is a mind-body intervention that focuses on the interaction of brain, body, mind, spirit and behavior to use the mind to change physical behavioral functions and improve psychologically and thus decrease anxiety. Five-finger hypnosis is self-hypnosis that is useful for psychological intervention in overcoming anxiety. The five-finger hypnosis exercise given to students is a fast, cost-effective and safe way of self-hypnosis to overcome anxiety in students.

Mental health nurses can positively provide nursing care to students to overcome anxiety with a non-pharmacological intervention: five-finger hypnosis exercises. Roy's theoretical framework contributed to the nursing care provided. Individuals in the context of students will be able to improve their health by maintaining adaptive behavior and being able to change ineffective behavior. Students must be able to adapt and maintain psychological well-being.

Limitations of the study

A limitation of this study is that it is difficult to thoroughly evaluate and explore the components of Roy's theory in the selected case study.

Contribution to the field of nursing, health or public policy

The case studies conducted contribute to managing anxiety experienced by students in the educational environment. Five-finger hypnotic therapy can be a standard nursing intervention given to anxiety experienced by college students.

Conclusions

Five-finger hypnotic therapy can be given as a mental health nursing intervention to overcome anxiety experienced by students. Students can do five-finger hypnotic therapy as a form of self-hypnosis to overcome anxiety experienced.

Competing interests

Authors have declared that they have no competing interests.

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ORIGINAL

Evaluation of the Effects of Cinnamon, CuO, and ZnO Nanoparticles on the Antibacterial Properties of a Luting Glass Ionomer Orthodontic Bands Cements: A Systematic Review and Meta-analysis

Evaluación de los efectos de las nanopartículas de canela, CuO y ZnO sobre las propiedades antibacterianas de cementos para bandas de ortodoncia de ionómero de vidrio: una revisión sistemática y un metanálisis

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Abstract

Objective: Cinnamon, Zinc oxide, and Copper oxide nanoparticles have been investigated for their antibacterial effects in the current study. Systematic Review and Meta-analysis were performed to evaluate the antibacterial properties of luting glass ionomer cement used in orthodontic bands containing cinnamon, CuO, and ZnO nanoparticles.

Material and methods: Using the PRISMA 2020 checklist, a systematic review and meta-analysis are presented in this study. EBSCO, ISI Web of Knowledge, PubMed, Scopus, Web of Science, and Embase databases were searched for systematic literature until May 2023. An inverse-variance method and a fixed effect model were used for mean differences to calculate a 95% confidence interval. The meta-analysis was carried out using Stata/MP V.17.

Results: The initial review screened abstracts from 213 studies, two authors reviewed 31 full texts, 7 studies were selected for the secondary review, and duplicate studies were eliminated. The mean difference in antibacterial effect on S. mutans between 4% cinnamon NPs vs. the control group was 12.33 (MD, 12.33 95% CI 12.11, 12.55; p=0.00). The mean difference in antibacterial effect on S. mutans between 4% Copper oxide nanoparticles was 10.02 (MD, 10.02 95% CI 9.97, 10.07). The addition of 4% ZnO NPs caused a significant increase and empowered the antibacterial property against S. mutans bacteria.

Conclusion: The present meta-analysis shows that cinnamon, zinc oxide, and copper oxide nanoparticles are effective against S. mutans.

Key words: Dental Cements, Glass Ionomer Cements, Nanoparticles, Orthodontics, Streptococcus mutans.

Resumen

Objetivos: En el presente estudio se han investigado las nanopartículas de canela, óxido de zinc y óxido de cobre por sus efectos antibacterianos. Se realizaron una revisión sistemática y un metanálisis para evaluar las propiedades antibacterianas del cemento de ionómero de vidrio utilizado en bandas de ortodoncia que contienen nanopartículas de canela, CuO y ZnO.

Métodos: Utilizando la lista de verificación PRISMA 2020, en este estudio se presenta una revisión sistemática y un metanálisis. Se realizaron búsquedas de literatura sistemática en las bases de datos EBSCO, ISI Web of Knowledge, PubMed, Scopus, Web of Science y Embase hasta mayo de 2023. Se utilizaron un método de varianza inversa y un modelo de efectos fijos para las diferencias de medias para calcular un intervalo de confianza del 95%. El metanálisis se realizó utilizando Stata/MP V.17.

Resultados: La revisión inicial examinó los resúmenes de 213 estudios, dos autores revisaron 31 textos completos, se seleccionaron 7 estudios para la revisión secundaria y se eliminaron los estudios duplicados. La diferencia media en el efecto antibacteriano sobre S. mutans entre las NP de canela al 4 % versus el grupo de control fue de 12,33 (DM, 12,33; IC del 95 %: 12,11, 12,55; p = 0,00). La diferencia media en el efecto antibacteriano sobre S. mutans entre las nanopartículas de óxido de cobre al 4 % fue de 10,02 (DM, 10,02; IC del 95 %: 9,97 a 10,07). La adición de 4% de NP de ZnO provocó un aumento significativo y potenció la propiedad antibacteriana contra la bacteria S. mutans.

Conclusión: El presente metanálisis muestra que las nanopartículas de canela, óxido de zinc y óxido de cobre son efectivas contra S. mutans.

Palabras clave: Cementos Dentales, Cementos de Ionómero de Vidrio, Nanopartículas, Ortodoncia, Streptococcus mutans.

Introduction

Orthodontic bands were an essential component of fixed orthodontic treatments introduced at the end of the 19th century[1]. These bands had disadvantages, including the higher demineralization of tooth enamel. Also, problems such as difficulty brushing teeth and plaque accumulation were other disadvantages[2]. During fixed orthodontic treatment, the incidence of white spot lesions (WSL) is high; studies show this prevalence is 45.8% to 68.4%[3]. Recently, Glass ionomer cement (GICs) has been considered one of the best options for cementing orthodontic bands, which has good biocompatibility and chemical adhesion to teeth[4]. Studies have shown that GICs have the most vital anti-caries activity among dental materials, and this advantage could be due to their fluoride-releasing ability and remineralization potential[5]. Some studies have shown that GICs have a low activity rate against microorganisms[6-8]. In order to solve this problem, adding nanoparticles to GICs is suggested to increase the antimicrobial activity of cement[9]. Studies have investigated the effect of adding ceramic bioactive particles, glass powders, and other chemicals to GIC powder to increase antibacterial properties.

Nanoparticles can facilitate antimicrobial activity due to their small size and increased surface-to-volume ratio. However, there are challenges in this regard because researchers believe that nanoparticles may change the biological metabolic pathways of human cells and lead to the development of cancer or other diseases; therefore, maintaining human health is very important[10,11]. The use of traditional and herbal materials against bacteria has been reported in some studies[12]. Cinnamon is one of the substances with anti-inflammatory properties and is known as an anti-caries substance. On the other hand, its other benefits are having antioxidant, antimicrobial, and cardioprotective propertie[13]. Studies have shown that cinnamon nanoparticles had antibacterial activity against Streptococcus mutans (S mutans)[12]. Studies have also reported the strong antimicrobial properties of zinc oxide (ZnO) nanoparticles. The literature shows antimicrobial properties when adding zinc oxide nanoparticles to dental materials[14,15]. Other nanoparticles with antimicrobial activity reported in some studies are copper oxide (CuO) nanoparticles[16,17]. In order to provide strong evidence, a comprehensive investigation of the antimicrobial effectiveness of cinnamon, CuO, and ZnO nanoparticles for cementing orthodontic bands is essential. The present study evaluates a glass ionomer cement's antibacterial properties for luting orthodontic bands using cinnamon, CuO, and ZnO nanoparticles.

Material and Methods

Search strategy

The PRISMA 2020 checklist was used for systematic reviews and meta-analyses[18]. The study used keywords related to its objectives to search all international databases, including PubMed, Scopus, Science Direct, ISI, Web of Knowledge, and Embase, until May 2022. In addition, related articles were found using the Google Scholar search engine. MeSH keywords:

("Orthodontic Appliances, Fixed"[Mesh]) OR "Orthodontic Appliances"[Mesh]) AND "Dental Cements"[Mesh]) OR "Dental Bonding"[Mesh]) OR "Glass Ionomer Cements"[Mesh]) AND "Nanoparticles"[Mesh]) OR ("Nanoparticles/microbiology"[Mesh] OR "Nanoparticles/ organization and administration"[Mesh] OR "Nanoparticles/ statistics and numerical data"[Mesh] OR "Nanoparticles/ toxicity"[Mesh])) AND "Zinc Oxide"[Mesh]) AND "cupric oxide" [Supplementary Concept]) AND "cinnamon oil, leaf" [Supplementary Concept]) AND "Streptococcus mutans"[Mesh]) AND ("Anti-Bacterial Agents"[Mesh] OR "Anti-Bacterial Agents" [Pharmacological Action] OR "Microbial Sensitivity Tests"[Mesh]).

The Data items, selection process, and data collection

The checklist included the author's name, year of publication, study design, sample size, number of control groups, number of intervention groups, type of intervention group, assess the antimicrobial property and antibacterial activity assessment was extracted and reported in **table II**. Additionally, meta-analysis data were extracted from the studies, including antibacterial effects. We selected all articles based on the inclusion criteria, screened the records independently by two reviewers, and retrieved each report.

Eligibility criteria

Inclusion criteria: A response to PICO was the inclusion criterion, as shown in **table I**. Articles published in English, in-vitro, and in-vivo studies and studies that assessed the antibacterial effect of adding cinnamon CuO and ZnO nanoparticles on glass ionomer cement.

Exclusion criteria

Case studies, Review papers, and case reports. Access to full-text studies is not available.

Study risk of bias assessment

In order to assess the quality of studies, modified CONSORT criteria (Reporting guidelines for preclinical in

Table I: PICO strategy.

PICO Strategy	Description
P	Population: Orthodontic bands
I	Intervention: A luting GIC was constructed using cinnamon, zinc oxide, and copper oxide NPs
C	Comparison: Non-modified GIC
O	Outcome: Antibacterial activity

vitro studies on dental materials) were used[19]. Each study was reviewed based on 14 items, and a yes or no answer indicates the parameters. The items were as follows:

A structured summary includes the trial design, a detailed description of the research methods, results, and conclusions. Including the scientific background and explanation of rationale, specific objectives, and hypothesis, and the intervention of each group, including when and how it was administered, replicable with sufficient detail, completely defined. Measuring the outcome according to predefined primary and secondary criteria, a description of how and when they were assessed, how the sample size was determined, a method for generating random allocation sequences, the random allocation sequence mechanism, which generates random allocation sequences, who was blinded after intervention assignment, comparison of groups using statistical methods, the results for each group and estimates of the effect size and precision, the limitations of the trial, sources of potential bias, where to find the full trial protocol, imprecision, if the relevant multiplicity of analysis, funding, and other support are available.

A modified and adapted version of the Cochrane risk of bias tool was used. Scores were assigned to each item ranging from 2, 1, or 0. Scores of 0 to 3 indicate a low risk of bias, scores of 4 to 7 indicate a moderate risk, and scores of 8 to 10 indicate a high risk of bias. The lowest score in this tool was 0, and the highest score was 10[20].

Data analysis
The data analysis was carried out using STATA/MP V.17. The inverse-variance method and fixed effect models were used to calculate the 95% confidence interval. I^2 showed heterogeneity due to using random effects to deal with potential heterogeneity. Values above 50% indicate moderate or high heterogeneity, whereas values below 50% indicate low heterogeneity.

Results

Study selection
During the initial search, 213 articles related to the keywords were identified. The records of 5 studies were

duplicates, 4 articles were removed due to automation tools marking them as ineligible, and 11 were removed for other reasons. As a next step, 193 abstracts were reviewed, and after that, 162 articles were excluded from the research based on the exclusion criteria. In reviewing the full texts of 31 articles, 24 studies were excluded according to the inclusion criteria, and seven studies were selected (**Figure 1**).

Study characteristics
The data extracted from the studies are presented in **table II**.

Figure 1: PRISMA 2020 Checklist.
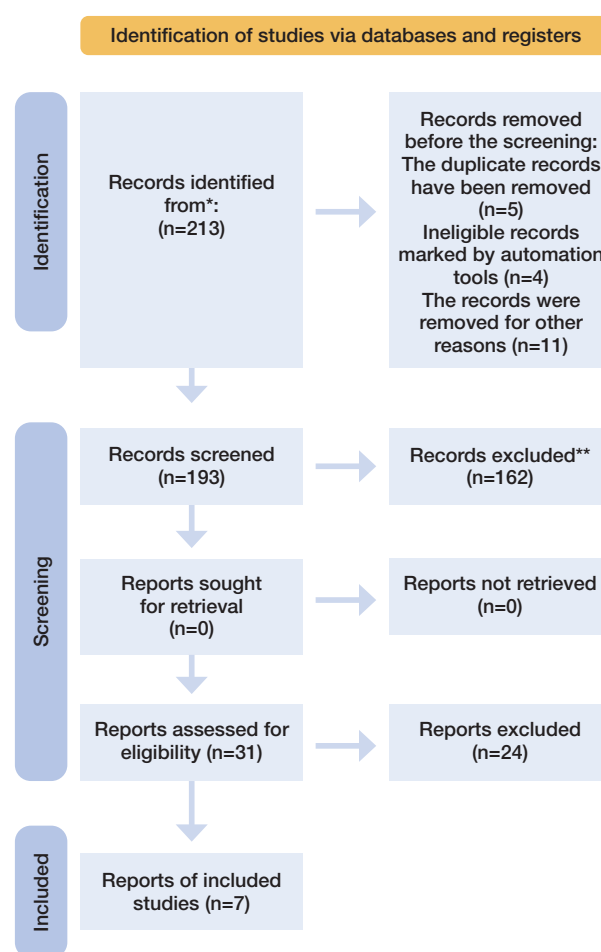
Table II: Summary of data.

No	Study. Years	Study design	Sample size	Nanoparticle type (n)	Number of the control group	Assess the antimicrobial property	Bacterial strain
1	Shafaee et al., 2022[21]	In-vitro	78	Cinnamon (26), ZnO (26), and CuO (26)	26	Agar disc diffusion test	S. mutans
2	Pourhajibagher et al., 2022[22]	Ex-vivo	50	ZnO (45)	5	Biofilm inhibition test	S. mutans
3	Malekhoseini et al., 2021[14]	Ex-vivo	50	ZnO (40)	10	Mueller-Hinton agar culture medium	S. mutans
4	Aguilar-Perez et al., 2020[6]	In-vitro	15	Cuo (12)	3	Agar diffusion test	S. mutans
5	Toodehzaeim et al., 2018[23]	In-vitro	40	Cuo (30)	10	Agar diffusion test	S. mutans
6	Garcia et al., 2017[24]	In-vitro	27	ZnO (18)	9	Antibacterial test	S. mutans and S. sanguinis
7	Vanajassun et al., 2014[25]	In-vitro	10	ZnO (5)	5	Agar diffusion test	S. mutans

S. mutans: Streptococcus mutant

The risk of bias in studies

The bias assessment tool identified four studies with a moderate risk of bias and three with a low risk of bias (**Tables III** and **IV**).

Based on the bias assessment tool, four studies were identified as moderate risk of bias and three as low risk of bias (**Tables III** and **IV**).

Antibacterial activity
Cinnamon nanoparticles

Figure 2 shows the effects of cinnamon nanoparticles on the antibacterial properties of glass ionomer cement. Mean differences of antibacterial effect on S. mutans between 1% cinnamon NPs, 2% cinnamon NPs, and 4% cinnamon NPs vs. control group was 10 (MD, 10 95% CI 9.33, 10.67; p=0.00), 11 (MD, 11 95% CI 10.94,

Table III: Quality of the included studies.

Study. Years	Item													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Shafaee et al., 2022[21]	🟢	🟢	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🟢	🔴	🔴	🔴	🔴
Pourhajibagher et al., 2022[22]	🟢	🟢	🟢	🟢	🟢	🟢	🔴	🔴	🔴	🟢	🟢	🟢	🔴	🔴
Malekhoseini et al., 2021[14]	🟢	🟢	🟢	🟢	🟢	🔴	🔴	🔴	🔴	🟢	🟢	🟢	🟢	🔴
Aguilar-Perez et al., 2020[6]	🟢	🟢	🟢	🟢	🟢	🟢	🔴	🔴	🟢	🟢	🟢	🟢	🟢	🔴
Toodehzaeim et al., 2018[23]	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🟢	🟢	🟢	🔴	🔴
Garcia et al., 2017[24]	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🟢	🟢	🟢	🔴	🔴
Vanajassun et al., 2014[25]	🟢	🟢	🟢	🟢	🔴	🔴	🔴	🔴	🔴	🟢	🟢	🟢	🔴	🔴
	🟢	🟢	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🟢	🔴	🔴	🔴	🔴

Yes: 🟢 No: 🔴

Table IV: The assessment of risks.

Study. Years	The concealment of allocations	Sample size	Blinding	Assessment methods	Reporting selective outcomes	Risk of bias
Shafaee et al., 2022[21]	1	1	2	0	0	Moderate
Pourhajibagher et al., 2022[22]	1	0	2	0	0	Low
Malekhoseini et al., 2021[14]	1	0	2	0	0	Low
Aguilar-Perez et al., 2020[6]	1	0	2	0	0	Low
Toodehzaeim et al., 2018[23]	1	1	2	0	0	Moderate
Garcia et al., 2017[24]	1	1	2	0	0	Moderate
Vanajassun et al., 2014[25]	1	1	2	0	0	Moderate

Figure 2: Cinnamon nanoparticles addition into the GIC.
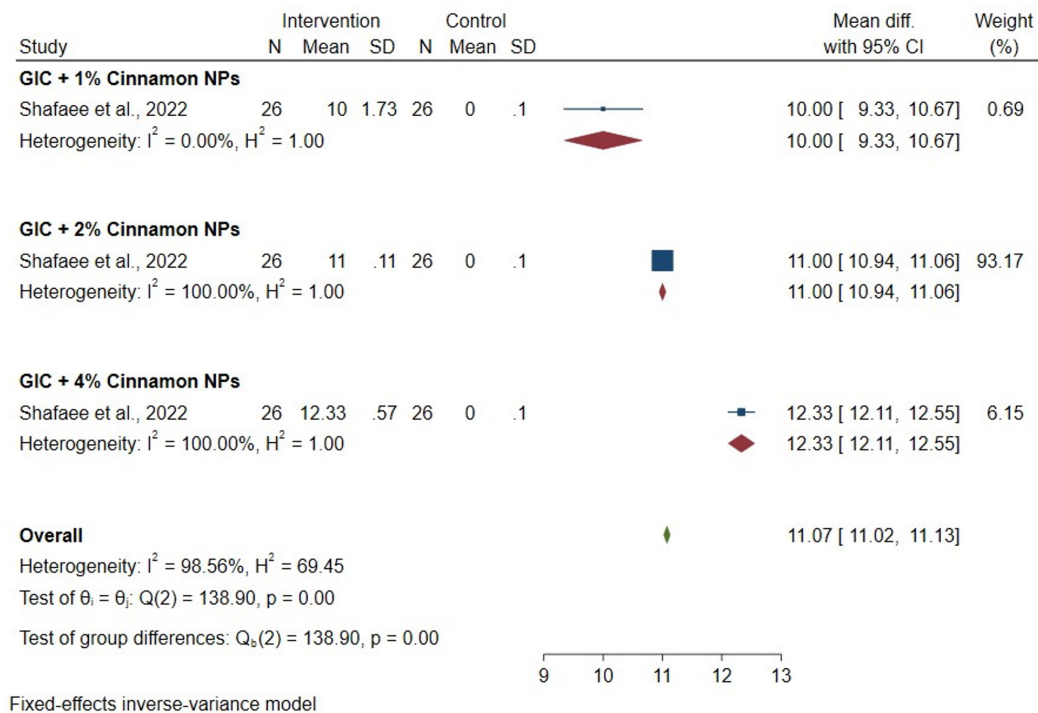
11.06; p=0.00), 12.33 (MD, 12.33 95% CI 12.11, 12.55; p=0.00), respectively. With the addition of 4% cinnamon nanoparticles, the antibacterial activity was significantly enhanced against S. mutans bacteria (**Figure 2**). Overall mean differences of antibacterial effect were 11.07 (MD, 11.07 95% CI 11.02, 11.13). The test of group differences showed significant differences between groups (p=0.00).

CuO nanoparticles

Figure 3 shows how adding CuO NPs to glass ionomer cement affects its antibacterial properties. Mean differences in antibacterial effect on S. mutans between 1% cinnamon NPs, 2% cinnamon NPs, and 4% cinnamon NPs, 0.01% cinnamon NPs, and 0.5% cinnamon NPs vs. control group was 8.79 (MD, 8.79 95% CI 8.74, 8.84; I²=99.99%, high heterogeneity), 1.49 (MD, 1.49 95% CI 1.33, 1.64; I2=99.89%, high heterogeneity), 10.02 (MD, 10.02 95% CI 9.97, 10.07; I²=99.99%, high heterogeneity) and 2 (MD, 2 95% CI 1.77, 2.23), 3 (MD, 3 95% CI 2.81, 3.19) respectively. The addition of 4% CuO NPs caused a significant increase and empowered the antibacterial property against S. mutans bacteria (**Figure 3**). Overall mean differences of antibacterial effect were 8.64 (MD, 8.64 95% CI 8.61, 8.68). The test of group differences showed significant differences between groups (p=0.00).

Figure 3: CuO nanoparticles addition to the GIC.
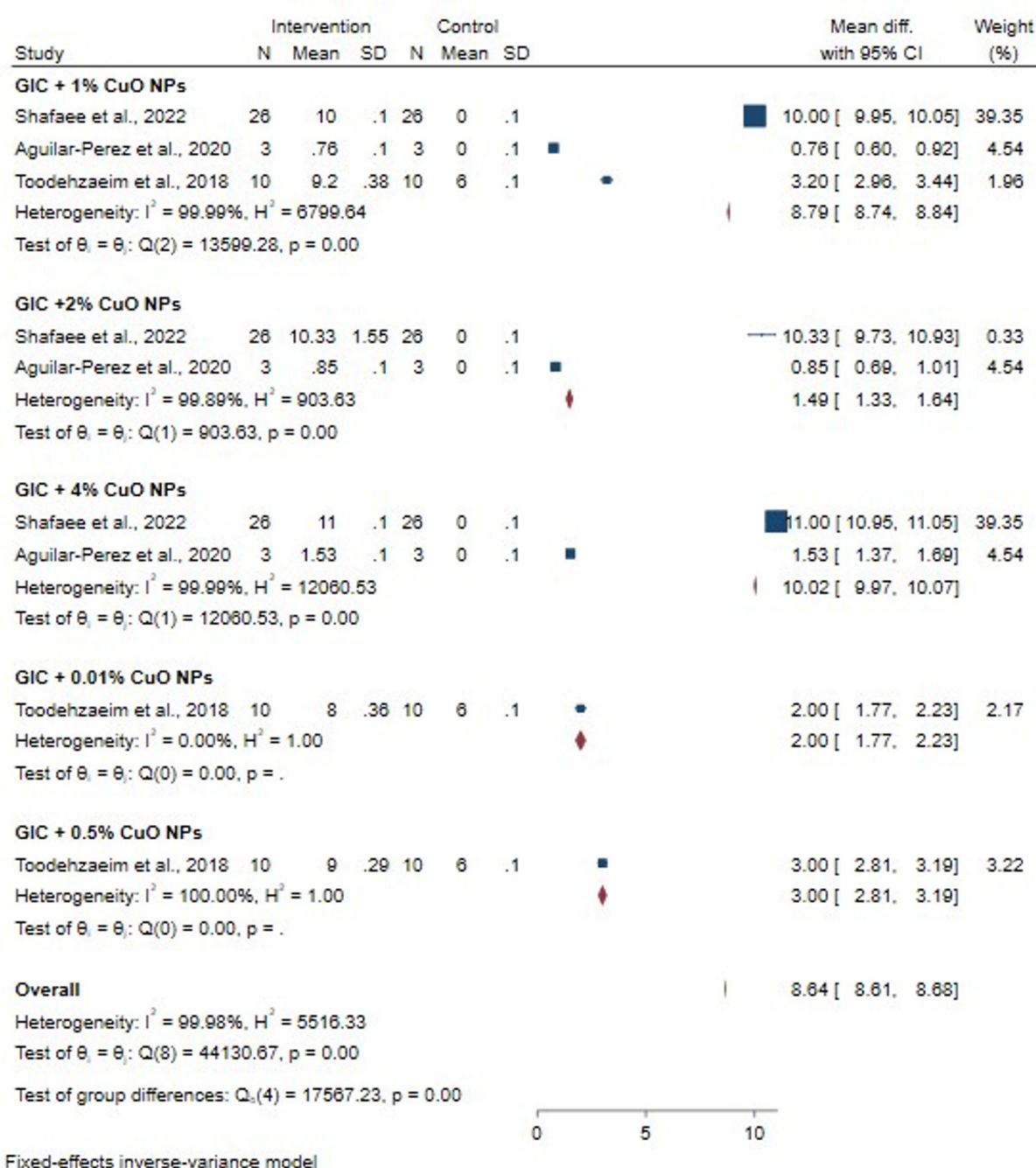
ZnO nanoparticles

Figure 4 shows how adding ZnO nanoparticles to glass ionomer cement affects its antibacterial properties. Mean differences of antibacterial effect on S. mutans between 1% ZnO NPs, 2% ZnO NPs, 4% ZnO NPs, and 3% ZnO NPs vs. control group was 0 (MD, 0 95% CI -0.08, 0.09; I^2=99.80%, high heterogeneity), 7.72 (MD, 7.72 95% CI 7.67, 7.76; I^2=99.99%, high heterogeneity), 8.11 (MD, 8.11 95% CI 8.06, 8.16; I^2=100%, high heterogeneity) and -1.79 (MD, -1.79 95% CI -1.88, -1.70; I^2=98.17%, high heterogeneity), respectively. A significant increase was observed with the addition of 4% ZnO NPs and empowered the antibacterial property against S. mutans bacteria (**Figure 4**). Overall mean differences of antibacterial effect were 5.98 (MD, 5.98 95% CI 5.95, 6.01). The test of group differences showed significant differences between groups (p=0.00).

Figure 4: ZnO nanoparticles addition into the GIC.
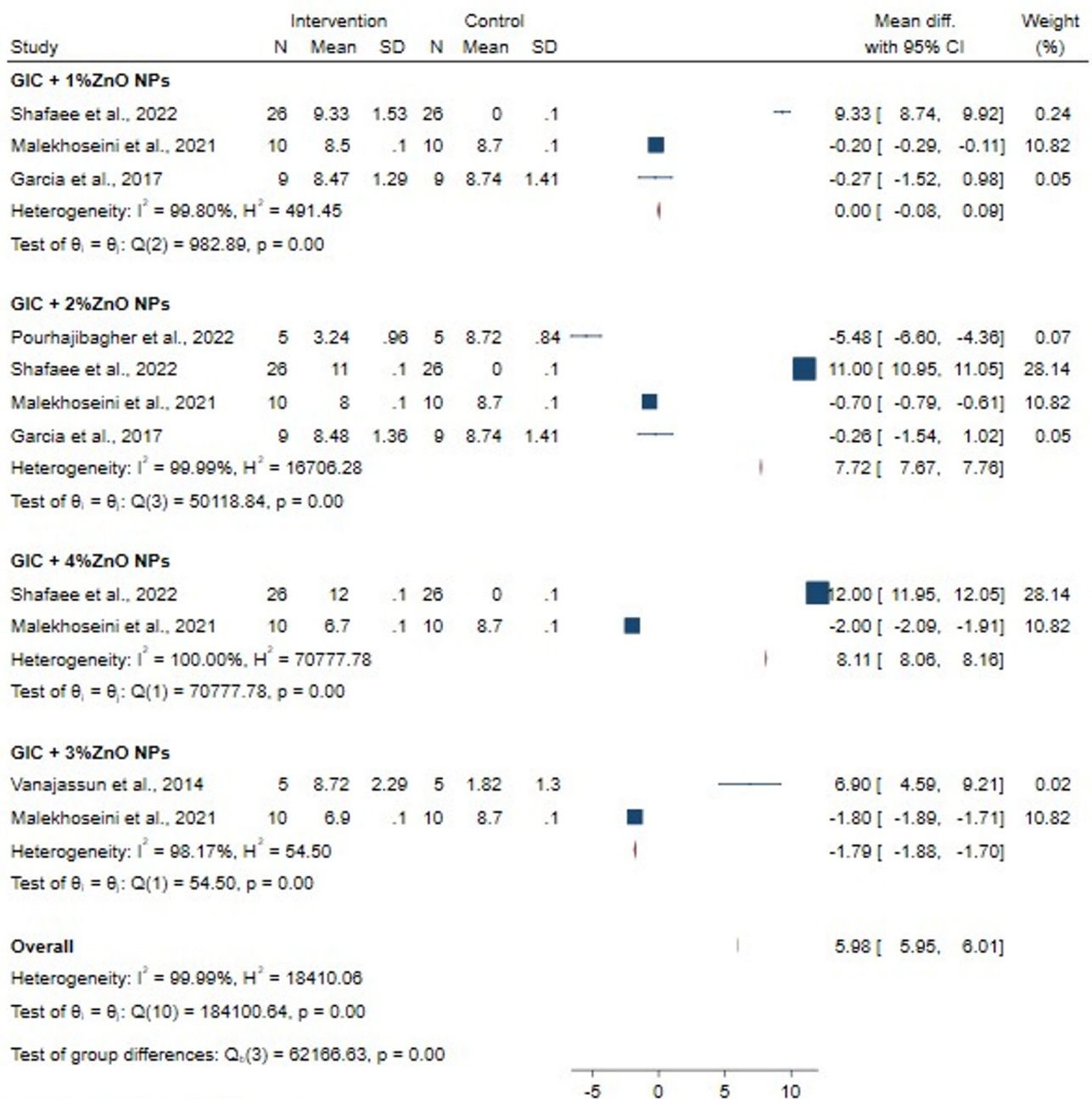
Discussion

According to our knowledge, this is the first meta-analysis investigating the effectiveness of GICs containing cinnamon, ZnO, and CuO nanoparticles against S. mutans. According to the present meta-analysis, the addition of 4% of cinnamon nanoparticles showed the strongest antibacterial effect against S. mutans. According to the studies, cinnamaldehyde, eugenol, benzoic acid, and cinnamic acid in cinnamon NPs have caused cinnamon NPs to have antimicrobial properties[26,27]. In a study where cinnamon nanoparticles were added to an orthodontic composite, it was observed that the induction of the antimicrobial effect of 3% cinnamon nanoparticles against S. mutans is higher than adding 1% cinnamon nanoparticles[12]. Based on the study findings, the minimum concentration used against caries-causing bacteria is 0.21 to 0.63 mg/ml[28]. The present meta-analysis showed that GIC containing 4% of ZnO NPs had the best antimicrobial properties against S. mutans bacteria compared to other percentages of ZnO NPs. ZnO NPs can prevent the growth of bacteria by destroying the cell wall and producing hydrogen peroxide[25]. Also, a meta-analysis showed that glass ionomer cement with 4% CuO NPs had stronger antimicrobial properties against S. mutans bacteria than other percentages. According to the selected studies and the analysis of their results, comparing the three investigated nanoparticles, it was observed that the cytotoxicity of CuO nanoparticles was higher than the other two nanoparticles, and the least cytotoxicity was related to cinnamon NPs[29]. A study has reported some cytotoxicity from cinnamon oil[30]. CuO nanoparticles are highly cytotoxic due to the production of reactive oxygen species, which cause oxidative stress[31]. A study that investigated the effect of zinc oxide nanoparticles on the toxicity of human gingival cells showed that high concentrations of zinc nanoparticles have high cytotoxicity in human gingival fibroblast cells[32].

Also, another study that examined the toxicity of Al2O3, CeO2, TiO2, and ZnO nanoparticles showed that the highest cytotoxicity is related to ZnO[33]. The present study had limitations; firstly, despite the small sample size of the studies, higher samples are needed for future research. Also, the selected studies were laboratory evaluations, which are needed to provide stronger evidence, showing the oral conditions completely. Only one ex vivo study was found, and future in vivo studies could help achieve better results. Also, it is important to interpret the findings of the present study with caution due to the high heterogeneity between the studies. Probably, this heterogeneity is related to the cognitive methodology of the studies.

Conclusions

According to the present meta-analysis, adding cinnamon, zinc oxide, and copper oxide nanoparticles to glass ionomer cement (GIC) for luting effectively against S. mutans, especially the use of cinnamon nanoparticles, zinc oxide nanoparticles, and copper oxide in weight percentages of 4%. It is suggested that future studies be conducted in-vivo with a larger sample size. Future studies should investigate the antibacterial properties of Cinnamon, CuO, and ZnO Nanoparticles on other bacteria. Also, more studies should be done in relation to Cinnamon.

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ORIGINAL

Motivational profiles of nursing students in Morocco: a descriptive study

Perfiles motivacionales de los estudiantes de enfermería en Marruecos: un estudio descriptivo

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Abstract

Purpose: Motivation is considered to be an essential component that generates the will to persevere and engage in learning activities. This study aims to identify the motivational profiles of nursing students and the associated factors.

Methods: This is a cross-sectional study conducted in 2022 at the Higher Institute of Nursing Professions and Health Technics in Ouarzazate in the south-east Morocco. The target population for this study was all students (N =242). Data were collected using an anonymous self-administered questionnaire on 3 main sections: socio-demographic data, the scale of Motivation in Education-University Studies, and reasons for choosing the nursing profession.

Findings: The response rate was 79.75%, with a female predominance of 78.8%. When examining the motivational profiles of the students, extrinsic motivation came first, followed by intrinsic motivation. The average motivation differs from semester to semester and tends to a low score around the 6th semester. Students' reasons for choosing a nursing career have been found to be related to their motivation to learn.

Conclusion: The analysis of motivation from the perspective of self-determination theory has allowed us to understand the nature of student motivation; however, further studies are needed to further investigate the issue of motivation and the factors that influence it.

Implications for nursing practice: In order to maximize professional performance, institutions and nurse educators must take into account the significance of motivation as the primary driving force behind nurse education.

Key words: Learning motivation, Nursing student, Self-determination theory, motivational profile.

Resumen

Propósito: La motivación se considera un componente esencial que genera la voluntad de perseverar y participar en actividades de aprendizaje. Este estudio tiene como objetivo identificar los perfiles motivacionales de los estudiantes de enfermería y los factores asociados.

Métodos: Este es un estudio transversal realizado en 2022 en el Instituto Superior de Profesiones de Enfermería y Técnicas de Salud en Ouarzazate, en el sureste de Marruecos. La población objetivo para este estudio fueron todos los estudiantes (n=242). Los datos se recopilaron mediante un cuestionario anónimo autoadministrado que constaba de tres secciones principales: datos sociodemográficos, la escala de Motivación en Educación-Estudios Universitarios y las razones para elegir la profesión de enfermería.

Hallazgos: La tasa de respuesta fue del 79.75%, con una predominancia de mujeres del 78.8%. Al examinar los perfiles motivacionales de los estudiantes, la motivación extrínseca fue la primera, seguida de la motivación intrínseca. La motivación promedio difiere de un semestre a otro y tiende a un puntaje bajo alrededor del sexto semestre. Se encontró que las razones de los estudiantes para elegir una carrera en enfermería están relacionadas con su motivación para aprender.

Conclusión: El análisis de la motivación desde la perspectiva de la teoría de la autodeterminación nos ha permitido comprender la naturaleza de la motivación de los estudiantes; sin embargo, se necesitan más estudios para investigar más a fondo el tema de la motivación y los factores que la influyen.

Implicaciones para la práctica de enfermería: Para maximizar el rendimiento profesional, las instituciones y los educadores de enfermería deben tener en cuenta la importancia de la motivación como la principal fuerza impulsora detrás de la educación en enfermería.

Palabras clave: Motivación para el aprendizaje, Estudiante de enfermería, Teoría de la autodeterminación, Perfil motivacional.

Introduction

The issue of motivation for achievement in the classroom is a critical issue in today's society, not only for young people in school, but also for adults who need to improve their skills throughout their lives, as well as for educators, parents and employers[1,2] .According to educational psychology, learning processes can be mapped out along three dimensions: cognitive (what to learn), affective or motivational (why to learn), and metacognitive (how to learn)[3]. While there are many aspects that influence students' learning experiences, motivation has emerged as a key predictor of students performance and wellbeing[4].

A motivated person develops a sense of pride and belonging to his or her field and tries to add value to it. Motivation is not only about happiness and pleasure at work, it is also about productivity and wealth creation[5]. On the other hand, when an individual is unmotivated, he does not act, or he acts without intention and in a passive way, he just follows the movement. Amotivation is the sensation that one cannot accomplish their goals because they believe they lack the required abilities or do not value the activity or the outcome of it[6].

Many universities, including those that train people for careers in healthcare, are concerned about the serious issue of students' lack of motivation for higher education[7]. Due to their involvement in a very specific training program that prioritizes human life, nursing students need to be motivated[8]. When properly prepared in a motivating and well-organized learning environment, a student in the healthcare sector can demonstrate appropriate ethical and professional behaviors[9-11].

The study of motivational profiles is based on the widely held belief that individuals' motivational types matter more than their level of motivation. Deci and Ryan (1985) introduced the self-determination theory, a significant motivational framework widely applied today. This theory of motivation, in contrast to the common view of motivation as a unitary concept that varies only in amount, postulates qualitatively diverse types of motivation that have varying effects on educational outcomes. The theory suggests that behavior can be classified into three categories: intrinsic motivation, extrinsic motivation, and amotivation. Intrinsic motivation refers to participating in an activity purely for the pleasure and satisfaction it brings (Deci & Ryan, 1985). Conversely, extrinsic motivation is prompted by external factors, where engagement is driven by outside rewards. Amotivation (AM) indicates a lack of intent in pursuing an activity, indicating a lack of interest or consideration for its significance or outcome (Deci & Ryan, 1985). Self-determination theory has gained particular attention among theories of motivation and has produced evidence in many domains, including psychology, education, and health[12-15]. This approach suggests that behavior can be viewed as intrinsically motivated, externally motivated, or amotivated. This theoretical position has been the subject of much research in recent years and appears to be very relevant to the education sector[16].

In the Moroccan context, the working conditions, the inadequacy of legal protection for the nursing profession, and many other factors, may make this profession less attractive to many prospective students. In the classroom, a number of behaviours occur among nursing students, such as absenteeism, a lack of engagement in various theoretical, practical, and clinical learning activities, and dropout by some students. These behaviours can be explained, among other things, by the low motivation of students towards learning, which affects their performance and their attachment to this profession. The consequences of a sustained lack of motivation among nursing professionals can be far-reaching. Gradually, we may witness a significant exodus of talent from the nursing field. This migration of skilled individuals may stem from the frustration of working in an environment that doesn't nurture their passion or support their professional growth. As these dedicated professionals seek more conducive work environments, it's not uncommon for them to explore opportunities in other countries. This trend could have profound implications for healthcare systems worldwide, potentially leading to shortages of experienced and qualified nursing staff in regions grappling with their own healthcare challenges.

Understanding motivation in nursing students is crucial for tailoring education and support to their specific needs and aspirations. This knowledge empowers educators to employ teaching strategies that resonate with students' motivational orientations, ultimately leading to improved learning outcomes and higher retention rates. Additionally, recognizing diverse motivational profiles allows for personalized interventions, fostering a more inclusive and supportive learning environment. By aligning curriculum design and resources with students' motivations, educational institutions can optimize program development and resource allocation, ultimately contributing to a more engaged, satisfied, and successful nursing student body poised for a thriving professional career.

In this context, the purpose of this study is to determine the motivational profiles of nursing students and examine the associations between motivation profile and gender, year of study, and reason for nursing career selection.

Methods

Study design
This is a descriptive cross-sectional study conducted at the higher institute of nursing professions and health techniques, in the southeast of Morocco. Data was collected from April to May 2022.

Participants
Our study was conducted among nursing students at the higher institute of nursing professions and health techniques, which is one of the higher education institutions not affiliated with the university. The institute provides preparation and awarding of national diplomas organized into three study cycles in the fields of Nursing Professions and Health Techniques (Bachelor's Degree Cycle, Master's Degree Cycle, and Doctorate Cycle). We employed a census sampling technique based on the selection of all students enrolled in the professional bachelor's degree cycle's second, fourth, and sixth semesters that were open during the study period (N = 242).

Measurement
Data was collected by means of a self-administered questionnaire composed of three main sections. The first section includes sociodemographic information such as gender, age, and year of study. The second section is the Scale of Motivation in Education-University Studies (EME-U28), developed and validated by Vallerand et al. in 1989[17], based on self-determination motivation theory. The instrument allows for the differentiation of the various motivational types based on 28 items grouped into seven subscales that correspond to the seven motivational categories: amotivation, extrinsic motivation by external regulation, introjected extrinsic motivation, extrinsic motivation by identification, intrinsic motivation to know, intrinsic motivation to accomplish, and intrinsic motivation to experience stimulation. For each of the 28 items on the instrument, the student was asked to indicate, on a 7-point Likert scale, the extent to which the proposed statement corresponds to a reason for pursuing his studies at the nursing institute, ranging from 1 (does not match at all) to 7 (matches very strongly). A student's average score on one of the seven types of motivation is the average of the four items that make up the subscale. The scale's general reliability was high (Cronbach α=.96). The sub-scale evaluating extrinsic motivation by external regulation provided the lowest reliability for the scale in this study (Cronbach α =.75); whereas the highest value of Cronbach's alpha was recorded on the sub-scale measuring extrinsic motivation by identification and introjected extrinsic motivation (Cronbach α = .89). **Table I** shows values of Cronbach's alpha for all subscales. The third section of the questionnaire is based on literature reviews and asks respondents to give their reasons for choosing the nursing profession[18,19].

To evaluate the comprehensibility and clarity of the questionnaire, we conducted a pre-test among 34 students from another nursing institute. The content validity of the tool was assessed by giving it to three experts from the field of nursing.

Statistical methods
Following the data collection via the questionnaire, a data base was created using an Excel table, which was then subjected to a statistical analysis using the program SPSS version 22. Quantitative variables were expressed as mean ± standard deviation. Qualitative variables are expressed as frequencies and percentages. For the correlation between variables, the ANOVA test was applied. The statistical significance level was set at P <0.05.

Ethics statement
Prior to conducting the study, it was approved by the higher institute of nursing professions and health technics, and the administrative permission was obtained. Before gathering data, the following ethical guidelines were respected and disclosed to the respondents: (a) explaining the study's purpose to the students who took part in the survey; (b) maintaining participants' anonymity; (c) obtaining their consent, and (d) guaranteeing the confidentiality of the data.

Table I: Cronbach's alpha values for EMS-U28 subscales.

	Number of items	Cronbach's alpha	General Cronbach's alpha of the scale
Intrinsic Motivation to know	4	0,87	
Intrinsic Motivation to accomplish	4	0,85	
Intrinsic Motivation to experience Stimulation	4	0,85	
Extrinsic motivation by identification	4	0,89	0,96
Introjected extrinsic motivation	4	0,89	
Extrinsic motivation by external Regulation	4	0,75	
Amotivation	4	0,80	

Results

Out of 242 targeted students, 193 responded to the survey, making the response rate 79.75%. The average participant age was 19.79 +/- 1.33 years, and 78.8% of the participants were female. 133 students are pursuing training to become general nurses, 29% study to become nurses in anesthesia and intensive care, and 39% to become emergency and intensive care nurses. In terms of study level, there are 70 (36,30%) students in the first year., 72 (37,30%) in the second year, and 51 (26,40%) students in the third year. **Table II**.

The purpose of the present study is to identify the motivational profiles of nursing students and examine if students with various motivational profiles show variations according to their sociodemographic characteristics and their reason for choosing nursing careers. Average scores for the various types of motivation are shown in **figure 1**.

Figure 1: Average scores for the various types of motivation.

The assessment of motivation using the motivation scale revealed a predominance of extrinsic motivation (3.89), of which the subtype "Extrinsic motivation by identification" had the highest mean (4.20), followed by intrinsic motivation with a mean score of (3.71), with the component "intrinsic motivation to know" having the highest mean score (4.06).

When it comes to the average of several types of motivation among students according to gender. The **figure 2** demonstrates the dominance of extrinsic motivation in both sexes, with females being more extrinsically and less intrinsically motivated than males. In terms of amotivation, male participants are less motivated than female participants.

By comparing the motivation of students between semesters, we notice that the more they progress in the training, the more they tend towards less intrinsic and extrinsic motivational scores, and towards higher scores of amotivation **figure 3**. The intrinsic and extrinsic motivation differences throughout the years of study are statistically significant with P=0.00 and P = 0.001 respectively.

When asked if their decision to pursue a career in nursing was a personal or not (three reasons are considered in this study), the majority of students (68.4%) have decided to enroll in this training by their personal decision. Some students chose this profession based on recommendations from family or friends (24.9%), and only 4.1% have chosen the nursing profession because

Figure 2: Types of motivation among students according to gender.

Figure 3: Student's motivation scores according to their year of study.
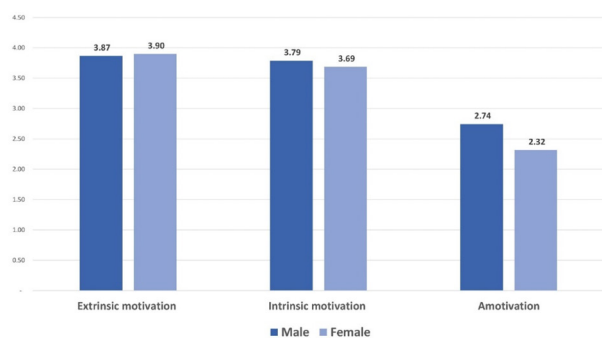
Table II: Population characteristics.

Characteristic		N	Percentage %
Gender	M	41	21,20
	F	152	78,80
Age	(mean±SD)	19.79 ± 1.33 years	
Speciality	General nurse	133	68,90
	Emergency and critical care nurse	31	16,10
	Nurse in anesthesia and intensive care	29	15,00
Year of study	First year	70	36,30
	Second year	72	37,30
	Third year	51	26,40
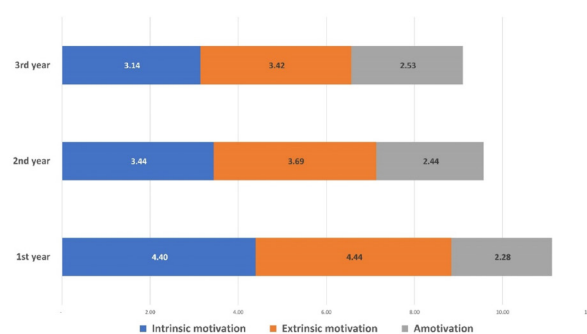
Table III: Distribution of student motivation types by their reasons for choosing a nursing career.

	Personal choice	Recommendations of family and friends	Having a relative working in healthcare field	F	P value
Intrinsic motivation	3.91	3.21	3.9	2,21	0.042
Extrinsic motivation	4.05	3.49	4.26	3,23	0.113
Amotivation	2.3	2.44	2.69	0,35	0.701

of having a family member working in the field. Students who chose nursing as a career out of their own free will are more intrinsically motivated and less "amotivated." On the other hand, those who made this career choice based on the recommendations of family and friends are more extrinsically motivated. Students who chose this profession because they have a family member working in the field have the highest amotivation mean score. The difference in intrinsic motivation scores according to the students' reasons for choosing the nursing profession is statistically significant with P = 0. 042. **Table III**.

Discussion

Our results revealed that extrinsic motivation was the most dominant type among participants (M=3.89), students engage in educational activities even if they do not enjoy them and they may be guided by external factors. at the extrinsic motivation level, intrinsic motivation by Identified Regulation is the component having the highest score. That is, students participate in an activity because it is important to them, even if it is not necessarily interesting. In the second place, a significant portion of students are intrinsically motivated (M=3.71) of which intrinsic motivation to knowledge is the most representative. An intrinsically motivated student is one who engages in an activity because of the pleasure of discovering, trying, and learning new things. According to the self-determined perspective, autonomous motivation tends to produce better psychological health and more effective performance. It also leads to greater persistence that lasts over the long term[20].

When examining the motivational profile of students for each semester, the levels of intrinsic and extrinsic motivation decline and amotivation scores increase as the semesters progress. This could be due to factors related to the pedagogical and organisational aspects of the training and to other factors related to the students themselves and to their perceptions that change as they progress through the training. The individual will, in fact, develop a highly self-determined motivational profile if he believes that his failures and successes are related to controllable causes. On the other hand, his perception of autonomy will be reinforced by attributing his successes and failures to internal causes[21]. In terms of reasons for choosing the nursing profession, personal choice was reported as one of the primary reasons for choosing nursing as a career among students. Intrinsic motivation was significantly related to personal choice to join the nursing profession. A personal interest in health care

seemed to be an important motivation in choosing the nursing profession. This interest might be explained by the altruistic nature that emerges in the desire to assist others and to pursue a career in the field. it should also be noted that the post-pandemic context in which this study took place might have had an influence on the students' career choices.

Previous studies conducted among students from institutions with regulated access[22] and medical students[23] reported that for the extrinsic motivation level, motivation by identified regulation had the highest score (M = 5.52) and for the intrinsic motivation level, intrinsic motivation to knowledge registered the highest score (M= 5.32). However, in contrast to our results, the study conducted among Moroccan medical students revealed that intrinsic motivation (5±1.07) comes first, followed by extrinsic motivation (4.9±1.29).

Our findings demonstrated a slight gender-based variance in motivation, with females exhibiting higher levels of extrinsic motivation. This aligns with the findings of a study conducted by H. Wu and colleagues in 2020[24]. However, this result contrasts with the study by Kusurkar and colleagues, which suggested that females displayed greater intrinsic motivation than males in medical educational settings[25]. Nonetheless, our results indicate that men tend to exhibit higher levels of amotivation compared to women. This incongruity could potentially be explained by the prevailing societal norms dictating the roles of men and women within the domain of healthcare professions and education. In North African region, there is a notable cultural inclination towards guiding female students towards careers perceived as stable, reliable, and promising in terms of rewards. Among these career options, nursing emerges as a particularly favored choice(Ait Ali et al., 2022).

In line with the results of the present research, a Swedish study found that the average motivation score varied significantly as the semester progressed and tended to be low by the 5th semester. Nevertheless, another study from France indicated a statistically significant variation between nursing students' levels of motivation according to their year of study, with the third-year class having the largest proportion of motivated students (x2 = 22.9476; p = 0.0109)[27].

Similar to our findings, a study investigating motivational factors in medical education highlighted that external motivation displayed favorable connections with certain elements. This included gender, particularly being female,

and a natural inclination towards selecting medicine as a field of study. Conversely, internal motivation was found to be linked with the perception of familial encouragement and an individual's independent choice to pursue a career in medicine[28].

Motivation is essential to fostering professional development in all health care disciplines. The prevalence of extrinsic motivation, particularly among students influenced by familial or peer recommendations, underscores the need for educational institutions to foster a deeper sense of personal commitment and intrinsic drive in aspiring nurses. Recognizing gender-based differences in motivation emphasizes the importance of tailoring support strategies to address unique motivational needs. Additionally, the observed shift towards higher levels of amotivation as students progress in their studies suggests a potential need for interventions to sustain motivation over the course of their education. Moreover, understanding how different motivations correlate with reasons for entering the nursing profession highlights the importance of providing diverse avenues for career exploration and guidance. Ultimately, these insights can inform the development of more effective educational approaches and support systems to nurture a motivated, engaged, and resilient nursing workforce.

Understanding motivation in nursing students is crucial for tailoring education and support to their specific needs and aspirations. This knowledge empowers educators to employ teaching strategies that resonate with students' motivational orientations, ultimately leading to improved learning outcomes and higher retention rates. Additionally, recognizing diverse motivational profiles allows for personalized interventions, fostering a more inclusive and supportive learning environment. By aligning curriculum design and resources with students' motivations, educational institutions can optimize program development and resource allocation, ultimately contributing to a more engaged, satisfied, and successful nursing student body poised for a thriving professional career.

To our knowledge, this is the first research to empirically address an investigation around the motivation of nursing students in Morocco. However, some limitations apply to this study and should be considered. The concept of motivation is a multidimensional latent variable, as such, the choice of a specific instrument to measure the targeted motivational dimension, as well as the timing of the assessment, can impact the results obtained. The adoption of a solely quantitative approach and the monocentric nature of this survey can also be considered limitations of our study. Therefore, generalizations of the results should be made cautiously. Additional research will be required to further the investigation into the motivation issue by introducing additional factors that can affect the degree of motivation among nursing students such as autonomy level facilitated by classroom instructors. Employing a longitudinal approach would provide insights into how motivations evolve as students advance through their respective programs, addressing motivational fluctuations over time.

Conclusion

The analysis of motivation as a research variable from the perspective of self-determination theory allowed us to understand the nature of students' motivation as well as some factors affecting this motivation. Given the international and national shortage of nursing staff, the retention of nursing students is recognized as a priority. In this context, it's critical for educators to understand why students choose to pursue studies as healthcare professionals as well as the nature of their learning motivation. This allows educators to implement effective strategies to support students' intrinsic motivation, prevent academic disengagement, reduce attrition, and improve learners' academic success.

Supplementary Materials
Supplement 1. The Scale of Motivation in Education-University Studies (EME-U28)

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ORIGINAL

Micro-CT-Based Comparison of the Effects of Three NiTi Rotary Systems on Root Canal Morphology

Comparación basada en micro-TC de los efectos de tres sistemas rotatorios de NiTi en la morfología del conducto radicular

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Abstract

Introduction and aim: Micro-CT imaging is becoming an increasingly popular method for evaluating root canal preparation techniques. The purpose of this study was a micro-CT imaging-based comparison of the effects of three different NiTi systems (ProTaper Gold (PTG), ProTaper Next (PTN), and WaveOne (WO)) on root canal morphology after instrumentation.

Methods: The study employed a search strategy using four databases (Google Scholar, PubMed, Web of Science, and Cochrane), with identical keyword patterns including micro-CT, rotary, NiTi, instrumentation, and root canal preparation.

Results: The results of the study showed that each system had its own advantages and disadvantages. PTG is similar to ProTaper Universal (PTU) but has a gold proprietary processing that provides better cyclic fatigue resistance and greater flexibility. In comparison to PTN, which is designed for rotary users to minimize the number of files and has an advanced swaggering motion that can reduce the risk of instrument fracture, PTG showed comparable volume and surface area enlargement in the coronal third and middle third of the canal. PTN, on the other hand, resulted in less resin removal and better centering ability. WO, a single-file system designed for inexperienced dentists or those seeking simplicity, enabled more centralized biomechanical preparation, particularly in the apical third of the root canal system compared to the shaping ability of PTG.

Conclusion: The research emphasizes the significance of data-driven decision-making for selecting the most appropriate NiTi system for specific clinical cases. It highlights the value of micro-CT imaging for objective assessment of root canal preparation techniques and suggests that system choice should consider individual needs and practitioner experience. Ultimately, as endodontics continue to advance, further research and development are vital for more efficient root canal enlargement systems that match the intricacies of the root canal system's original anatomy.

Key words: Micro-CT, Root canal preparation, Rotary, ProTaper Gold, ProTaper Next, WaveOne.

Resumen

Introducción y objetivo: La microtomografía computarizada se está convirtiendo en un método cada vez más popular para evaluar las técnicas de preparación del conducto radicular. El objetivo de este estudio fue comparar mediante micro-TC los efectos de tres sistemas NiTi diferentes (ProTaper Gold (PTG), ProTaper Next (PTN) y WaveOne (WO)) sobre la morfología del conducto radicular tras la instrumentación.

Métodos: El estudio empleó una estrategia de búsqueda utilizando cuatro bases de datos (Google Scholar, PubMed, Web of Science y Cochrane), con idénticos patrones de palabras clave que incluían micro-CT, rotatorio, NiTi, instrumentación y preparación del conducto radicular.

Resultados: Los resultados del estudio mostraron que cada sistema tenía sus propias ventajas y desventajas. PTG es similar a ProTaper Universal (PTU), pero tiene un procesamiento patentado de oro que proporciona una mejor resistencia a la fatiga cíclica y una mayor flexibilidad. En comparación con PTN, que está diseñado para usuarios rotatorios con el fin de minimizar el número de limas y tiene un movimiento de balanceo avanzado que puede reducir el riesgo de fractura del instrumento, PTG mostró un aumento comparable del volumen y la superficie en el tercio coronal y el tercio medio del conducto. PTN, por otro lado, dio como resultado una menor eliminación de resina y una mejor capacidad de centrado. WO, un sistema de lima única diseñado para odontólogos inexpertos o que buscan simplicidad, permitió una preparación biomecánica más centrada, especialmente en el tercio apical del sistema de conductos radiculares, en comparación con la capacidad de modelado de PTG.

Conclusiones: La investigación subraya la importancia de la toma de decisiones basada en datos para seleccionar el sistema NiTi más adecuado para casos clínicos específicos. Destaca el valor de la microtomografía computarizada para la evaluación objetiva de las técnicas de preparación del conducto radicular y sugiere que la elección del sistema debe tener en cuenta las necesidades individuales y la experiencia del profesional. En última instancia, a medida que avanza la endodoncia, es vital seguir investigando y desarrollando sistemas de ampliación de conductos radiculares más eficaces que se adapten a las complejidades de la anatomía original del sistema de conductos radiculares.

Palabras clave: Micro-TC, Preparación del conducto radicular, Rotatorio, ProTaper Gold, ProTaper Next, WaveOne.

Introduction

The biomechanical preparation of a root canal is a crucial step in endodontic therapy. The target is adequate cleaning and shaping of root canal space for residual pulp tissue, infected dentin, and bacteria removal; besides the correct shaping of the canal for the preservation of the original and initial profile of root canal anatomy and the apical foramen position. Complete cleaning and shaping lead to a successful root canal obturation. However, cleaning and shaping are more challenging especially in the case of heavily curved root canals where the prepared canal is always in danger of being diverted away from the original shape[1]. Canal configuration-based root canal instrumentation requires comprehensive and profound morphology knowledge to achieve successful obturation and sealing efficacy and prevention of iatrogenic procedural errors such as perforations, zip, elbow, and asymmetrically poor preparation.

A profound impact on the effective result of endodontic therapy is achieved by the shaping ability of the files. Considering numerous available rotary systems in the market with different shaping abilities, clinicians need to evaluate the features of these techniques impartially to select the superior one according to their clinical demands. Consequently, in order to assess factors such as the shaping capacity of endodontic instruments, several studies focus on the morphometric examination of teeth[2]. Furthermore, several methods have been proposed to identify the canal anatomy, such as radiography, diaphonization, computed tomography (CT), and more recently, micro-CT[3].

In order to choose the most appropriate endodontics rotary systems available on the market to be used in clinical settings, dentists need an unbiased evaluation of capabilities of different systems. The purpose of the present literature review study was to compare different mechanized root canal enlargement methods introduced by Dentsply, Maillefer company with nickel-titanium (NiTi) files and quantifying changes of root canal geometry after instrumentation via the assistance of the micro-CT.

Methodology

The search strategy was proceeded using four databases (Google Scholar, PubMed, Web of Science, and Cochrane), with identical keyword patterns including micro-CT, rotary, NiTi, instrumentation, root canal preparation. The search was executed between February to April 2023, and there was no publication year or journal restriction. The search fields were "Title, Abstract, and Keywords". Initially, 260 full papers were chosen, which later were read and screened. Finally, 33 articles were selected and reviewed for this literature review study.

The article selection strategy and criteria were the micro-CT analysis of the mechanized (rotary and reciprocating) root canal biomechanical instrumentation. In addition, only experiments in English language that examined mechanized root canal systems by using human natural or artificial teeth (any form of tooth group and root canal) or articles that investigated three-dimensional (3D) and two-dimensional (2D) root canal system factors before and after preparation were included in order to minimize the possibility of bias.

Micro-computed tomography applications in endodontics

In the 1980s, Jim Elliott developed x-ray micro-computed tomography (micro-CT or µCT)[4]. Micro-computed tomography is a low scale (micrometer voxel size) but high-resolution 3D imaging modality that nondestructively provides volumetric information from microstructure. Therefore, it has been extensively employed as a reliable approach for quantitatively assessing root canal preparation procedures[5,6].

In other words, in endodontics, by scanning the teeth and comparison of images before and after the instrumentation, microtomography enables us to analyze the root canal systems qualitatively and quantitatively at the micrometer level while maintaining root integrity[2].

In 1989, Tachibana and Matsumoto examined the suitability of the computed tomography (CT) in root canal therapy[7]. Micro-CT results has better resolution quality to conventional CT[2] by providing 3D high resolution pictures of hard tissues that allows evaluation of external morphology and complex internal root canal system[1]. Consequently, this imaging modality has been regarded as the gold standard for laboratory research in the field of endodontics to investigate the effects of different mechanized instrumentation methods[2,8].

To characterize the efficiency of various root canal preparation procedures, micro-CT imaging studies have been employed to analyze three-dimensional parameters, including volume alteration (ΔV), alteration in surface area (ΔSA), surface area to volume alteration ratio ($\Delta SA/\Delta V$), center of mass change (CM shift), structure model index alteration (ΔSMI), and two-dimensional factors such as area, perimeter, roundness and form factor of the canal, major and minor diameter[1,5,6,9,10].

Although ex vivo micro-CT (refers to the systems that scan items that used to be alive or samples excised from something that had been alive) is very common in root canal investigations, research conducted on upper molars demonstrated no distinction in canal detection between micro-CT and CBCT images[11]. Moreover, CBCT images obtained with a voxel size below 300 µm have proven to be compatible with micro-CT images for the morphological analysis of hard tissues[12]. Micro-CT has the disadvantage to be slower for scanning compared to

CBCT, and consequently, the levels of radiation exposure are higher. Therefore, micro-CT is recommended for laboratory and ex vivo researches, whereas CBCT is indicated to in vivo analysis[4].

Nickel-titanium rotary preparation

Over the past two decades, endodontic technology has evolved dramatically by many revolutionary changes from the first generation (passive cutting design) to the fifth generation (Offset Design)[13]. In 1988, nickel-titanium (NiTi) alloy called Nitinol composed of 55% nickel and 45% titanium was used in construction of endodontic files which were identical with stainless steel files in size but 2-3 times more flexible. Engine-driven nickel-titanium (NiTi) rotary files need air or electric motors for their motions that can be full rotation like in ProTaper which is a serial files system or reciprocating (incomplete rotation) like in WaveOne which is single file system.

In addition to simplifying and expediting root canal preparation, the utilization of automated NiTi instruments has provided consistent, predictable, and reproducible canal shaping while significantly reducing iatrogenic effects[14]. Gandhi and Gandhi (2011)[7] by using micro-CT showed less transportation as well as better canal centering ability of rotary files in human curved canals compared to hand files.

To evaluate the efficacy of instrumentation of canals, both extracted natural and simulated resin teeth have been widely utilized[2,7,10,15-18]. However, using resin canals with rotary instruments can create possible side effects because the generated heat during instrumentation makes the resin softer. Additionally, due to the micro-hardness difference between dentine (35 to 40 kg/mm^2) and resin material (20 to 22 kg/mm^2), the resin is not cut and instrumented like dentine[7]. Furthermore, the necessity for human operator interference is a significant limitation of the majority of the canal enlargement studies. Therefore, new errorless automatic enlargement studies measuring the canal without the intervention of any operator have been recently proposed[16].

ProTaper Gold

ProTaper family developed by Dentsply is among the most convenient rotary systems in the market for endodontic treatment and retreatment that has NiTi files with progressive but variable conicities and triangular convex cross-sectional architecture with an innovative flute design that integrates several tapers within the shaft[7]. The instrumentation speed and force, kinematics and torque values, and the number of instruments utilized in instrumentation are several factors that may affect the final quality of root canal preparation[19].

ProTaper Gold (PTG) instruments have a progressively tapered design and advanced metallurgy that enhances cutting efficiency and safety using heat treatment technology[20]. ProTaper Gold is identical to ProTaper

Universal (PTU) files regarding the morphology of the files involving taper, sizes and cross-section. However, PTG has 24% more flexibility and more than twice the resistant to cyclic fatigue due to its modern metallurgy (gold thermal treatment), ensuring a more centered preparation of curved canals. Greater flexibility of ProTaper Gold is extremely crucial in finishing files, during negotiation of difficult curved apical parts[21].

According to Silva et al. (2016)[16], PTG system compared to PTU produces less transportation of curved canals due to their different manufacturing processes that makes PTG files more flexible and decreases their affinity to become straight and unbend in curved canals. In fact, more flexible instruments produce more centrally positioned canal preparations which is the case in PTG compared to PTU[16].

Similarly, another micro-CT imaging study showed the superior potential to preserve the thickness of dentin and less transportation of PTG and PTN in contrast to PTU[22].

In comparison, in spite of their dissimilar size and dimensions, PTG and PTN methods exhibited comparable volume and surface area enlargement in the coronal third and middle third of the canal. It may be suggested that thermal treatment of the PTG instruments alloy can induce plastic deformation of files and cutting edges damage during usage that result in reduced cutting ability[22].

CBCT imaging analysis of shaping ability of PTG continuous rotary files based on M-wire technology compared with WaveOne Gold (WOG) reciprocating files based on G-wire technology on moderately curved (25-30 degree) canals of mandibular molars showed PTG has significantly larger removal dentine volume and canal transportation and the less centering ratio at 3mm, 5mm and 7mm from apex Indeed, in this study, WOG respected the initial morphology of the canal more than the PTG file[23]. This result is consistent with Berutti et al. (2012)[31] findings that in comparison to continuous rotary motion, reciprocating movement enables more centralized biomechanical preparation, particularly in the apical third of the root canal system.

ProTaper Next

The ProTaper Next (PTN) system by Dentsply Maillefer represents a relatively modern approach that utilizes specific heat-treated M-wire nickel-titanium instruments, which evidently improves cyclic fatigue resistance and flexibility. PTN produces a special swaggering rotation outside and external to the center of mass of the file as a result of variable regressive or reduced taper pattern and symmetrical bilateral rectangular cross-sectional offset from the rotation axis[13].

According to manufacturer company, PTN instruments are designed to reduce taper lock and screw effect,

reduce file contact with dentinal wall that generates greater space debris, improved flexibility and less fatigue in the instrument[22]. Apart from less PTN file stress, coronally directed debris removal due to the off-centered cross-sectional design, leads to better cutting performance[24].

In a study conducted using micro-CT, which involved twenty-four mandibular first molars, PTG and PTN demonstrated improved preservation of furcation dentin thickness and less transportation compared to ProTaper Universal[22]. Nevares et al. (2016)[25] documented the efficacy of PTN in gutta-percha obturation removal from highly curved canals and its potential application in endodontic re-treatment. Nevertheless, PTN may not achieve complete obturation material removal, necessitating additional supplementary procedures to optimize root canal cleaning. ProTaper Next instruments result in less amount of debris extrusion compared to PTU instruments which can be attributed to their difference in cross-sectional design[25]. In other words, PTN with rectangular geometry allows more coronal elimination of the dentinal debris compared to convex triangular cross-sectional geometry of PTU. Comparison of the peak torque and force of the PTU and PTN instruments during root canal preparation confirmed that the PTN had a higher peak torque consistency that may be attributable to the asymmetric interaction between the dentine and ProTaper Next instrument[19]. Moreover, compared with ProTaper Universal instruments, ProTaper Next instruments offer less dentinal cracks.

Gagliardi et al. (2015)[22] studied shaping abilities of ProTaper Universal, ProTaper Gold, and ProTaper NEXT in aggressive root canals. Surprisingly, although PTN and PTG share neither metallurgy nor geometric design, their centering ability was not influenced drastically by their differences. The results showed PTG and PTN had significantly less transportation and percentage decrease in dentin thickness compared with PTU. Moreover, PTN showed less canal wall contact, therefore, showed more dentine preservation. Also, PTN had less increase in perimeter, the minor diameter of the canals, and surface area compared to PTG and PTU. This finding is supported by the fact that unlike similar geometry of the PTU and PTG, ProTaper NEXT file with the smaller size, the off-centered rotational mass, and the regressive taper minimizes the area of contact with the canal and hence the cutting ability is reduced as well[22].

The centering ability of the file is very critical since it enables the canal walls to be homogeneously shaped and the untouched dentinal wall areas at the end of the instrumentation to be minimized. Another study on the comparative evaluation of centering and shaping abilities of PTN (multifile asymmetrical rotational system) and WaveOne (single-file reciprocating system) in simulated canals revealed that although both systems are made of M-wire, PTN resulted in less resin removal with better centering ability[17]. In disagreement with the theory that files with an off-centered mass have a bigger motion envelope relative to files with the same size and symmetrical mass design, this article reported PTN with superior centering ability. In addition, it was highlighted that the creation of glide paths obviously increased the shaping ability of both systems, and also the number of pecking motions of the WaveOne file to reach the full working length (WL) was reduced by the establishment of reproducible glide paths[17].

In the preparation of curved mesial roots of mandibular molars, micro-CT evaluation ProTaper Next, WaveOne Gold, Reciproc, and ProDesign Logic systems verified that they were significantly identical in terms of increased root canal volume (VI), dentine removed (DR), accumulated hard tissue debris volume (AD) and untouched surface area of the root (UA) parameters, except the structure model index (SMI). SMI is used as a numerical representation of the canal's geometry. After PTN and WOG instrumentation, the SMI change was larger, indicating that these systems generate more rounded preparations[26].

It can be inferred that PTN instruments have a wider taper than those defined by their manufacturer due to their rectangular cross-section and the rotation outside the center of mass, producing a sinuous movement, resulting in a more conical shape preparation. With regard to the effect of the SMI and based on the root morphology, it could be expected that higher SMI values would be optimal from a clinical point of view, given that this would provide more free space for better obturation. In the case of flatter and thinner root canals, on the other hand, an increase in the SMI could contribute to root fragility[26].

WaveOne
Recently, in root canal enlargement, the emphasis is on the principle of "less is more," which implies that the entire cleaning and shaping of the root canal system can be achieved with just one single file[13]. Hence, WaveOne (WO), the single-file NiTi reciprocating system, was introduced into the dentistry market in 2010 by Dentsply Tulsa Dental Specialties. It is a straightforward concept in root canal preparation because unlike many ordinary complicated serial file systems in the market that advocate the application of several NiTi files of various tapers and size to gradually enlarge the canal, WO simply needs a single hand file accompanied by a single WaveOne file to rapidly instrument and prepare the root canal to an acceptable size, shape, and taper from the beginning to the end.

WO files are made out of a unique NiTi alloy so-called "memory wire" (M-wire), produced through a special advanced heat treatment method that gives more instrument flexibility and up to 4 times more resistance to cyclic fatigue as a considerable improvement when compared with other rotary NiTi files[27].

WaveOne instruments are single-use to prevent cross-contamination and to reduce file fatigue, which is even more significant since the work traditionally conducted by three or more rotary NiTi files is done by only one WO file. WO files are distinguished along the whole length of the file with multiple and different cross-sectional designs. At the apical end cross-section, a modified convex triangular geometry with radial land is designed, while at the coronal end, a convex triangular cross-section with a neutral rake angle is seen[28]. This design increases the files stiffness at the level of 5 mm from the apex, which results in lower centering abilities in spite of its reciprocal motion[1].

It should be noticed that WaveOne files should be used with progressive three to four times up and down pecking movements, with only little apical force. If the reproducible glide path is not possible in heavily curved root canals, preparation of apical third should be completed by hand[28]. On the contrary, the previous report paradoxically contradicts the results of Beak et al. (2014)[1] implying creation of a glide path before usage of WO in canals with a sharp curve is beneficial.

Bürklein et al. (2011)[15] demonstrated that the WO rotary instrument offers effective shaping of regularly curved canals in extracted teeth, displaying strong centering capabilities. In an investigation involving 18 extracted mandibular molars treated with the Twisted File (TF), WaveOne (WO), and ProFile (PF) systems, the study evaluated canal volume (CV) and surface area (SA) using micro-CT. Results found that instrumented canals were wider and larger than uninstrumented canals and had larger surface area. Yet, there was no significant difference in the quantity of the surface area canal the volume after instrumentation[15]. Consistent to this result, Nagendrababu and Ahmed (2019)[29] observed no difference between reciprocating and rotary systems in the canal volume and the surface area changes by instrumentation.

Another research showed no significant differences between One-Shape, PTU, TF Adaptive, Reciproc, PTN, and WO systems on transportation and canal curvature in curved mesiobuccal canals of lower molar[19].

Santa et al. (2016)[3] found no significant disparity in canal transportation and shaping efficacy when comparing two Single-file Systems (WO and OneShape) in the instrumentation of 10 maxillary molars featuring single mesiobuccal heavily curved canals, as assessed by micro-CT.

Çapar and Arslan (2016)[19] reported that compared with WaveOne system, PTN, and TF Adaptive systems shows fewer dentinal cracks.

Conclusion

Root canals cleaning and shaping efficiency has been significantly enhanced by NiTi files over the last two decades. Numerous brands are currently available in the market, each offering NiTi alloys with diverse characteristics, including variable cutting edges, cross-sectional shapes, tapering, and variations in the number and spacing of flutes. Appropriate evidence-based data of the shaping properties of reciprocation and rotary files is highly important to help the physicians choose effective systems for different clinical cases.

ProTaper Gold is primarily developed for users of ProTaper Universal who are reluctant to change their technique but would benefit from the improved safety offered by the new metallurgy innovation so-called "gold proprietary processing".

ProTaper Next (5th generation of rotary systems) is designed for rotary users who want to reduce the number of employed files in practice and benefit from the advanced swaggering motion in order to adopt a minimally invasive technique[30].

WaveOne (4th generation of rotary systems) is designed for inexperienced rotary users who seek simplicity[30]. Single-file systems such as WO is recommended to save the time for both the clinicians and the patients, improve root canal shaping quality and prevent pulpal prion cross-contamination between different patients. The WO file has a different cross-sectional design over its entire active portion that despite the usage of a reciprocating motion, it can affect the centering ability of file. Therefore, tip size and taper of different instruments are suggested to be carefully considered[1]. According to Berutti et al. (2012)[31], when the glide path was created, less canal curvature modification was achieved by WO-reciprocating files. As a consequence, the glide path establishment before application of both reciprocating and rotary motion instrumentation tends to be necessary, particularly in canals with curvature[1,17].

Rotary NiTi systems preserve longitudinal root canal shape, but file separation remains the key disadvantage. In an effort to minimize torsional stress during rotation, various forms of reciprocation movements have been developed, and these have been used either in current or modern file systems. The results indicated better resistance to torsional stresses than rotary files; nevertheless, no existing system can fulfill all the requirements of the ideal instrumentation system[29].

Due to the increasing diversity of rotary and reciprocating systems that are continuously introduced into endodontic practice, well-organized micro-CT studies of root canal system are indispensable for investigating the shaping ability of these systems to explain the mechanisms behind the occurrence of the corresponding procedural errors

and therefore to help dentists to choose the system that fits their expectations and their clinical demands.

A large amount of data can be collected from a µCT scan. The slices can be reconstructed on any plane and the details can be viewed as 2D or 3D pictures. It is possible to display the internal and external anatomy simultaneously or separately, analyze the pictures quantitatively and qualitatively, and evaluate the root canal system32. As a consequence of micro-CT imaging, modifications in the root canal surfaces subjected to instrumentation, the procedural errors, the volume and width of the canal, and the volume of removed dentin can be evaluated to facilitate the comparison of post-instrumentation changes with pre-instrumentation condition[32].

In various research studies, acrylic blocks have been commonly employed to assess the efficacy and safety of different root canal enlargement systems[10,16]. The use of resin blocks in these investigations facilitates the standardization of root canal anatomy, including diameter, length, angle, and curvature radius, thus minimizing variations during the instrumentation process. Nevertheless, it's important to note that resin blocks exhibit distinct properties compared to human teeth, as they do not provide information about the residual dentin thickness after preparation[33]. Therefore, studies utilizing acrylic block specimens should be complemented by an analysis of the shaping capability of enlargement systems in human teeth[18].

Finally, automated rotary and reciprocating armamentaria are excellent aids to improve the efficiency of the endodontic therapy and to achieve good outcomes for patients, providing the considerations of their applications depending on the clinical case are carefully met. Considering the advantages and limitations of the systems, it is the practitioner's decision based on available research evidence to choose the best system that satisfy their requirements and their experience levels. Furthermore, despite many advances in the current root canal enlargement systems, more research conduction is indispensable for developing more effective mechanized root canal enlargement system in the future that would efficiently and quickly clean the entire root canal system with respect to the original anatomy of the canal.

Conflict of interests
The authors declare that there is no conflict of interests.

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ORIGINAL

Association between Smart Phones Addiction and Digital Eye strain Syndrome among Private Universities Students in Riyadh

Asociación entre la adicción a los teléfonos inteligentes y el síndrome de fatiga visual digital entre los estudiantes de universidades privadas de Riad

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Abstract

Background: Nowadays, smartphones play an important role in our lives, but despite their importance, many studies have shown that using smartphones for long periods of time has negative health effects, especially on the eyes. The most prevalent ocular illnesses brought on by excessive smartphone and computer use are dry eye, diplopia and, digital eye strain syndrome. This study aims to assess the association between smart phones addiction and digital eye strain syndrome among private universities students in Riyadh.

Method: This cross-sectional study was conducted in private universities in capital city of Saudi Arabia, Riyadh. A target population was medical and non-medical females and males private universities students. The questionnaire was used as tool for collecting the data. It was consisted of Arabic version of the problematic use of mobile phones (PUMP) scale. The PUMP scale is a 20-item questionnaire that assesses mobile phone use based on the DSM-5 criteria for substance use disorder. In addition to, Digital eye strain report: convergence insufficiency symptoms questionnaire. The questionnaire was distributed to students manually and online. Time period for study was 8 months from January to August 2019.

Results: The study included 527 participants in total. Almost two-quarters of the participants were medical students, whereas one-quarter were non-medical students. Females made up the majority of the participants, accounting for 427 (81%) of the total, with males accounting for 100 (19%). This survey discovered that 45% of participants used smart gadgets for 7 hours or more, followed by n=217 (41.2%) who used them between 4-6 hours, and just 14% who used them between 1-3 hours. Participants n=485 (92% used a smartphone), followed by a laptop n=25 (4.7%), an iPad n=9 (1.7%), and less than 1% utilized a desktop computer or video games.

Conclusion: According to the study's findings, most college students use their smartphones for seven hours or longer every day. This discovery was strongly linked to the emergence of digital eye strain syndrome.

Key words: Smartphones, addiction, digital eye strain syndrome, university students.

Resumen

Antecedentes: Hoy en día, los teléfonos inteligentes desempeñan un papel importante en nuestras vidas, pero a pesar de su importancia, muchos estudios han demostrado que el uso de teléfonos inteligentes durante largos períodos de tiempo tiene efectos negativos para la salud, especialmente en los ojos. Las enfermedades oculares más prevalentes provocadas por el uso excesivo de smartphones y ordenadores son el ojo seco, la diplopía y, el síndrome de tensión ocular digital. Este estudio tiene como objetivo evaluar la asociación entre la adicción a los teléfonos inteligentes y el síndrome de tensión ocular digital entre los estudiantes de universidades privadas en Riad.

Metodología: Este estudio transversal se llevó a cabo en universidades privadas de la capital de Arabia Saudí, Riad. La población objetivo eran estudiantes de universidades privadas de ambos sexos, médicos y no médicos. Se utilizó un cuestionario como herramienta de recogida de datos. Estaba compuesto por la versión árabe de la escala de uso problemático del teléfono móvil (PUMP). La escala PUMP es un cuestionario de 20 ítems que evalúa el uso del teléfono móvil basándose en los criterios del DSM-5 para el trastorno por uso de sustancias. Además de, Informe de tensión ocular digital: cuestionario de síntomas de insuficiencia de convergencia. El cuestionario se distribuyó a los estudiantes de forma manual y en línea. El período de tiempo para el estudio fue de 8 meses de enero a agosto de 2019.

Resultados: El estudio incluyó 527 participantes en total. Casi dos cuartas partes de los participantes eran estudiantes de medicina, mientras que una cuarta parte eran estudiantes no médicos. Las mujeres constituyeron la mayoría de los participantes, representando 427 (81%) del total, mientras que los hombres representaron 100 (19%). Esta encuesta descubrió que el 45% de los participantes utilizaban los gadgets inteligentes durante 7 horas o más, seguidos de n=217 (41,2%) que los utilizaban entre 4 y 6 horas, y sólo un 14% que los utilizaban entre 1 y 3 horas. Los participantes n=485 (92% utilizaban un smartphone), seguidos de un ordenador portátil n=25 (4,7%), un iPad n=9 (1,7%), y menos del 1% utilizaba un ordenador de sobremesa o videojuegos.

Conclusiones: Según los resultados del estudio, la mayoría de los estudiantes universitarios utilizan sus smartphones durante siete horas o más cada día. Este descubrimiento está estrechamente relacionado con la aparición del síndrome de fatiga visual digital.

Palabras clave: Smartphones, adicción, síndrome de fatiga visual digital, estudiantes universitarios.

Introduction

The term "smartphone" refers to a mobile phone that has many of the capabilities of a computer. It frequently has an operating system, a touch screen interface, and Internet access since it can run downloaded programs. Although the phrases smartphone, mobile phone, and cell phone are now commonly used synonymously, the primary functions of mobile phones and cell phones twenty years ago were calls and SMS messages[1].

Smartphones have become a big part of our lives because of all of their benefits, which include easy access to information, social networking, business applications, convenience of use, mobility, size, and so on. Additionally, cellphones are becoming essential in the medical area as both patients and medical professionals work to advance patient well-being. But in recent years, there has also been a rise in worry about the drawbacks of smartphone use[2].

Before smartphones became widely used, a Saudi Arabian study connected using a phone with a number of health risks, including headaches, sleep disruptions, tension, weariness, and dizziness[3]. Later, a Saudi Arabian study revealed that the medical student participants blamed their usage of mobile phones for their headaches, poor focus, memory loss, hearing loss, and exhaustion. Also, because users gaze at the screen for considerably longer than they do with regular mobile phones, smartphones may have negative health impacts, particularly on the eyes[4]. According to recent reports, the usage of a smartphone most adversely affects the eye. However, there is a dearth of information in the medical literature about how smartphones affect eyes. Visual problems are a widespread issue that affect people of all ages and have a significant impact on the financial and economic health of nations. The most prevalent ocular illnesses brought on by excessive smartphone and computer use, particularly in young adults who are regarded as the most frequent users of these gadgets, are dry eye, diplopia and digital eye strain syndrome[5].

Digital eye strain syndrome, also referred to as computer vision syndrome (CVS), is a transient condition caused by using smart devices for longer than two hours. Symptoms include eyestrain, tired eyes, irritation, redness, blurred vision, and double vision. The impact of digital eye strain on visual comfort and work productivity is significant. About 90%[6] of people reported having visual symptoms such as headache, ocular discomfort, diplopia, blurred vision, and dry eyes. The study's objective is to evaluate the relationship between digital eye strain syndrome and smartphone addiction among Riyadh's private university students. Computer vision syndrome (CVS), another name for digital eye strain syndrome, is a transient symptom that includes fatigue and eyestrain.

Methodology

Study design
The researcher used a cross-sectional study design to assess the association between smart phones addiction and digital eye strain syndrome among private universities students in Riyadh.

Participants
The study was conducted in private universities in capital city of Saudi Arabia, Riyadh. A target population was medical and non-medical females and males private universities students. Participants from universities, collages who were above 18 years and above, using smart phones regularly with no history of blindness or vision loss, mental and physical disabilities were included in the study.

Sampling procedure
The sample type was simple random technique. The sample size were 500 universities students including both females and males, a minimum sample size was 384 according to the formula $n = (z^2 (p) (1-p))/c^2$ where

z = standard normal deviation set at 95% confidence level (1.96)
p = percentage picking a choice or response ($p = 0.50$, $1 - p = 0.50$)
c = confidence interval (0.05)
For more precise results we increased the sample size to 500

Instruments
This study used a validated questionnaire as tool for collecting the data. The data were collected from study subjects by trained students using online and direct methods. A questionnaire was deployed to respondents who agreed to participate in the research and signed the consent form.

The questionnaire consists of three parts:

First part: It is a cover letter to greet the participants in the study, and to clarify the purpose and objective of the study, and that the information collected from the study has its privacy and is dealt with in strict confidence, and they have the right to participate in the study or refuse to participate.

Second part: These are demographic data to know the age, gender, marital status and other information about educational characteristics and smart devise usage.

Third part: This part contains Arabic version of the problematic use of mobile phones (PUMP) scale. The PUMP scale is a 20-item questionnaire that assesses mobile phone use based on the DSM-5 criteria for substance use disorder. In addition to, Digital eye strain report: convergence insufficiency symptoms questionnaire.

Ethical consideration

Consent was taken from the participants; all the information were used for statistical analysis only for more confidently.

Data collection

The questionnaire was distributed to students manually and online. Time period for study was 8 months from January to August 2019. The researcher eliminated all invalid, incomplete responses, or any responses that did not match the inclusion criteria. The number of valid questionnaires for statistical analysis was 527.

Statistical treatment

The statistical program SPSS-20 was used to analyze the data of the study. The data was entered and analyzed using IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. Normality of PUMP score was checked through one-sample Kolmogorov – Smirnov test. As the data was normally distributed, therefore, mean + SD has been reported. Two-Independent Sample t test was used to compare the PUMP score and computer vision syndrome. One-Way Analysis of Variance (ANOVA) was also applied to compare PUMP score with variables having three categories and more. Post-HOC Tukey Test was applied to see which group means differ significantly. A p-value of <0.05 was considered as statistically significant.

Results

Table I: Socio-demographic characteristics of participants (n=527).

	n (%)
Age (years)	
18-25	465 (88.2)
26-33	43 (8.2)
34-41	13 (2.5)
42-49	3 (0.6)
50-55	3 (0.6)
Gender	
Male	100 (19.0)
Female	427 (81.0)
Marital Status	
Single	449 (85.2)
Married	73 (13.9)
Divorced	3 (0.6)
Widow / widowed	2 (0.4)

The age group of 18 to 25 years old comprised the majority of participants (n = 465, 88.2%), followed by the age group of 26 to 33 years old (n = 43, 8.2%). A small percentage of respondents (n=19, or 3.7% of the total) were in the 34-55 age range. Women made up the majority of participants, n=427 (81%) versus men, n=100 (19%). Of the participants, n=449 (85.2%) were single, 14% were married, and a smaller proportion were widowed and divorced.

The majority of the participants 240 (45.5%) were studying at Dar Al Uloom University (DAU), followed by 101 (19.2%) at Al Maarefa University (AMU), 60 (11.4%)

Table II: Educational characteristics and smart devise usage of participants (n=527).

	n (%)		n (%)
University		**Academic Level**	
DAU	240 (45.5)	1st – 2nd	97 (18.4)
AMU	101 (19.2)	3rd – 4th	96 (18.2)
PSU	60 (11.4)	5th – 6th	62 (11.8)
IMC	34 (6.5)	7th – 8th	70 (13.3)
KFU	33 (6.3)	9th – 10th	66 (12.5)
REU	31 (5.9)	11th – 12th	47 (8.9)
FC	12 (2.3)	13th – 14th	76 (14.4)
Others	5 (0.9)	Master	10 (1.9)
YU	4 (0.8)	Ph.D.	3 (0.6)
GC	4 (0.8)		
AOU	3 (0.6)		
Academic Performance		**Smart Device**	
Excellent	146 (27.7)	Mobile phone	485 (92.0)
Very Good	261 (49.5)	Laptop	25 (4.7)
Good	105 (19.9)	iPad	9 (1.7)
Poor	15 (2.8)	Video game	5 (0.9)
		Desktop computer	3 (0.6)
Hours Spending (hours)		**Specialty**	
1-mar	73 (13.9)	Non-medical	189 (35.9)
4-jun	217 (41.2)	Medical	338 (64.1)
7 and above	237 (45.0)		

at Prince Sultan University (PSU), and nearly 6% at Riyadh Elm University (REU), King Faisal University (KFU), and Inaya Medical College (IMC). Participants came from Al Farabi College (FC), Al Yamamah University (YU), Al Ghad Colleges (GC), Arab Open University (AOU), and other institutions. Academic performance of the majority of participants was very good (n=261 (49.5%), with approximately 28% achieving excellent performance, one-fifth achieving good academic performance, and only n=15 (2.8%) achieving poor academic performance. According to hours spent, 45% of participants used smart devices for 7 hours or more, followed by 217 (41.2%) who used them between 4-6 hours, and only 14% used them between 1-3 hours. The distribution of participants studying in grades 1st-2nd and 3rd-4th was nearly equal (18%). Around 15% were in their 13th-14th year, followed by the 7th-8th (13.3%), 9th-10th (12.5%), 9% in their 11th-12th year, 2% in their master's, and a small number in their Ph.D. Participants 485 (92% used a smartphone), followed by a laptop 25 (4.7%), an iPad 9 (1.7%), and less than 1% used a desktop computer or video games.

When computer vision syndrome was studied, n=316 (60%) of the participants reported headaches, complain of eye strain was stated by n=56 (10.6%), nearly one-fifth of the participants had blurred near and distant vision after using the smart devices. Around 15% of the participants reported glare, watery eyes n=27 (5.1%), itching n=95 (18%), red eyes n=413 (78.4%), back pain n=155 (29.4%), neck shoulder pain n=306 (58.1%), double vision n=47 (8.9%), dry eyes n=198 (37.6%) and burning was reported by n=193 (36.6%) of the participants. Almost 60% of the participants were using screens at lower level, more than one-quarter were using screens at the same level and around 6% were using the screens above the recommended level.

Table III: Computer Vision Syndrome (n=527).

Variables	n (%)		n (%)
Headaches		Red Eyes	
Yes	316 (60.0)	Yes	413 (78.4)
No	211 (40.0)	No	114 (21.6)
Eye Strain		Back Pain	
Yes	56 (10.6)	Yes	155 (29.4)
No	471 (89.4)	No	372 (70.6)
Blurred Near Vision		Neck Shoulder Pain	
Yes	104 (19.7)	Yes	306 (58.1)
No	423 (80.3)	No	221 (41.9)
Blurred Distant Vision		Double Vision	
Yes	88 (16.7)	Yes	47 (8.9)
No	439 (83.3)	No	480 (91.1)
Glare		Dry	
Yes	74 (14.0)	Yes	198 (37.6)
No	453 (86.0)	No	329 (62.4)
Watery Eyes		Burning	
Yes	27 (5.1)	Yes	193 (36.6)
No	500 (94.9)	No	334 (64.4)
Itching		Center Screen	
Yes	95 (18.0)	Lower	310 (58.8)
No	423 (82.0)	Same Level	185 (35.1)
		Above	32 (6.1)

A significant difference was observed between the problematic use of mobile phones (PUMP) Score and computer vision syndrome. Results presented in **table I** showed that the PUMP score was significantly raised in participants who had headaches (p<0.001), eye strain (p=0.047), blurred near and distant vision (p<0.001) respectively, dry eyes (p=0.012), watery eyes (p=0.016), burning (p<0.001), itching (p<0.001), red eyes (p<0.001), back pain (p<0.001), neck & shoulder pain (p<0.001) and having double vision (p<0.001). However, PUMP score and glare was not statistically significant (p=0.078).

Results presented in **table II** showed that PUMP score was not significantly different when compared with age (p=0.072) and marital status (p=0.086). However, it was significant when compared between males and females (p<0.001). PUMP score of males was significantly higher as compared to females.

Table V: Comparison of PUMP score with socio-demographic data.

	n	Mean + S.D	p-value
Age			
18-25	465	58.65 + 14.77	0.772
26-33	43	57.74 + 19.10	
34-41	13	54.15 + 22.03	
42-49	3	53.67 + 21.07	
50-55	3	63.67 + 28.02	
Marital Status			
Single	449	58.79 + 14.82	0.086
Married	73	55.88 + 18.75	
Divorced	3	76.67 + 5.85	
Widow / Widowed	2	54.00 + 2.82	
Gender			
Male	100	64.95 + 14.64	< 0.001*
Female	427	56.95 + 15.24	

Table IV: Comparison of PUMP score with Computer Vision Syndrome.

	PUMP SCORE		
	No Mean + SD	Yes Mean + SD	p-value
Headache	55.42 + 15.89	60.50 + 14.80	< 0.001*
Eye Strain	58.02 + 15.43	62.21 + 15.12	0.047*
Blurred Near Vision	57.27 + 15.26	63.36 + 15.23	< 0.001*
Blurred Distant Vision	56.96 + 15.08	66.01 + 15.05	< 0.001*
Glare	57.99 + 15.25	61.41 + 16.28	0.078
Dry Eyes	57.16 + 15.51	60.64 + 15.10	0.012
Watery Eyes	58.09 + 15.21	65.41 + 18.08	0.016
Burning	56.68 + 15.50	61.57 + 14.86	< 0.001*
Itching	57.06 + 15.02	64.87 + 15.76	< 0.001*
Red Eyes	57.14 + 15.30	63.27 + 15.03	< 0.001*
Back Pain	56.81 + 15.16	62.45 + 15.41	< 0.001*
Neck & Shoulder Pain	54.61 + 15.57	61.25 + 14.75	< 0.001*
Double Vision	57.46 + 14.95	68.77 + 16.70	< 0.001*

*statistically significant at 5% level of significance

Table VI: Comparison of PUMP score with academic data and computer usage.

	n	Mean + S.D	p-value		n	Mean + S.D	p-value
University				**Academic Performance**			
DAU	240	56.21 + 15.39		Excellent	146	54.35 + 14.24**	< 0.001*
AMU	101	60.57 + 13.42		Very Good	261	58.97 + 15.26	
REU	31	57.45 + 16.33		Good	105	62.70 + 15.54**	
PSU	60	61.40 + 13.74		Poor	15	60.33 + 20.33**	
KFU	33	59.42 + 18.50					
IMC	34	56.35 + 12.82	0.563				
YU	4	62.00 + 10.98		**Specialty**			
GC	4	72.25 + 33.51		Medical	338	59.41 + 15.17	0.680
AOU	3	58.67 + 35.92		Non-Medical	189	56.79 + 15.80	
FC	12	70.25 + 14.07					
Others	5	61.40 + 21.19					
Year				**Center Screen**			
1st - 2nd	97	58.28 + 15.42		Lower	310	59.74 + 15.27**	0.017*
3rd - 4th	96	56.09 + 16.00		Same Level	185	55.90 + 15.72**	
5th - 6th	62	61.37 + 16.41**		Above	32	61.06 + 13.73	
7th - 8th	70	59.44 + 13.32**					
9th - 10th	66	57.86 + 15.61	0.031*	**Hours Spending**			
11th - 12th	47	57.02 + 13.13		1-mar	73	52.99 + 16.61	< 0.001*
13th - 14th	76	60.62 + 15.56		4-jun	217	55.38 + 13.84	
Master	10	61.10 + 19.88		7 and above	237	62.92 + 15.28**	
Ph.D.	3	30.67 + 2.309**					

*statistically significant at 5% level of significance.
**Tukey's test significant multiple comparisons.

A significant difference was observed in PUMP score when compared with year of study (p=0.031). Post-Hoc analysis showed that those having Ph.D. had a significant lower PUMP score as compared to those studying in 5th-6th grade (p=0.021) and 7th-8th grade (p=0.040). PUMP score was significantly different in academic performance (p<0.001). Post-Hoc analysis showed that participants having excellent academic performance had a significantly lower PUMP score as compared to participants having good (p<0.001) and very good (0.018) academic performance. PUMP score was also significantly different among participants who were using the computer screen at different levels (p=0.017). Post-Hoc analysis revealed that participants who were using same level had a significantly lower PUMP score when compared with lower level (p=0.020). Hours spending and PUMP score were also statistically significantly different (p<0.001). Post-Hoc analysis showed that participants who were spending 7 hours and above had a significantly higher PUMP score as compared to those who were spending 4-6 hours (0.021) and 1-3 hours (0.032).

Discussion

Smartphone use can have a negative impact on eye health. This study looked at the prevalence and pattern of smart phone addiction and digital eye strain syndrome among Riyadh students attending private universities. The survey was completed by 527 medical and non-medical students who participated in the study. Almost two-quarters of the participants were medical students, while one-quarter were non-medical students. Females made up the majority of the participants, accounting for 427 (81%) of the total, with males accounting for 100 (19%). This study discovered that 45% of participants used smart devices for 7 hours or more, followed by n=217 (41.2%) who used them between 4-6 hours, and only 14% who used them between 1-3 hours.

According to these findings, smartphone addiction affects between 9.3% and 48% of the global population[7]. In contrast to our findings, a study of 2367 respondents in the Kingdom of Saudi Arabia discovered that the majority (61%) of study participants reported using their smartphones for at least 5 hours per day, with 27.2% using them for more than 8 hours per day[7]. Another cross-sectional study with 2435 participants was conducted in Saudi Arabia using an online Google survey form. A cross-sectional survey of 203 sixth-year medical students at King Abdul-Aziz University's School of Medicine in Jeddah discovered that 66 (36.5%) of them were addicted to smartphones[8]. According to a mixed-method study that used a systematic review and meta-analysis, India has a 39-44% smartphone addiction rate[9]. A second investigation was carried out on a sample of 587 pupils from the discredited school. The smartphone addiction scale (SAS), which was used to assess student behavior, revealed that 53.62 percent of students were low smartphone users and 33.33 percent were heavy users[10].

Regarding to visual disturbances accompanying smartphone use, it was found that eye strain, glare, watery eyes, itching, red eyes, double vision, dry eyes, burning were more prevalent in smartphone users especially on spending long duration using the devices. In addition, other common health problems among smartphone users include headache, back pain, and neck shoulder pain.

Similarly, some research looked into the effects of electronic gadgets generally on Saudi Arabian female nursing college students in terms of their reliance, sociability, and health. This cross-sectional study found that headache and visual disturbance were the most common complaint among the students who were using visual materials[11]. Other Studies have looked at several health issues related to smartphone use in Indian college students. Student participants in the study ranged in age from 17 to 23. Headache, difficulty concentrating, impatience, anxiety, loss of sleep, tiredness, eye strain, and fatigue were the main symptoms that were assessed. The most prevalent symptom, experienced by 50% of the respondents surveyed, was a headache; visual symptoms were ranked sixth[12]. In a study with 576 teenagers conducted in India, there was a significant relationship between lying down while using a screen-enabled device and symptoms of digital eye strain. The majority of students had eye fatigue by the end of the day, which was caused by using digital screens[13]. In a survey of 409 medical college students in Jamaica, eye strain (67%), dry eyes (26.2%), double vision (28.9%), and blurred vision (51.6%) were identified as prevalent symptoms[14]. Research conducted in South Korea revealed that exposure to content on any digital screen, particularly a smartphone, increases the chance of developing DES in teenagers[15]. In general, smartphone addiction could cause significant digital eye strain Syndrome and other eye problems as a result of looking and exposure to electronic screen lighting for long hours.

Conclusion

In conclusion, the use of smartphone has expanded among college students. This can be related to the striking changes in student lifestyles in Saudi Arabia. The current study found that smartphones are a significant part of university students' daily lives. There was a direct correlation between smartphone use and the digital eye strain syndrome. This study made clear the necessity to raise awareness of the harmful effects that prolonged smartphone use has on our health.

Conflict of interests
The authors declare that there is no conflict of interests.

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Association between Smart Phones Addiction and Digital Eye strain Syndrome among Private Universities Students in Riyadh

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ORIGINAL

Examination of the Promotor Methylation of the *TRIM3* Gene in Obesity

Examen de la Metilación Promotora del Gen TRIM3 en la Obesidad

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Abstract

Background: Understanding the root causes of obesity, which is defined as having an increased amount of body fat, is crucial. Pathogenesis of obesity is influenced by environmental, genetic, and epigenetic factors.
Methods: The TRIM3 gene has been studied in this study to better understand how obesity develops. This study's goal was to determine the interaction between obesity and the methylation status of TRIM3.
Results: However, no statistically significant differences existed between the obese participants and the control group.
Conclusions: This study was the first to demonstrate how the TRIM3 gene and obesity interact, according to the literature.

Key words: TRIM3, methylation, obesity.

Resumen

Antecedentes: Es fundamental comprender las causas profundas de la obesidad, que se define como el aumento de la cantidad de grasa corporal. En la patogénesis de la obesidad influyen factores ambientales, genéticos y epigenéticos.
Metodología: En este estudio se ha estudiado el gen TRIM3 para comprender mejor cómo se desarrolla la obesidad. El objetivo de este estudio era determinar la interacción entre la obesidad y el estado de metilación de TRIM3.
Resultados: Sin embargo, no existían diferencias estadísticamente significativas entre los participantes obesos y el grupo de control.
Conclusiones: Este estudio fue el primero en demostrar cómo interactúan el gen TRIM3 y la obesidad, según la bibliografía.

Palabras clave: TRIM3, metilación, obesidad.

Introduction

The worldwide obesity issue is being highlighted by the World Health Organization in a number of ways. In order to manage and guard against obesity and overweight, a wide range of standards must be established. Aside from advice, nations must also receive assistance with implementation[1]. Nearly every system in the body is impacted by obesity. Since it has a detrimental effect on the reproductive and cardiovascular systems[2]. Genetics are a major contributor to obesity[2].

The first patients with congenital leptin insufficiency were discovered as a result of the discovery of leptin and its receptor genes, which were thought to be candidate genes for human obesity. Most of the obesity-related monogenic mutations have been found in populations of people with severe and early-onset obesity[3]. Common polymorphisms in candidate genes were examined for any potential associations with obesity incidence, BMI, or different aspects of body composition. The link between obesity outcomes and variations in candidate genes *ADRB3, BDNF, CNR1, MC4R, PCSK1*, and *PPARG* has been demonstrated to be consistent[4]. Several studies have found interaction between *PTH, FSHR*[5], *CLOCK, BMAL1*[6], *RANKL*[7] methylation and the obesity.

The broad, diverse, and ancient protein family known as TRIM proteins is involved in a variety of processes, including cellular differentiation, autophagy, apoptosis, DNA repair, and tumor suppression[8].

Apoptosis, cell cycle regulation, viral response, cell proliferation, oncogenesis, and antiviral defense are only a few of the physiological activities that TRIM proteins, which are present in humans in about eighty-fold abundance, are involved in. Their alteration inevitably results in a wide range of pathological illnesses, as well as problems with the heart, the brain, the immune system, the musculoskeletal system, development, and cancer[9]. Each disease, such as obesity, cancer, bacterial or viral infections, autoimmune diseases, developmental abnormalities, neuropsychiatric disorders, and congenital defects, are affected by TRIM proteins differently[10,11]. Obesity's etiology has been connected to TRIM3 expression. A CpG location in the TRIM3 gene shows lower methylation levels in obesity, according to a genome-wide methylation analysis of peripheral blood leukocytes[10]. In this study, we aim to determine whether there is a connection between obesity and the *TRIM3* gene's methylation state.

Material and Methods

Study Case

There were 59 obese and 62 non-obese participants in this study. The study's goal was to investigate the relationship between TRIM3 DNA methylation status and obesity. The Near East University's Scientific Research Ethics Committee approved the study, and informed permission was established among all participants (YDU/2021/96-1425).

Each patient was assessed prior to inclusion for the presence of malignancy, diabetes mellitus, hypertension, dyslipidemias, liver cirrhosis, thyroid, cardiovascular, or any active inflammatory condition. In this study, professional athletes were not included. All subjects completed written informed consent forms and provided information about their medical histories. The Near East University's Research Ethics Committee gave its approval to the study protocol, which was carried out in conformity with the Helsinki Declaration.

Determination of the Biochemical Parameters

After a 12-hour fasting, peripheral blood samples from the subjects were collected in the morning. A fully automated clinical biochemistry analyzer was used to measure the levels of serum fasting glucose, triglycerides (TG), total cholesterol, high-density, low-density lipoprotein cholesterol (LDL-C), and lipoprotein cholesterol (HDLC) (Abbott Architect C8000). Additionally, serum levels of leptin, resistin, and adiponectin were measured using ELISA kits in accordance with manufacturer's instructions (DRG Intl., Inc., USA for leptin and Biovendor Laboratory, Inc., Brno, Czech Republic for resistin and adiponectin).

Methylation Sensitive High-Resolution Melting Analysis

Patients with obesity and patients with normal controls had their peripheral blood samples taken. The AllPrep DNA/RNA/Protein isolation kit was used to isolate DNA (Qiagen in Manchester, United Kingdom). A NanoDrop ND-1000 Spectrophotometer was used to measure the DNA content (Thermo Fisher Scientific, Waltham, MA USA). The sodium bisulfite modification was done using the Epitect Bisulfite Modification Kit from Qiagen in Manchester, UK. Based on the MS-HRM PCR Guide, a collection of primer sequences was created. (Qiagen, Manchester, UK). EpiTect was used to determine the methylation status of the TRIM3 promotor. MS-HRM PCR Handbook guidelines (Rotor-Gene Q, Qiagen)7.

Statistical Analysis

For data analysis, GraphPad Prism 7 software was employed. For continuous variables, data in tables are shown as mean ± standard deviation (SD), and for discrete variables, absolute values (percentages). A statistically significant difference was defined as $p<0.05$.

Results

Patients with obesity had a mean average age of 43,58±11,21 years and a BMI of 36,31±7,86 kg/m². The mean age of control group was 42,16±13,68 years and their mean BMI was 23,66±2,45 kg/m². **Table I** displays the anthropometric and metabolic features of the patients.

Table I: The Anthropometric and Metabolic Characteristics of Studied Patient Population.

Parameter	Non-obese subjects			Obese subjects		
	Methylated (31)	Unmethylated (31)	p	Methylated (24)	Unmethylated (35)	p
Age	42,16±13,68	41,35±13,09	0,81	43,58±11,21	44,34±9	0,77
BMI (kg/m²)	23,66±2,45	23,81±2,68	0,82	36,31±7,86	34,4±4,57	0,24
Waist circumference (cm)	83,52±8,17	84,94±8,69	0,51	117,9±15,65	112,5±13,14	0,15
Hip circumference (cm)	100,5±7,27	99,52±6,80	0,57	120,3±10,14	119,6±10,05	0,79
Fasting glucose (mg/dL)	88,16±7,74	89,19±5,64	0,55	101,5±18,64	104,3±22,85	0,61
Total cholesterol (mg/dL)	202±25	202,7±22,14	0,91	222,7±29,71	224,6±40,5	0,84
LDL-cholesterol (mg/dL)	127,6±25,83	130,7±25,73	0,63	137,4±25,77	138,5±34,31	0,89
HDL-cholesterol (mg/dL)	56,74±7,35	58,39±10,76	0,48	43,42±7,50	47,4±9,98	0,1
Triglycerides (mg/dL)	100,5±34,91	90,35±40,59	0,29	177,8±73	162,1±67,19	0,39
HOMA-IR	1,94±0,55	1,91±0,62	0,81	4,02±2,26	4,23±2,44	0,73
Leptin (ng/ml)	8,94±3,71	9,6±6,47	0,62	23,42±14,07	21,04±10,81	0,46
Adiponectin (μg/mL)	18,86±8,93	22,03±9,14	0,17	10,54±4,96	10,39±5,15	0,91
Resistin (ng/mL)	6,303±2,32	5,99±3,02	0,64	8,85±2,37	8,74±2,68	0,87

Determination of *TRIM-3* gene methylation pattern
In 24 out of 59 obese patients (40,68%) and 31 out of 62 non-obese people (50%) the TRIM-3 gene was methylated. **Figure 1** shows that there was no methylation status–obesity relationship that was statistically significant (p > 0.05). Methylation status of TRIM-3 in obese and control subjects has been shown in **table II**.

Table II: Distribution of *TRIM-3* methylation.

Subjects	TRIM gene		
	Methylation	**Unmethylation**	**p Value**
Obese	40,68%	59,32%	0,36
Non-obese	50%	%50	

The universally methylation control of the *TRIM3* gene was displayed as blue, whereas the universally unmethylated control was displayed as purple. Temperature (⁰C) is plotted along the X-axis, and fluorescence (dF/DT) is displayed along the Y-axis. The averaged melting curves of the dilution standards demonstrate the optimization process in the TRIM3 promoter region (**Figure 1**).

Relationship between TRIM3 methylation level, anthropometric, and metabolic characteristics
Investigations were conducted into the associations between TRIM3 methylation status and measurements of the waist, hips, BMI, age, insulin concentration, HOMA-IR, leptin, adiponectin, and resistin as well as levels of circulating glucose, triglycerides (TG), total cholesterol, HDL-C, and LDL-C. However, there was no evidence of a significant relationship between anthropometric or metabolic traits and TRIM3 methylation status (**Table III**).

Discussion

The development of obesity is significantly influenced by the interaction between genetics and epigenetics. Several studies have shown a relationship between obesity and epigenetic changes. An epigenetic mechanism called DNA methylation contributes to the development of obesity and its metabolic side effects[7,12].

Epigenetic changes in the following genes have been linked to obesity: CLOCK, BMAL1, PER2, UBASH3A, TRIM3, LEP, ADIPOQ, PGC1, IGF-2, IRS-1, LY86, MEST, PEG3, NNAT, PLAGL1, MEG3, NPY, IL6, TNF, TFAM, GLUT4, RANKL, and c-FOS[7,13,14,15,16]. Several studies have found interaction between PTH, FSHR[5], CLOCK, BMAL1[6], RANKL[7] methylation and the obesity.

A genome-wide methylation investigation revealed that TRIM3 methylation levels were decreased in obese individuals[17]. The DNA methylation pattern in peripheral blood leukocytes of obese people was identified using a genome-wide strategy.

Figure 1: Increasing The Annealing Temperature Improves Assay Sensitivity When PCR Primers Include CpG Dinucleotides.
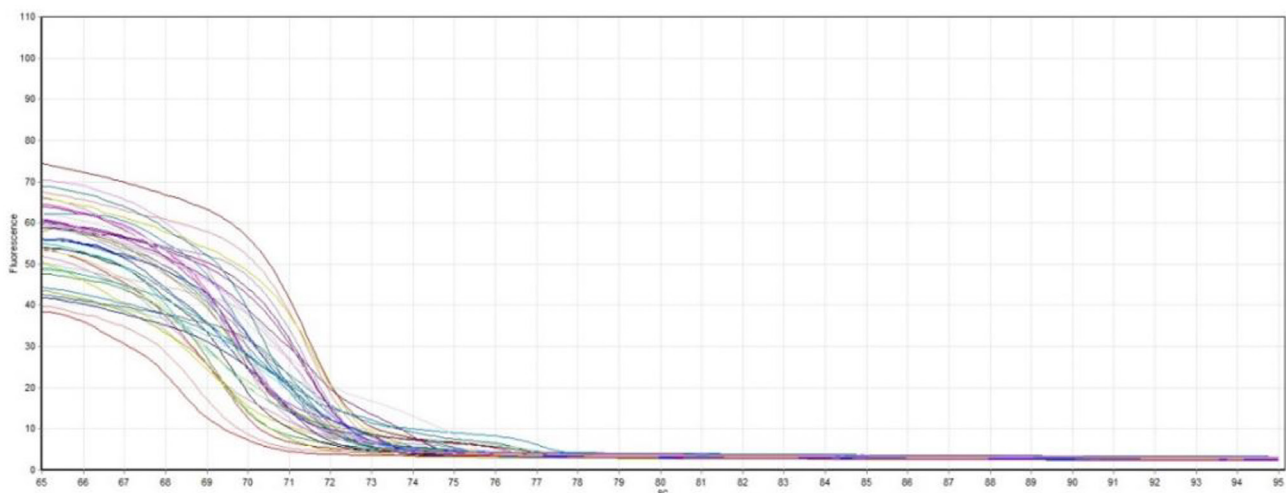
Table III: *TRIM3* gene and obesity status.

TRIM3		OBESE STATUS			
		nonobese	**obese**	**total**	**p-value**
unmethylated	observed %within column	31 50.0%	35 59,32%	66 66.0%	p>0,36
methylated	observed %within column	31 50.0%	24 40,68%	55 55.0%	
Total	observed %within column	62	59	121	

A genome-wide approach was used to define the DNA methylation pattern in peripheral blood leukocytes of obese subjects. Significant changes in CpG methylation were detected between obese participants and controls in the genome-wide methylation investigation. Both the monitoring and replicating cohorts showed reduced methylation of the promoter CpG island in obese individuals[17,10]. According to Wang et al. (2010), obese subjects had altered methylation patterns at one CpG site in the UBASH3A gene and one in the TRIM3 gene, respectively, both during the genome-wide analysis and the verification process (P = 0.008 and P = 0.001 for the UBASH3A and TRIM3 genes, respectively)[17].

Despite the fact that there is evidence connecting obesity with TRIM3 methylation, little is understood about the precise mechanisms at play. We hypothesized that DNA methylation might contribute to obesity based on growing evidence that epigenetic regulation regulates gene expression. The aim of this study was to investigate whether or not methylation of the TRIM3 gene is associated with obesity.

Patients with obesity had a mean age of $43{,}58\pm11{,}21$ years and a BMI of $36{,}31\pm7{,}86$ kg/m^2. The average age and BMI of the control group were $42{,}16\pm13{,}68$ years and $23{,}66\pm2{,}45$ kg/m^2, respectively. In 24 out of 59 obese patients (40,68%) and 31 out of 62 control subjects (50%) the *TRIM-3* gene was methylated. There was no statistically significant association between obesity and methylation status ($p > 0.05$). In 35 out of 59 obese patients (59,32%) and 31 out of 62 non-obese people (50%) had the *TRIM-3* gene unmethylated. Unmethylation status and obesity were not statistically different from one another ($p > 0.05$).

In this study, the methylation and unmethylation status of the *TRIM3* gene were compared to the mean age of the individuals. The TRIM3 gene's mean age was $44{,}34\pm9$ (mean ± Std. Deviation), while the methylated TRIM3 gene's mean age was $43{,}58\pm11{,}21$ (mean ± Std. Deviation). The statistical analysis revealed no significant associations between the age of the obese participants and their TRIM3 gene methylation status ($p = 0.77$).

This research presents evidence that obesity is linked to DNA methylation modifications by identifying differences in the TRIM3 methylation status between obese participants and control controls. Obese subjects have excessively high leptin levels. Leptin resistance is the term used to describe this phenomenon[18]. In obese individuals, visceral body fat may have an impact on medical issues through an abnormal adipokine production. The concentration of total adiponectin and adiponectin with a high molecular weight decreases in obesity and increases after weight loss, indicating that adiponectin plays a critical role in energy homeostasis. Adiponectin production and release may be impacted by the growth of adipose tissue[19]. Extreme insulin sensitivity

has been linked to higher levels of resistin in humans than conventional insulin action. Resistin may therefore be crucial in the development of insulin resistance[20].

In our study, the methylated *TRIM3* participants had a mean leptin level of $21{,}04\pm10{,}81$ (mean ± Std. Deviation) while the unmethylated *TRIM3* subjects had a mean leptin level of $23{,}42\pm14{,}07$ (mean ± Std. Deviation) ($p = 0,46$). Unmethylated TRIM3 patients had a mean level of adiponectin of $10{,}39\pm5{,}15$ (mean ± Std. Deviation,), whereas methylated TRIM3 subjects had a mean level of $10{,}54\pm4{,}96$ (mean Std. Deviation) ($p = 0,91$). The mean levels of resistin were $8{,}74\pm2{,}68$ (mean Std. Deviation) in the unmethylated TRIM3 patients and $8{,}74\pm2{,}68$ (mean ± Std. Deviation) in the methylated TRIM3 subjects ($p = 0,87$). As a result, there was no statistically significant correlation between anthropometric or metabolic traits and TRIM3 methylation status (**Table I**).

Conclusion

An important part of obesity is played by genetic and epigenetic factors. The importance of the interaction between genetic and environmental variables on the etiology of obesity is highlighted by studies and changes of epigenetic regulators. Numerous obesity susceptibility genes have been found by researchers, along with their function in the progression of disease.

Accordingly, epigenetic changes and how they interact with the environment have the potential to become biomarkers for obesity. According to these findings, a number of studies have looked into possible biomarkers of obesity in an effort to raise the quality of life for those who are affected, lessen their symptoms, assist them in adjusting to daily life, and strengthen and improve their attitudes towards interpersonal interactions. This study was unable to find a connection between obesity and the TRIM3's methylation pattern. There haven't been many studies on epigenetics in this field. Our research thus clarifies epigenetics and provides crucial data for next investigations, such as those looking for biomarkers for obesity.

Funding

Data Availability

The genetics data that support the findings of this study are available on request from the corresponding author (RK).

Declarations
Conflict of Interest

The authors affirm that they do not have any competing interests.

Ethical Approval

All subjects signed written consent forms after being fully informed. The study protocol was approved by the Research Ethics Committee of the Near East University and performed in accordance with the Declaration of Helsinki (YDU-2021/96–1425).

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ORIGINAL

Influence of tobacco consumption on the values of different cardiometabolic risk scales in 418,343 spanish workers

Influencia del consumo de tabaco en los valores de diferentes escalas de riesgo cardiometabólico en 418.433 trabajadores españoles

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Summary

Introduction and objectives: Cardiometabolic diseases are very prevalent and include different pathologies such as elevated blood pressure, obesity, dyslipidemia, and elevated blood glucose. All these entities make up what is known as the metabolic syndrome (MS) and some associated conditions such as hypertriglyceridemic waist circumference (CHTG) and diabesity, among others. The aim of the study was to assess the influence of some sociodemographic variables and tobacco consumption on these pathological entities.

Material and methods: A descriptive, cross-sectional study in a large group of Spanish workers in which the prevalence of MS was assessed by applying several criteria, CHTG, diabesity and high values of atherogenic indices and a prediabetes risk scale. The influence of different sociodemographic variables (age, sex, and social class) and tobacco consumption on these pathologies was assessed.

Results: All the sociodemographic variables increased the risk of presenting these cardiometabolic disorders, with sex and age showing higher odds ratios in all cases. Tobacco consumption also had an influence, but to a lesser extent.

Conclusions: The profile of the person with the highest risk of presenting these cardiometabolic disorders is an older male, belonging to social class III, and a smoker.

Key words: Metabolic syndrome, hypertriglyceridemic waist, diabesity, atherogenic index, prediabetes, smoking.

Resumen

Introducción y objetivos: Las enfermedades cardiometabólicas son muy prevalentes y engloban diferentes patologías como la elevación de la tensión arterial, la obesidad, la dislipemia y la elevación de la glucemia. Todas estas entidades conforman lo que conocemos como síndrome metabólico (SM) y algunos cuadros asociados como la cintura hipertriglicerídemica (CHTG) o la diabesidad entre otras. El objetivo del estudio es valorar la influencia de algunas variables sociodemográficas y el consumo de tabaco sobre estas entidades patológicas.

Material y métodos: Estudio descriptivo y transversal en un amplio colectivo de trabajadores españoles en los que se valora la prevalencia de SM aplicando varios criterios, CHTG, diabesidad y valores elevados de índices aterogénicos y de una escala de riesgo de prediabetes. Se valora la influencia que distintas variables sociodemográficas (edad, sexo y clase social) y el consumo de tabaco tienen sobre estas patologías.

Resultados: Todas las variables sociodemográficas incrementan el riesgo de presentar estos trastornos cardiometabólicos siendo el sexo y la edad las que muestran valores de odds ratio superiores en todos los casos. El consumo de tabaco también influye pero con una potencia menor.

Conclusiones: El perfil de persona con mayor riesgo de presentar estas alteraciones cardiometabólicas es un varón de edad avanzada, perteneciente a la clase social III y fumador.

Palabras clave: Síndrome metabólico, cintura hipertriglicerídemica, diabesidad, índice aterogénico, prediabetes, tabaco.

Introduction

Cardiometabolic diseases are a group of pathologies that are highly prevalent throughout the world[1] and cause a high morbidity and mortality rate in both sexes[2,3]. These pathologies include very prevalent conditions such as obesity[4], hyperglycemia,[5,6] dyslipidemia[7], and elevated blood pressure[8], all of which are included in what is known as the metabolic syndrome (MS)[9].

MS has been known for many decades and is not easy to define since there are numerous criteria for its diagnosis, namely: WHO[10] (World Health Organization), EGIR[11] (European Group for the Study of Insulin Resistance), NCEP ATPIII[12] (National Cholesterol Education Program Adult Treatment Panel III), IDF[13] (International Diabetes Federation), JIS[14] (Joint Interim Statement), among others.

There are also other parameters that are closely related to MS since they share some of its elements, such as hypertriglyceridemic waist circumference (CHTG)[15] (elevated triglyceride values and abdominal waist circumference), diabesity[16] (presence of diabetes and obesity), and atherogenic indices[17].

The aim of this study was to determine how different sociodemographic variables such as age, sex, social class, and tobacco consumption affect the appearance of MS, CHTG, diabesity, and elevated values of atherogenic indices.

Methods

Between January 2017 and December 2019, a descriptive, cross-sectional study was conducted in 418,343 Spanish employees from different regions and productive sectors. Individuals were selected from among those who underwent regular health examinations in the different participating companies.

The following were the requirements to participate in the study: being aged 18 to 69 years, working for a company included in the study, not being temporarily incapacitated, and signing the informed consent to participate in the study and to use their data for epidemiological purposes.

The flow diagram of the study participants is shown in **Figure 1**.

Table I shows the characteristics of the population, with all anthropometric, clinical, and analytical variables showing higher or less favorable values in men. The most frequent age was between 30 and 49 years. Most of the employees belonged to social class III and had only a primary education. Approximately every third person in the study smoked.

Figure 1: Flowchart.

421625 workers started the study

729 were under 18 or over 69 years old

656 did not agree to participate

1897 lacked a variable to calculate CVR

418,343 (246,061 men and 172,282 women) finally entered the study
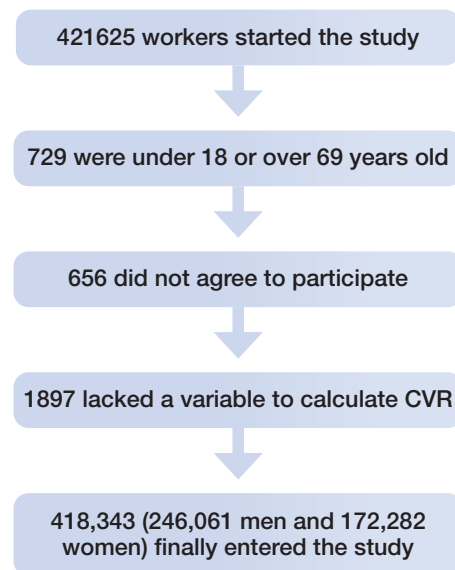
Measurement and data collection

Anthropometric measurements (height, weight, and waist circumference) were performed clinically and analytically by health professionals in all the companies participating in the study; measurement techniques had previously been standardized.

Weight and height were obtained with a SECA 700 measuring scale. A SECA measuring tape was used, with the person standing, feet together, trunk erect, and abdomen relaxed to measure waist circumference. The tape was placed parallel to the ground and more or less at the end floating rib.

Blood pressure was obtained with the person seated and after a rest of at least 10 minutes, using a calibrated OMRON M3 automatic sphygmomanometer. Three measurements were taken with a period of one minute between them and the mean of the three was recorded. Analytical parameters were obtained after at least 12 hours of fasting. Total cholesterol, triglycerides, and blood glucose were acquired using automated enzymatic methods. Meanwhile, a precipitation process with dextran sulfate-MgCl2 was used to obtain HDL-c. The Friedewald formula was used to calculate LDL-c indirectly. Each analysis parameter was expressed in mg/dL.

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

The presence or absence of MS was assessed by applying the validated diagnostic criteria of the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) of the International Diabetes Federation (IDF) and the Joint Interim Statement (JIS)[18].

Hypertriglyceridemic waistline[19] is defined as the coexistence of elevated triglyceride values (over 150 mg/

dL) and elevated abdominal waist circumference values (over 102 cm in men and over 88 cm in women).

Diabesity[20] is established when diabetes and obesity (body mass index over 30 kg/m²) are found in the same person.

The risk of prediabetes was determined by applying the PRISQ (prediabetes risk score Qatar)[21] scale.

The following atherogenic indices were calculated[22]: Total cholesterol/HDL-c index: low risk is considered as values lower than 5 in men and lower than 4.5 in women; moderate risk: between 5 and 9 in men and between 4.5 and 7 in women; and high risk: higher than 9 in men and higher than 7 in women. LDL-c/HDL-c ratio: low risk below 3 and high risk above 3.

Smokers were those who had consumed at least one cigarette a day (or its equivalent in any of the consumption modalities) in the previous month or if they had quit smoking less than one year before.

The Spanish Society of Epidemiology[23] establishes three categories of social classes according to profession, as proposed by the social determinants group. Directors, managers, sportsmen and artists, university professionals and skilled self-employed workers belong to Class I. Unskilled self-employed workers and intermediate occupations belong to Class II. Unskilled workers belong to Class III.

Statistical analysis

The frequency and distribution of categorical variables were calculated, and a descriptive analysis was performed. The mean and standard deviation of quantitative variables were calculated by presenting the variables with a normal distribution.

For independent samples, the Chi-squared test and Student's t-test were used. When circumstances required it, Fisher's exact statistic was corrected. To perform multivariate analysis, multinomial logistic regression was used to calculate odds ratios and their 95% confidence intervals. Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) version 28.0 Windows program, which had an accepted statistical significance level of 0.05.

Ethical considerations and/or aspects

The research group is committed to compliance with national and international ethical standards for health sciences research (Declaration of Helsinki), paying special attention to the anonymity of the participants and the confidentiality of the data collected. The Ethics and Research Committee of the Balearic Islands (CEI-IB) approved the study with number IB 4383/20. Since participation in the study was voluntary, participants gave their consent verbally and in writing after receiving sufficient information about its nature. To achieve this,

they were given an informed consent form as well as an information sheet explaining the purpose of the study. By using codes to identify the survey data, only the survey administrator can link them to the participants. The identity of participants will not be disclosed in any report of this study. The researchers will refrain from disclosing information that could identify them. In any event, the research group undertook to comply with the provisions of the Organic Law 3/2018, of December 5, on the protection of personal data and guarantee of digital rights, which guarantees research participants the rights of access, rectification, cancellation, and objecting to the data set.

Results

The anthropometric and clinical characteristics of the 418,343 workers (246,061 men and 172,282 women) who participated in the study are shown in **table I**.

Most of the participants in this group were between 30 and 49 years old, with a mean age of 40.2 ± 11 years. In men, all variables showed more negative values. One third of the workers smoked and three quarters belonged to the most disadvantaged social class.

Table II shows the prevalence of MS, CHTG, diabetes, high values of atherogenic indices, and high values of PRISQ according to smoking in both sexes. In all cases, the prevalence was higher in the group of smokers (statistically significant differences). Moreover, prevalence was always higher in men.

Table III shows the results of the multivariate analysis using multinomial logistic regression. The reference variables were aged under 30 years, female sex, social class I, and being a non-smoker.

All the sociodemographic variables included in the study, especially age and sex, and tobacco use, increased the risk of presenting MS when applying the three criteria; and also CHTG, diabesity, high risk of the two atherogenic indices, and high risk of prediabetes when applying the PRISQ scale.

Discussion

In our study, the risk of presenting MS applying any of the criteria, such as CHTG, diabetes or high values of atherogenic indices, or the risk of prediabetes applying the PRISQ scale is influenced by all the sociodemographic variables analyzed, and fundamentally by age and sex (those with the highest odds ratios). Tobacco consumption also increases all of the above, although to a lesser extent. We found a prevalence of MS that ranges in men between 13.2% if we apply the IDF criteria and slightly more than 27% if we use the ISB criteria; whereas

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
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
Glycemia	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	29.7	27.6	28.4	
40-49 years	29.6	30.0	29.9	
50-59 years	16.8	19.7	18.5	
≥60 years	3.2	3.9	3.6	
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	
Non-smokers	67.2	66.6	66.9	<0.0001
Smokers	32.8	33.4	33.2	

Table II: Mean values of the insulin resistance, non-alcoholic fatty liver disease, and liver fibrosis scales according to smoking by sex.

	Women			Men		
	Non-smokers n=115727 %	Smokers n=56555 %	p-value	Non-smokers n=163920 %	Smokers n=82141 %	p-value
MS NCEP ATPIII	9.4	9.7	<0.0001	16.7	16.9	<0.0001
MS IDF	9.2	9.4	<0.0001	13.2	13.3	<0.0001
MS JIS	11.0	11,2	<0.0001	27.3	27.7	<0.0001
HTGW	1.5	1.6	<0.0001	8.2	8.4	<0.0001
High AI CT/HDL	0.1	0.2	<0.0001	0.2	0.3	<0.0001
High AI LDL/HDL	7.6	13.1	<0.0001	25.8	25.9	<0.0001
Diabesity	1.6	1.7	<0.0001	3.2	3.4	<0.0001
High PRISQ	6.2	6.9	<0.0001	14.0	14.7	<0.0001

MS metabolic syndrome; NCEP ATPIII National Cholesterol Education Program Adult Treatment Panel III; IDF International Diabetes Federation; JIS Joint Interim Statement; HTGW hypertriglyceridemic waist circumference; AI atherogenic index; TC/HDL total cholesterol/high-density lipoprotein; LDL/HDL low-density lipoprotein/high-density lipoprotein; PRISQ prediabetes risk score Qatar

Table III: Multinomial Logistic Regression.

	MS NCEP ATPIII OR (CI 95%)	MS IDF OR (CI 95%)	MS JIS OR (CI 95%)	HTGw OR (CI 95%)	High AI CT/HDL OR (CI 95%)	High AI LDL/HDL OR (CI 95%)	Diabesity OR (CI 95%)	High PRISQ OR (CI 95%)
Women	1	1	1	1	1	1	1	1
Men	1,81 (1.77-1.85)	1.39 (1.36-1.42)	3,04 (2.99-3.10)	5.52 (5.30-5.75)	1.38 (1.27-1.47)	2.31 (2.27-2.35)	1.83 (1.75-1.91)	2.48 (2.42-2.54)
18-29 years	1	1	1	1	1	1	1	1
30-39 years	1.64 (1.58-1.70)	1.11 (1.06-1.15)	1.62 (1.56-1.68)	1.06 (1.04-1.08)	1.56 (1.20-2.04)	1.24 (1.19-1.28)	1.60 (1.51-1.70)	1.58 (1.47-1.69)
40-49 years	3.35 (3.23-3.47)	1.56 (1.50-1.63)	3.34 (3.23-3.47)	1.11 (1.04-1.19)	2.89 (2.20-3.79)	2.16 (2.08-2.23)	4.26 (4.00-4.53)	4.16 (4.01-4.32)
50-59 years	7.59 (2.85-3.11)	2.98 (2.85-3.11)	6.94 (6.69-7.20)	1.66 (1.55-1.77)	4.82 (3.58-6.49)	4.53 (4.37-4.70)	15.58 (14.31-16.97)	18.30 (17.59-19.03)
60-69 years	17.92 (17.04-18.85)	6.17 (5.86-6.50)	13.78 (13.20-14.38)	3.74 (3.46-4.04)	16.44 (10.33-26.14)	12.93 (12.36-13.53)	72.95 (60.91-87.39)	60.70 (57.83-63.71)
Social class I	1	1	1	1	1	1	1	1
Social class II	1.35 (1.32-1.39)	1.27 (1.24-1.30)	1.34 (1.31-1.37)	1.07 (1.31-1.37)	1.07 (1.03-1.11)	1.16 (1.13-1.18)	1.79 (1.69-1.91)	1.19 (1.16-1.23)
Social class III	1.53 (1.46-1.60)	1.44 (1.38-1.51)	1.46 (1.41-1.52)	1.28 (1.41-1.52)	1.32 (1.21-1.43)	1.27 (1.21-1.33)	2.19 (1.95-2.46)	1.35 (1.28-1.43)
Non-smokers	1	1	1	1	1	1	1	1
Smokers	1.04 (1.01-1.08)	1.05 (1.03-1.08)	1.06 (1.04-1.09)	1.05 (1.02-1.09)	1.15 (1.08-1.23)	1.04 (1.01-1.08)	1.06 (1.01-1.11)	1.03 (1.01-1.05)

MS metabolic syndrome; NCEP ATPIII National Cholesterol Education Program Adult Treatment Panel III; IDF International Diabetes Federation; JIS Joint Interim Statement; HTGW hypertriglyceridemic waist circumference; AI atherogenic index; TC/HDL total cholesterol/high-density lipoprotein; LDL/HDL low-density lipoprotein/high-density lipoprotein; PRISQ prediabetes risk score Qatar

in women the prevalence is lower, slightly more than 9% applying the NCEP ATPIII and IDF criteria, and about 11% if the criteria are the ISB ones.

With regard to data from the National Health and Nutrition Examination Survey (NHANES), in the US adult population, the prevalence of MS experienced a large increase in recent decades, going from 22% between 1988 and 1994, to 33% between the years 2007 and 2012[24,25]. For the period 2011-2016, the figure rose to 34.7%. In South America, an overall prevalence of MS is estimated to be between 18.8-43.3%[26]. A Colombian study conducted in Medellín observed a prevalence in adults of almost 40%[27].

The higher prevalence of MS in men was also found in another Colombian study conducted in young university students[28]. The results of a meta-analysis that included different studies carried out in ten Spanish autonomous communities[29] showed that the prevalence of MS was 31% (32% in men and 29% in women).

Data from the China Nutrition and Health Surveillance[30] (2015-2017), which included a total of 130,018 residents aged 20 years or older using NCEP ATPIII criteria found that the factors that most influenced the occurrence of MS were female sex, older age, high socioeconomic status, and tobacco use, data that in some cases differ from those found by us.

A study carried out in Iran[31] in which more than 10,000 persons were included found no relationship between MS and socioeconomic level. However, another study carried out in the same country[32] did find a higher prevalence of MS in people with a lower socioeconomic level. A Spanish study[33] conducted in 42,146 workers also found that MS was more prevalent in people with low socioeconomic status, and this effect of social class was stronger in women.

There is evidence of the relationship between the smoking habit in pregnant women and the subsequent appearance of metabolic disorders in their children when they reach adulthood. The children of women who smoke are born with lower birth weight, which increases the risk of being overweight or obese in adulthood. Some studies have shown an increased risk of insulin resistance, type 2 diabetes, and hypertension, although this evidence is weaker than for overweight[34]. A Palestinian study in refugee youth associated tobacco use with an increased prevalence of MS[35]. Another study in India also found an association between smoking and MS[36].

In a Chinese study[37] conducted in more than 3000 persons aged 40 years and older, the prevalence of HTGW was 7.5% (7.4% in men and 7.5% in women), this higher overall prevalence could be due to the fact that the waist circumference values applied in that study were much lower than those applied by us. A Brazilian study carried out in people aged 60 years and older found a prevalence of HTGW of 21.7%, which was also higher in women[38].

A Brazilian study conducted in more than 1000 adolescents with low socioeconomic status found a high prevalence of HTGW[39].

Data from the PREDIMED-Plus study conducted in almost 7000 people aged between 45 and 65 years showed an increased prevalence of HTGW in smokers[40].

An Egyptian study carried out in 2003 as part of the Africa Wits-INDEPTH Association for Genomic Research (AWI-Gen)[41] revealed, as we did, that the prevalence of elevated values of atherogenic indices was higher in men.

The strengths of the study include, on the one hand, the large sample size, which gives great power to the results obtained in the study, and on the other hand, the large number of cardiometabolic risk scales used.

As a main limitation it is worth noting that by including people in the study only between 18 and 69 years of age, our results may not be able to be extrapolated to the general population.

Conclusions

All the cardiometabolic risk scales analyzed (metabolic syndrome, hypertriglyceridemic waist circumference, diabesity, atherogenic indices, and prediabetes) are influenced by all the sociodemographic variables included in the study, such as social class, and especially age and sex. Tobacco consumption also has an influence, although in a less intense manner.

The profile of a person at high risk of presenting MS, hypertriglyceridemic waist circumference, diabetes, high values of atherogenic indices or high risk of prediabetes he would be an elderly male, belonging to social class III and a smoker.

Conflict of Interest
The authors declared that there is no conflict of interest.

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ORIGINAL

Influence of sociodemographic variables and healthy habits on the values of type 2 diabetes risk scales

Influencia de variables sociodemográficas y hábitos saludables en los valores de escalas de riesgo de diabetes tipo 2

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Abstract

Introduction: Type 2 diabetes is one of the most prevalent metabolic diseases worldwide and is responsible for a large number of complications. There are many factors that increase the risk of presenting this pathology.
Objectives: The aim was to assess the influence of sociodemographic variables and healthy habits on the values of different risk scales for type 2 diabetes.
Methodology: Observational, descriptive, cross-sectional study in 386924 Spanish workers. We assessed how different sociodemographic variables (age, sex, social class and level of education) and healthy habits (physical exercise, Mediterranean diet and smoking) influence the level of risk of presenting type 2 diabetes by applying different scales. Results. All the sociodemographic variables and healthy habits analyzed in this study will influence the values of the type 2 diabetes risk scales. Those that show the greatest influence are physical activity, Mediterranean diet, and age.
Conclusions: The profile of a person at high risk of developing diabetes according to the different scales is an elderly male, with a low socioeconomic level, sedentary, with low adherence to the Mediterranean diet and a smoker.

Key words: Diabetes, Mediterranean diet, physical activity, finrisk, tobacco, socioeconomic status.

Resumen

Introducción: La diabetes tipo 2 es una de las enfermedades metabólicas más prevalentes en todo el mundo y además es responsable de un gran número de complicaciones. Existen muchos factores que incrementan el riesgo de presentar esta patología.
Objetivos. Se pretende valorar la influencia de variables sociodemográficas y hábitos saludables en los valores de diferentes escalas de riesgo de diabetes tipo 2.
Metodología. Estudio observacional, descriptivo y transversal en 386924 trabajadores españoles. Se valora como diferentes variables sociodemográficas (edad, sexo, clase social y nivel de estudios) y hábitos saludables (ejercicio físico, dieta mediterránea y tabaco) influyen en el nivel de riesgo de presentar diabetes tipo 2 aplicando diferentes escalas.
Resultados. Todas las variables sociodemográficas y hábitos saludables analizados en este estudio van a influir en los valores de las escalas de riesgo de diabetes tipo 2. Los que muestran mayor influencia son la actividad física, la dieta mediterránea y la edad. Conclusiones. El perfil de persona con alto riesgo de presentar diabetes con las diferentes escalas es un varón de edad avanzada, nivel socioeconómico bajo, sedentario, con baja adherencia a la dieta mediterránea y fumador.

Palabras clave: Diabetes, dieta mediterránea, actividad física, finrisk, tabaco, estatus socioeconómico.

Introduction

Diabetes is a chronic metabolic disease characterized by high blood glucose levels[1], which over time can lead to damage to various organs such as the heart[2], blood vessels[3], eyes[4], kidneys[5] and nervous system[6]. Type 2 diabetes, which occurs when the body becomes insulin resistant[7] or fails to produce enough insulin[8], is the most common type of diabetes. The prevalence of type 2 diabetes has been increasing significantly in all developed and developing nations over the past thirty years[9]. Type 1 diabetes, also known as insulin-dependent diabetes or juvenile diabetes, is a chronic genetic disease in which the pancreas produces little or no insulin[10].

Because type 2 diabetes is very common and persistent, treatment can be expensive for patients, their families, and the healthcare system[11]. Understanding the costs associated with these conditions and the consequences of inadequate care and management of the disease on society and the economy is essential for an appropriate approach[12,13]. According to experts, if diabetes education programs were successfully implemented and promoted[14], the overall costs of the disease could be significantly reduced and the quality of life of patients could be significantly improved[15]. The therapeutic measure with the greatest impact on reducing complications such as amputations, diabetic comas and days of hospitalization may be diabetes education[16].

Type 2 diabetes is a complex chronic noncommunicable disease, and like them is very complex and represents a challenge for society and health systems worldwide. The increase in the prevalence of type 2 diabetes worldwide has been attributed to a variety of socioeconomic[17], demographic[18] and environmental19 factors, as well as to the increase in risk factors for the development of diseases related to unhealthy lifestyles, such as low levels of physical activity[20] and overweight/obesity[21]. Type 2 diabetes therefore requires a comprehensive understanding that considers both the biological factors of individuals and the social context in which they develop.

The aim of this study is to determine how different sociodemographic variables and healthy habits affect the values of different scales that measure the risk of presenting type 2 diabetes.

Methods

We conducted a study on a total of 386924 workers from different laboral sectors and who performed their activity in several Spanish autonomous communities. We retrieved the data from occupational medical check-ups, performed from January 2019 to June 2020.

The sample selection was made based on inclusion criteria that included:

- Age between 18 and 69 years.
- Existence of an employment contract in one of the companies participating in the study.
- Signing a consent form to participate in the study.
- Permission to use the data for epidemiological purposes.

The flow diagram of the study participants is shown in **figure 1**.

Figure 1: Flow-chart of participants in the study.

386,924 finally entered the study

448 did not agree to participate

2,421 lack some parameter for calculating the scales

388 are under 18 or over 69 years of age

390,181 people start the study
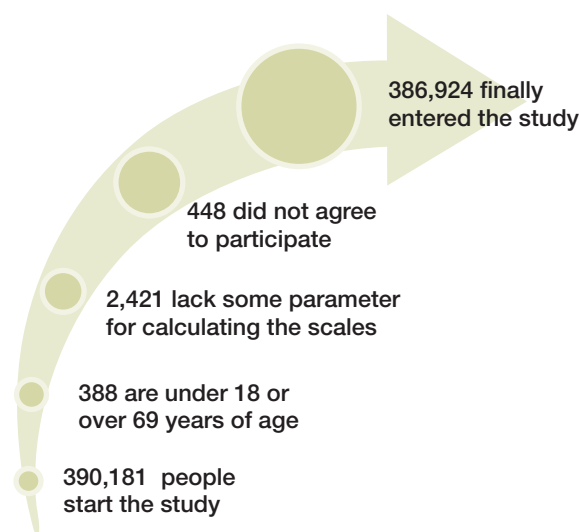
Determination of variables

Each of the health professionals of the participating companies was responsible for obtaining the data needed to calculate the different scales analyzed in this study. The data were obtained by means of:

- Clinical history. Including sociodemographic variables (age, sex, social class and level of education) and healthy habits (tobacco, alcohol, Mediterranean diet and physical activity).
- Anthropometric and clinical determinations. Includes height, weight, waist and hip circumference, systolic and diastolic blood pressure.
- Blood tests. These include lipid profile and blood glucose.

To mitigate the appearance of bias, the measurements of the different variables were standardized.

Weight and height were obtained with the worker standing upright and wearing only underwear. The arms are placed parallel to the thorax and the head must face forward. Measurements are taken with a SECA model scale-measuring device and the data are given in centimeters and kilograms.

The abdominal waist circumferencewas determined with a SECA model measuring tape placed at the level of the last floating rib and parallel to the floor. The worker was in a standing position with the abdomen relaxed. The hip circumference is obtained in the same position and placing the tape measure parallel to the floor at the level of the widest part of the gluteal area.

The OMROM-M3 blood pressure monitor was used to measure blood pressure. The person must be seated and at rest for at least ten minutes to be evaluated correctly. Cuffs of different sizes are available because they should be placed around the arm without being too tight. We perform three separate one-minute tests. The assessment was based on the average of the three figures.

Blood measurements were obtained by venous puncture and after a 12-hour fast. Samples are processed and stored refrigerated for proper preservation, never more than 48 to 72 hours. Reference laboratories use similar methodologies to analyze the samples. Blood glucose, total cholesterol and triglycerides are determined by enzymatic techniques, while HDL cholesterol is determined by precipitation techniques. The Friedewald formula, valid as long as triglycerides do not exceed 400 mg/dL, is used to indirectly estimate LDL cholesterol. If the value is higher than 400 mg/dL, LDL is determined directly. All analytical variables are shown in milligrams per deciliter.

Sex is stated as male and female.

Age is calculated by subtracting the date of birth from the date of the medical examination.

The educational level considered is the highest of all those taken. Primary, secondary and university studies are the three levels established.

The type of work is divided into two categories[22]:

- Non-manual. This includes managerial personnel, university-educated professionals, professional athletes and artists, intermediate professions and skilled self-employed workers.
- Manual. Includes low-skilled workers.

We consider a person to be a smoker if he/she has consumed any form of tobacco at least once a day in the last 30 days or has stopped smoking less than 12 months ago.

Adherence to the Mediterranean diet was determined by applying a fourteen-question questionnaire, which is scored with 0 or 1 point. Scores of 9 indicate high adherence to Mediterranean pattern[23].

The International Physical Activity Questionnaire (IPAQ) was used to determine a person's level of physical activity.

The purpose of this self-administered questionnaire is to calculate the amount of physical activity performed in the last seven days[24].

The type 2 diabetes risk scales calculated are:

- Finrisk[25]. It needs for its calculation le age, sex, Body Mass Index (BMI), waist circumference, physical exercise, fruit and vegetable consumption, consumption of antihypertensive drugs, personal history of hyperglycemia and family history of diabetes. Values above 15 points are considered high.
- QDiabetes-score[26]. Its calculation uses age, sex, race, height, weight, blood glucose, smoking, history of stroke, family history of diabetes, use of antihypertensive drugs, presence of schizophrenia or depression, use of steroids or statins, history of polycystic ovary disease or gestational diabetes. Since there are no cut-off points, we considered high values when the relative risk presented values of 3 or more.
- Canrisk[27]. In order to calculate it, we need sex, age, physical activity, fruit and vegetable consumption, history of hypertension, history of hyperglycemia, family history of diabetes, ethnicity and education. Values above 43 indicate high risk.
- TRAQ-D[28]. Age, sex, BMI, family history of diabetes, smoking, and race are required.
- Oman[29]. We require age, waist circumference, body mass index, family history of diabetes and hypertension status.

Ethical considerations and aspects
All ethical standards that should govern research, as well as the 2013 Declaration of Helsinki, were complied with. The confidentiality and anonymity of the participants have always been assured. The Balearic Islands Research Ethics Committee (CEI-IB), which granted consent under number IB 483/20, approved the study.

Only the principal investigator knows who the participants are because all data are coded. Organic Law 3/2018, enacted on December 5, 2018, protects personal data and protects digital rights, allows and guarantees that study participants can access, rectify, cancel, and oppose the use of the collected data at any time.

Statistical analysis
Quantitative data were analyzed using Student's t test, calculating means and standard deviations. Prevalence was determined using the chi2 test for quantitative variables. Odds ratios with 95% confidence intervals were calculated and multinomial logistic regression analysis was used. SPSS 28.0 software was used to perform the statistical analysis. The accepted level of statistical significance for this study was $p < 0.05$.

Results

Table I shows the anthropometric, clinical, analytical, sociodemographic, and healthy habits data of 386924 workers in the study. The mean age of the participants was just over 39 years. Except for LDL cholesterol, the rest of the variables have lower values in the group of women. Of the participants, 60.2% were men and 39.8% were women. The mean age of the population ranges between 30 and 49 years. Most of them have primary education and belong to socioeconomic class III. 45.5% of the men and 52.2% of the women regularly engage in physical activity, and 51.4% of the women and 41% of the men follow a Mediterranean diet. Thirty-seven percent of the men and 33% of the women were smokers.

Tables II a and **II b** present the means of the different type 2 diabetes risk scales analyzed in this study according to sociodemographic variables and healthy habits in both sexes. All the scales, in both men and women, increase their mean values as age increases and as socioeconomic and educational level decreases. All the scales show higher values in sedentary people, with low adherence to the Mediterranean diet and in smokers.

Table I: Characteristics of the population.

	Men n=232,814 Mean (SD)	Women n=154,110 Mean (SD)	p-value
Age (years)	39.8 (10.3)	39.2 (10.2)	<0.001
Height (cm)	173.9 (7.0)	161.2 (6.6)	<0.001
Weight (kg)	81.1 (13.9)	65.3 (13.2)	<0.001
Waist circumference (cm)	87.7 (9.1)	73.9 (7.9)	<0.001
Hip circumference (cm)	100.0 (8.4)	97.2 (8.9)	<0.001
Systolic blood pressure (mmHg)	124.4 (15.1)	114.4 (14.8)	<0.001
Diastolic blood pressure (mmHg)	75.4 (10.6)	69.7 (10.3)	<0.001
Total cholesterol (mg/dl)	195.9 (38.9)	193.6 (36.4)	<0.001
HDL-c (mg/dl)	51.0 (7.0)	53.7 (7.6)	<0.001
LDL-c (mg/dl)	120.5 (37.6)	122.3 (37.0)	<0.001
Triglycerides (mg/dl)	123.8 (88.0)	88.1 (46.2)	<0.001
Glycaemia (mg/dl)	88.1 (12.9)	84.1 (11.5)	<0.001
	%	%	p-value
20-29 years	17.9	19.5	<0.001
30-39 years	33.1	33.3	
40-49 years	29.7	29.4	
50-59 years	16.3	15.3	
60-69 years	3.0	2.5	
Primary school	61.2	51.8	<0.001
Secondary school	34.0	40.7	
University	4.8	7.5	
Social class I	5.3	7.2	<0.001
Social class II	17.4	33.2	
Social class III	77.3	59.8	
Non physical activity	54.5	47.8	<0.001
Yes physical activity	45.5	52.2	
Non healthy food	59.0	48.6	<0.001
Healthy food	41.0	51.4	
Non smokers	62.9	67.0	<0.001
Smokers	37.1	33.0	

HDL-c High density lipoprotein cholesterol. LDL Low density lipoprotein cholesterol

Table II a: Mean values of the type 2 diabetes risk scales according to sociodemographic variables and healthy habits in men.

		QD-Score RR	Finrisk	Canrisk	TRAQ-D	Oman
Men	n	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
20-29 years	25848	1.0 (1.9)	2.3 (3.2)	14.6 (6.1)	3.6 (2.2)	1.7 (2.2)
30-39 years	76960	1.2 (1.4)	3.5 (3.7)	16.3 (7.0)	5.0 (2.5)	2.4 (2.4)
40-49 years	69060	1.4 (1.4)	5.8 (4.3)	21.7 (8.8)	6.1 (2.7)	10.2 (2.8)
50-59 years	38028	1.5 (1.3)	8.3 (4.5)	30.0 (9.2)	8.3 (3.3)	11.0 (3.0)
60-69 years	7016	1.6 (1.2)	9.6 (4.5)	35.0 (8.9)	10.7 (2.9)	13.6 (3.0)
Primary school	131094	1.3 (1.6)	5.0 (4.5)	21.6 (9.7)	5.9 (3.2)	6.3 (5.1)
Secondary school	74980	1.2 (1.5)	4.8 (4.4)	18.7 (9.7)	5.6 (3.1)	6.3 (5.0)
University	10838	1.1 (1.3)	4.6 (4.3)	16.1 (9.2)	5.5 (3.1)	6.2 (4.9)
Social class I	11950	1.1 (1.3)	4.6 (4.4)	16.1 (9.2)	5.5 (3.1)	6.2 (4.9)
Social class II	38866	1.2 (1.4)	4.8 (4.4)	17.5 (9.5)	5.6 (3.1)	6.3 (5.0)
Social class III	166096	1.3 (1.6)	5.0 (4.5)	21.3 (9.7)	5.9 (3.1)	6.3 (5.1)
Non physical activity	122.912	1.9 (1.8)	7.9 (3.9)	25.7 (9.3)	6.9 (3.3)	8.4 (4.8)
Yes physical activity	94000	0.5 (0.3)	1.5 (2.0)	14.0 (5.7)	4.4 (2.3)	3.8 (4.1)
Non mediterranean diet	132672	1.8 (1.8)	7.4 (4.0)	24.9 (9.4)	6.8 (3.3)	8.1 (4.9)
Yes mediterranean diet	84240	0.5 (0.3)	1.4 (2.0)	13.8 (5.7)	4.4 (2.3)	3.7 (4.1)
Non smokers	137536	1.3 (1.4)	4.6 (4.4)	19.8 (9.3)	5.0 (2.9)	5.7 (5.0)
Smokers	79376	1.3 (1.7)	5.1 (4.5)	20.7 (10.0)	7.2 (3.0)	6.6 (5.1)

QD-Score RR Q-diabetes score relative risk. TRAQ-D Trinidad Risk Assesment Questionnaire.

Table II b: Mean values of the type 2 diabetes risk scales according to sociodemographic variables and healthy habits in women.

Women	n	QD-Score RR Mean (SD)	Finrisk Mean (SD)	Canrisk Mean (SD)	TRAQ-D Mean (SD)	Oman Mean (SD)
20-29 years	19410	1.1 (2.5)	2.1 (3.2)	6.6 (6.2)	1.4 (2.4)	1.2 (2.2)
30-39 years	51392	1.2 (2.1)	2.6 (3.5)	7.3 (7.0)	2.4 (2.6)	1.5 (2.5)
40-49 years	45288	1.3 (1.7)	4.5 (4.1)	12.5 (8.7)	3.5 (2.7)	9.2 (2.9)
50-59 years	23514	1.5 (1.6)	7.4 (4.3)	21.3 (9.0)	5.6 (3.6)	10.3 (3.5)
60-69 years	3928	1.5 (1.3)	9.0 (4.3)	27.1 (8.4)	8.1 (3.2)	13.0 (3.6)
Primary school	73848	1.5 (2.1)	4.7 (4.5)	14.9 (9.6)	3.6 (3.4)	6.2 (5.2)
Secondary school	58690	1.1 (1.7)	3.3 (3.8)	7.9 (8.0)	2.7 (2.9)	4.5 (4.7)
University	10994	1.0 (1.8)	2.8 (3.7)	5.6 (7.4)	2.3 (2.7)	3.8 (4.41)
Social class I	10312	0.9 (1.7)	2.7 (3.6)	5.5 (7.3)	2.3 (2.6)	3.9 (4.4)
Social class II	48318	1.0 (1.6)	3.0 (3.7)	7.3 (7.6)	2.6 (2.8)	4.2 (4.6)
Social class III	84902	1.5 (2.1)	4.6 (4.4)	14.3 (9.6)	3.6 (3.4)	6.2 (5.2)
Non physical activity	70.370	2.2 (2.5)	7.2 (3.8)	17.6 (9.4)	4.4 (3.7)	7.8 (5.1)
Yes physical activity	73162	0.5 (0.3)	1.0 (1.5)	5.6 (5.0)	2.0 (2.0)	3.1 (3.8)
Non mediterranean diet	71418	2.1 (2.5)	7.0 (4.0)	17.3 (9.5)	4.3 (3.7)	7.6 (5.1)
Yes mediterranean diet	72114	0.5 (0.3)	1.1 (1.7)	5.7 (5.3)	2.0 (2.1)	3.2 (3.8)
Non smokers	96796	1.3 (1.8	3.5 (3.9)	10.4 (8.4)	2.4 (3.1)	4.8 (4.7)
Smokers	46736	1.3 (2.2)	4.2 (4.4)	11.8 (10.0)	4.6 (2.9)	5.6 (5.2)

QD-Score RR Q-diabetes score relative risk. TRAQ-D Trinidad Risk Assesment Questionnaire.

Tables **III a** and **III b** show the prevalence of elevated values of the type 2 diabetes risk scales by age, education, social class and healthy habits in men and women. We observed the same trend as with the mean values, i.e. higher prevalence at older age, lower socioeconomic and educational level, in sedentary people, with low adherence to the Mediterranean diet and smokers.

Table III a: Prevalence of high values of type 2 diabetes risk scales according to sociodemographic variables and healthy habits in men.

Men	n	QD-Score RR >3 %	Finrisk high %	Canrisk %	TRAQ-D %
20-29 years	25848	6.2	0.4	1.5	0.2
30-39 years	76960	7.4	1.1	2.7	1.2
40-49 years	69060	9.8	3.6	11.5	2.0
50-59 years	38028	12.0	8.5	32.8	8.1
60-69 years	7016	12.6	14.1	51.8	17.8
Primary school	131094	9.5	3.5	13.4	3.2
Secondary school	74980	7.8	3.0	8.9	2.6
University	10838	7.1	2.5	5.6	2.4
Social class I	11950	7.6	2.8	5.9	2.5
Social class II	38866	7.4	3.1	7.2	2.6
Social class III	166096	9.4	3.4	12.9	3.1
Non physical activity	122.912	15.8	6.1	20.4	5.2
Yes physical activity	94000	0.5	0.3	0.8	0.3
Non mediterranean diet	132672	14.6	6.4	18.9	4.8
Yes mediterranean diet	84240	0.6	0.3	0.8	0.3
Non smokers	137536	8.7	2.9	9.5	1.3
Smokers	79376	9.5	3.5	12.6	5.8

QD-Score RR Q-diabetes score relative risk. TRAQ-D Trinidad Risk Assesment Questionnaire.

Table III b: Prevalence of high values of type 2 diabetes risk scales according to sociodemographic variables and healthy habits in women.

Women	n	QD-Score RR >3 %	Finrisk high %	Canrisk %	TRAQ-D %
20-29 years	19410	8.3	0.3	0.1	0.5
30-39 years	51392	9.7	0.7	0.3	0.6
40-49 years	45288	11.2	2.6	3.1	0.8
50-59 years	23514	14.4	7.3	12.0	4.5
60-69 years	3928	14.6	12.8	22.4	9.4
Primary school	73848	13.7	3.3	5.4	2.0
Secondary school	58690	8.1	1.6	1.3	0.8
University	10994	6.3	1.5	0.9	0.6
Social class I	10312	6.1	1.6	0.8	0.5
Social class II	48318	7.2	1.5	1.0	0.8
Social class III	84902	13.4	3.2	5.1	1.8
Non physical activity	70.370	22.0	5.2	7.1	2.9
Yes physical activity	73162	0.3	0.2	0.2	0.1
Non mediterranean diet	71418	21.7	5.5	7.0	2.8
Yes mediterranean diet	72114	0.3	0.4	0.1	0.1
Non smokers	96796	10.2	1.7	1.84	1.3
Smokers	46736	11.2	2.9	4.2	1.5

QD-Score RR Q-diabetes score relative risk. TRAQ-D Trinidad Risk Assesment Questionnaire.

Table IV shows the results of the multivariate analysis using multinomial logistic regression. The variables that most increase the risk of presenting high values of the different type 2 diabetes risk scales are physical activity, Mediterranean diet and age.

Table IV: Multinomial logistic regression.

	QD-Score >3 OR (95% CI)	Finrisk high OR (95% CI)	Canadian high OR (95% CI)	TRAQ-D high OR (95% CI)
Female	1	1	1	1
Male	0.59 (0.58-0.61)	1.12 (1.08-1.17)	4.20 (4.06-4.34)	1.75 (1.67-1.85)
20-29 years	1	1	1	1
30-39 years	1.16 (1.10-1.21)	1.71 (1.60-1.82)	2.38 (2.27-2.50)	3.20 (3.00-3.42)
40-49 years	1.17 (1.10-1.22)	3.73 (3.49-3.98)	8.59 (8.17-9.04)	13.95 (12.94-15.03)
50-59 years	1.26 (1.21-1.31)	9.77 (9.01-10.59)	35.02 (32.90-37.27)	20.06 (18.46-21.81)
60-69 years	1.35 (1.30-1.40)	17.98 (15.67-20.63)	44.30 (40.50-48.45)	42.95 (37.16-49.64)
Social class I	1	1	1	1
Social class II	1.30 (1.23-1.38)	1.06 (1.04-1.10)	1.85 (1.76-1.95)	1.04 (1.02-1.07)
Social class III	1.31 (1.26-1.37)	1.12 (1.02-1.22)	2.99 (2.76-3.24)	1.15 (1.12-1.19)
Yes physical activity	1	1	1	1
Non physical activity	53.33 (44.01-64.63)	68.32 (41.43-112.65)	8.05 (7.34-8.84)	7.21 (6.16-8.45)
Yes mediterranean diet	1	1	1	1
Non mediterranean diet	23.87 (19.81-28.76)	30.99 (18.78-51.13)	4.25 (3.84-4.71)	2.78 (2.37-3.27)
Non smokers	1	1	1	1
Smokers	1.09 (1.06-1.12)	1.08 (1.04-1.11)	1.22 (1.20-1.25)	4.49 (4.28-4.70)

QD-Score RR Q-diabetes score relative risk. TRAQ-D Trinidad Risk Assesment Questionnaire.

Discussion

In our study, sex, age, social class, level of physical activity, adherence to the Mediterranean diet and tobacco consumption influence the values of the type 2 diabetes risk scales analyzed.

In a systematic review assessing the influence of gender on the prevalence of type 2 diabetes, the authors found that there was a difference in prevalence between men and women, with a higher prevalence in men, linked to sex and not to gender[30]. Another study showed that sex is considered a very important factor that plays a fundamental role in regulating homeostasis and has a greater impact on cardiometabolic risk factors, as well as on the clinical presentation and management of DM[31].

According to data from the National Institute of Diabetes and Digestive and Kidney diseases (NIH), type 2 diabetes can occur in people at any age, including childhood. However, it is found preferentially in middle-aged and older people, especially from 45 years of age onwards[32]. A Spanish systematic review assessed the prevalence of type 2 diabetes in different age groups and found a higher prevalence at older ages[33]. Both studies reinforce the results found in our study.

In our study, the risk of presenting elevated values of the type 2 diabetes risk scales is higher in people with a low socioeconomic level (social class III and primary education); these data are in accordance with those found in several systematic reviews[34,35].

People with low levels of physical activity, or sedentary people, show higher values in all the type 2 diabetes risk scales in our study. A meta-analysis[36] that included 81 studies also found this association, between sedentarism and a higher prevalence of type 2 diabetes compared to people with moderate physical activity, and these, a higher prevalence than persons with high levels of physical activity. Other researchers found similar results[37-39].

We have found that persons with high adherence to the Mediterranean diet have lower values on the type 2 diabetes risk scales. A Spanish study[40] expresses itself in similar terms. A study[41] comparing the effects of two types of diet, ketogenic and Mediterranean, on diabetes concluded that both were effective, although the Mediterranean diet had some advantages.

Tobacco consumption increases the risk of presenting high values of the type 2 diabetes risk scales, especially if we apply the TRAQ-D criteria; our obtained data obtained are similar to those observed in other studies[42,43].

Strengths and limitations

As strengths, we would especially highlight the large size sample size, which gives the results great power, and the greatl number of type 2 diabetes risk scales analyzed.

The main limitation is that the study was conducted in the working population, which excludes people under 18 years of age or over 69 years of age, so that the results may not be extrapolated to the general population. In addition, some of the scales are designed for populations different from the Spanish population.

Conclusions

The variables that most increase the risk of presenting high values in the type 2 diabetes risk scales are low level of physical activity, low adherence to the Mediterranean diet and advanced age.

The prototype of a person at high risk of presenting type 2 diabetes would be a male (except for Q-diabetes), of advanced age, low socioeconomic level, sedentary, with low consumption of Mediterranean diet and smoker.

Conflict of Interest

The authors declare that there is no conflict of interest.

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ORIGINAL

Is Single Anastomosis Sleeve Ileal (SASI) Bypass Superior to Laparoscopic Sleeve Gastrectomy (LSG) among Patients with obesity in Kirkuk City? A Retrospective Study

¿Es el bypass ileal en manga con anastomosis única (SASI) superior a la gastrectomía laparoscópica en manga (LSG) entre los pacientes con obesidad de la ciudad de Kirkuk? Un estudio retrospectivo

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Abstract

Introduction and aim: In the past twenty years, bariatric surgery has witnessed a huge demand by patients with obesity, especially those who suffer from related diseases. The current study aimed to compare the outcomes of a single anastomosis sleeve ileal bypass (SASI) and laparoscopic sleeve gastrectomy (LSG).

Methods: In this cohort retrospective study, 80 obese adult patients who underwent bariatric surgery participated, 40 of them for SASI versus 40 others for LGS surgery in a private hospital in Kirkuk governorate, northern Iraq. All participants were followed up after the sixth and twelfth months after the operation. The outcomes were evaluated through of weighing loss, betterment of comorbidities, and complications that were observed after surgery.

Results: The results showed that the percentage of excess weight loss at six months after surgery was analogous between both surgeries while bypassing SASI showed a clear elevation of EWL% at twelve months postoperatively when compared with LGS. As for comorbidities, the improvement in type 2 diabetes mellitus and GERD by bypassing SASI was significantly better than that of LGS. As for postoperative complications, it has been proven that there are fewer complications after SASI surgery compared to LGS, but not significant.

Conclusions: It was concluded that bypassing the SASI gave better results, especially after twelve months of the operation, and further articles are needful to compare the outcomes of SASI bypass over a longer term.

Key words: Bariatric surgery, SASI, LSG, weight loss, comorbidities.

Resumen

Introducción y objetivo: En los últimos veinte años, la cirugía bariátrica ha sido testigo de una enorme demanda por parte de los pacientes con obesidad, especialmente los que padecen enfermedades relacionadas. El objetivo del presente estudio era comparar los resultados de la derivación ileal en manga con anastomosis única (SASI) y la gastrectomía en manga laparoscópica (LSG).

Metodología: En este estudio retrospectivo de cohortes participaron 80 pacientes adultos obesos que se sometieron a cirugía bariátrica, 40 de ellos para SASI frente a otros 40 para cirugía LSG en un hospital privado de la gobernación de Kirkuk, en el norte de Irak. Se realizó un seguimiento de todos los participantes al sexto y al duodécimo mes de la operación.

Resultados: Los resultados se evaluaron mediante la pérdida de peso, la mejora de las comorbilidades y las complicaciones observadas tras la intervención. Los resultados mostraron que el porcentaje de pérdida de exceso de peso a los seis meses de la intervención era análogo entre ambas cirugías, mientras que la derivación SASI mostraba una clara elevación del LPE% a los doce meses del postoperatorio en comparación con la LGS. En cuanto a las comorbilidades, la mejora de la diabetes mellitus tipo 2 y la ERGE mediante la derivación de la SASI fue significativamente mejor que la de la LGS. En cuanto a las complicaciones postoperatorias, se ha demostrado que hay menos complicaciones tras la cirugía del SASI en comparación con el LGS, pero no significativas.

Conclusiones: Se llegó a la conclusión de que la derivación del SASI daba mejores resultados, sobre todo a los doce meses de la operación, y son necesarios más artículos para comparar los resultados de la derivación del SASI a más largo plazo.

Palabras clave: Cirugía bariátrica, SASI, LSG, pérdida de peso, comorbilidades.

Introduction

Because of the prevalence of obesity and its causes, it can be considered that losing weight is one of the most important medical treatments currently[1]. Losing excess weight has a significant interest on health, survival, and quality of life, as with adequate weight loss, many patients will feel cured of their comorbidities[2]. Bariatric surgery has confirmed to be the preferred treatment for obesity[3], as it is advised for obese individuals with a BMI super than 40 kg/m² or greater than 35 kg/m² when related with comorbidities such as diabetes mellitus/ type 2[4,5]. Although the history of bariatric surgery dates back to the fifties of the last century through the ileojejunal bypass and the other procedures that followed, which achieved significant weight loss, but they failed to attract patients with obesity, and they were not appreciated[6]. By the 2000s, the implementation of a laparoscopic approach to composition abdominal operation, including bariatric surgery, and improved safety and better documentation of clinical efficacy led to an increase in surgery among patients with obesity in several countries[7]. Bariatric surgery includes a wide range of techniques, and the efficacy of each is relatively well-established. The choice of one technique over another is subject to many criteria, such as the clinical and psychological characteristics of the patient, the availability of appropriate infrastructure, the preference of the surgeon, and the expertise of the medical team[8-10]. Laparoscopic sleeve gastrectomy (LSG) is a common bariatric surgical technique due to its fewer complications compared to the rest, and it is considered a permanent and irreversible surgery[11]. It comprises laparoscopic amputation of further than three-quarters of the largest gastric curvature, resulting in the formation of a minimal parochial tube-like structure with a remaining bulk of 100 ml. This size leads to early satiation and weighing loss[12]. Single anastomosis sleeve ileal (SASI) bypass is a new metabolic operation count on a slight gastric bypass and Santoro operation in which side-to-side sleeve gastrectomy is followed[13]. The first documentation on the impact of SASI in patients with obesity showed perfect results for the recent surgical technique[14]. The current study aims to compare the short-term outcomes of SASI and LSG surgeries as curing options for patients with obesity.

Patients & methods

This retrospective cohort analytical study was conducted on 80 patients with obesity who underwent LSG (**Figure 1**) or SASI (**Figure 2**) bariatric surgery, which spanned from the beginning of 2019 to the end of 2021. Their data was obtained from Al-Salam Hospital, located in the center of Kirkuk Governorate, northern Iraq. Depending on the multidisciplinary protocol[15], inclusion criteria for the two surgeries in the current study were obese individuals with a BMI >40 kg/m² or >35 kg/m² with at least one co-morbidity, of both sexes and ages of 22 -55 years only who carried out twelve months of follow-up after SASI or LSG surgery.

On the other hand, the exclusion criteria were as follows: patients with incomplete data, less than 18 years of age, pregnant women who underwent SASI or LSG as revision surgery, and those who did not complete at least 12 months of follow-up. A comparison was made between patients with obesity who underwent one of the obesity operations, either SASI or LSG, in terms of the following: the main variables including gender (male/female), age (years), weight (kg), body mass index (kg/m²), medical comorbidities and postoperative complications. In order to evaluate the surgical outcomes between both types, a follow-up was conducted at 6 and 12 months postoperatively for the following: excessive weight loss, comorbidities, and postoperative complications.

Pre-operative procedures

All obese individuals conducted a preoperative assessment, including detailed history taking of each patient regarding eating habits, comorbidities, and prior medications for morbid obesity, if any. Then, a clinical and laboratory checking was complete, including the percentage of glucose in the blood and the lipid profile. The body mass index of each patient was calculated in addition to a complete pre-operative cardiopulmonary assessment for each patient.

Surgeries

Surgical techniques included both laparoscopic sleeve gastrectomy (LSG) and single anastomosis sleeve ileal (SASI) bypass, which were performed under general anesthesia by expert bariatric surgeons with a five-trocar approach (**Figure 3**) as previously described[16]. Pneumo-peritoneum was performed, and then a visible trocar (10 mm) was incorporated. Then, with a direct view, a trocar of diameter (5 mm) was positioned down the xiphoid process to introduce the Nathanson Liver Retractor. Also, two further working trocars (5 mm) were set in the right and left mid-clavicular lines and a 12 mm trocar for the stapler. Concerning SASI bypass, it is a modern proceeding that necessitate a sleeve gastrectomy with a single gastric-ileal anastomosis (usually, we count 250 cm of small bowel from the duodenojejunal junction). Determining the chosen of surgical techniques was established by a combined decision between the patient and the bariatric surgeon, taking into consideration the consultation of the obesity physician, dietician, and anesthesiologist.

Table I: Dates of the outpatient visit for follow-up after discharge from the hospital.

Visit times	Duration in months (Ms)
once/week	first M
once/month	for 3 Ms
once/every three months	for 12 Ms

Figure 1: LSG operation.
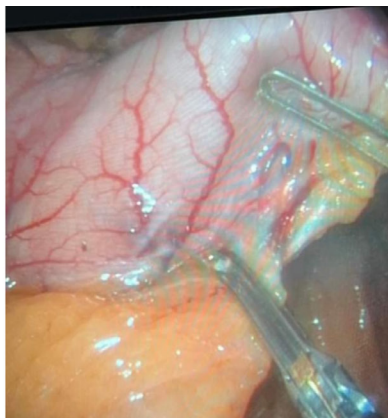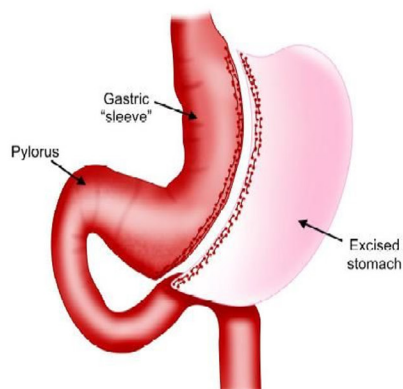
Figure 2: SASI bypass.
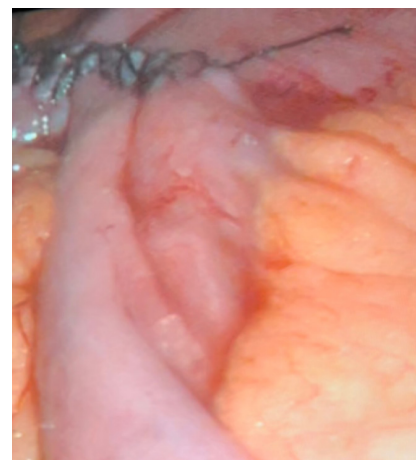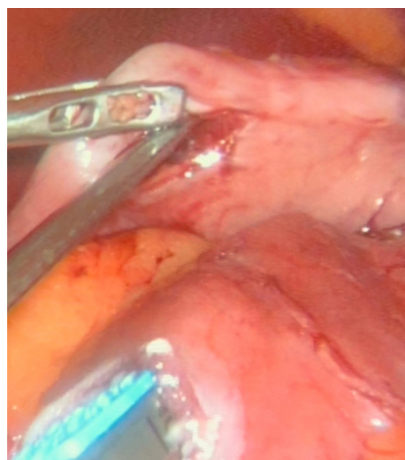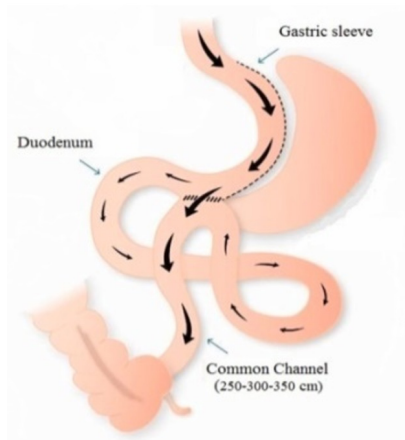
Figure 3: Trocar positions.

Study Outcomes

Concentrate on still up in the air as per recently detailed standard results by Brethauer and partners (2015) in bariatric and metabolic medical procedures[9] following a year of every system. Body weight and structure were evaluated occasionally utilizing bioelectrical impedance examination. The principal results were as per the following: first, the level of abundance weight reduction (% EWL) and the adjustment of the weight file. The level of EWL was determined as [(preoperative weight - weight at follow-up)/overabundance weight before surgery] x 100. Also, the improvement of comorbidity, here comorbidity improvement was checked by infectious prevention and drug apportioning. Improvement in diabetes mellitus/type 2 was considered as no less than 25% off in fasting plasma glucose and no less than 1% off in HBA1c with treatment with hypoglycemic medications. Thirdly, regarding postoperative difficulties, the characterization of products was adjusted as Class I to IV as per the Clavien-Dindo Order.

Statistical analysis

according to the use of SPSS, concentrate on information was broke down. The information was introduced as one or the other mean ± standard deviation (SD) or as numbers and rates. Both parametric and nonparametric procedures were utilized for spellbinding measurements as fitting. Contrasts between both SASI and LGS measures were looked at utilizing a chi-square investigation of patterns. Thinking about that outcomes at $p < 0.05$ were genuinely critical.

Results

Basic characteristics

This study evaluated 80 patients who underwent SASI or LSG bypass and finished 12 months of follow-up. As reviewed in the **table II**, 10 of them were men while 70 were women, with a mean age of 38.1±6.99 years. The mean weight was 129.88±17.30 (kg), and the BMI was 45.60±4.96 (kg/m²). Diabetes mellitus was detected in 31 (38.8%) patients, hypertension in 19 (23.8%) patients, GERD in 16 (20.0%) patients, hyperlipidemia in 13 (16.3%) patients, and obstructive sleep apnea in 8

(10.0%) patients. When comparing between 2 surgeries, no clear differences were noted with regard to the basic characteristics mentioned above, as well as the associated diseases.

Wight loss after SASI and LGS

According to the results, weight loss was registered at six- and twelve-month follow-ups after the two surgical techniques, as indicated by a reduction in weight and BMI compared to the preoperative baseline data. There was no considerable difference between SASI and LGS in weighing loss at six months postoperative. Rather, and were found a difference in mean ± sd in body weight (80.3±11.2 vs. 87.2±9.5) and body mass index (27.6±2.6 vs. 31.2±3.5) at the twelve-month follow-up with statistical significance. Same for EWL% at six months postoperative without a significant difference between SASI and LGS, but bypassing SASI caused a remarkable rising EWL% at twelve months (70.8±14.6) compared to LGS (62.4±11.7) as shown in **table III**.

Associated comorbidities improvements

Twelve months after surgery (**Table IV**), SASI bypass had a statistically greater rate of improvement in diabetes/type

Table II: Basic characteristics of patients with obesity (80) undergoing bariatric surgery.

Characteristics	Surgical Techniques			P-value
	Total N=80	SASI N=40	LGS N=40	
Male/ Female	oct-70	jul-33	mar-37	0.18
Age (years) Mean±SD	38.1±6.99	39.1±6.84	37.1±7.09	0.72
Weight (kg) Mean±SD	129.88±17.30	128.57±16.42	131.2± 18.26	0.36
BMI (kg/m²) Mean±SD	45.60± 4.96	44.82±5.37	46.37±4.45	0.67
Diagnosed Comorbidities NO. (%)				
Diabetes Mellitus	31 (38.8)	17 (21.3)	14 (17.5)	0.49
Hypertension	19 (23.8)	11 (13.8)	8 (10.0)	0.43
GERD	16 (20.0)	5 (6.3)	11 (13.8)	0.09
Hyperlipidemia	13 (16.3)	6 (7.5)	7 (8.8)	0.76
Obstructive Sleep Apnea	8 (10.0)	5 (6.3)	3 (3.8)	0.45

Table III: Weight loss upon follow-up in the 6 and 12 months after the operation.

Variables		Surgical Techniques		P-value
		SASI	LGS	
Wight	6-month postoperative	95.3±11.2	99.4±13.2	0.16
	12-month postoperative	80.3±11.2	87.2±9.5	0.01
	P-value	< 0.0001	< 0.0001	-
BMI	6-month postoperative	32.4± 4.9	34.8±4.6	0.31
	12-month postoperative	27.6±2.6	31.2±3.5	0.03
	P-value	< 0.0001	0.002	-
EWL %	6-month postoperative	45.3±11.4	41.7±10.2	0.12
	12-month postoperative	70.8±14.6	62.4±11.7	< 0.0001
	P-value	< 0.0001	< 0.0001	-

Table IV: Improvement in obesity-associated comorbidities at twelve months after two surgeries.

Comorbidities	Surgical Techniques		P-value
	SASI	LGS	
Diabetes Mellitus/Type 2	15/17 (88%)	7/14 (50%)	0.04
Hypertension	7/11 (64%)	5/8 (63%)	0.69
GERD	4/5 (80%)	3/11 (27%)	0.01
Hyperlipidemia	5/6 (83%)	5/7 (71%)	0.56
Obstructive Sleep Apnea	5/5 (100%)	3/3 (100%)	0.1

2 than LGS (88% vs. 50%, p = 0.04). Both measures showed approximate improvement in hypertension (p = 0.69), hyperlipidemia (p = 0.56), and sleep apnea (p = 0.1). After all patients with GERD underwent endoscopy before and after surgery during follow-up, SASI bypass showed significant improvement compared to GLS (80% vs. 27%, p = 0.01).

Complications

The study did not record any intra-operative complication, as well as deaths. There were 2 (5%) complications after bypass SASI versus 4 (10 %) after LGS surgery, indicating that LGS had a higher complications rate. Knowing that the variation between the two surgeries was not considerable (p = 0.70). Where bleeding occurred in one patient and obstruction in another patient after bypassing SASI. While the complications after LGS were as follows: bleeding in two patients, leakage in one patient, and obstruction in another patient. All these complications, whether bypassing SASI or LGS, were from the second to third grade on the Clavien-Dindo classification (**Table V**). There were 2 (5%) complications after the SASI bypass versus 4 (10%) after LGS surgery.

Discussion

The current study compared the results of two bariatric procedures (SASI and LGS). Bypassing SASI has been shown by follow-up results to be more effective for obesity with diabetes mellitus /type 2 and GERD than LGS, in addition to its higher ability to lose weight, especially after a year of operation. SASI can be considered as a new approach to surgical remediation of obesity based on the concept of bipartite division, which is essentially a technical amendment of else proceeding, sleeve gastrectomy with two transitional sections, pioneered by Santoro and his collagen[16]. SASI bypassing requires at least one gastric anastomosis. Practically, this procedure is based on SG, and in a previous study, the addition of an intestinal anastomosis was demonstrated to prompt early satiation and promote DM/T2 alleviation[14]. This sidestep permits quick passage of undigested chyme into the distal digestive tract, prompting

more proficient discharge of GLP-1 and PYY. These chemicals diminish the rate at which the stomach purges, making the stomach practically more modest (utilitarian limitation). Subsequently, insulin discharge is improved, and focal satiety is upgraded[18,19]. As for LGS, a common bariatric procedure, it is technically the simplest procedure. Although it provides better results, especially in superlative patients with obesity, but with a possible consequence of regaining weight up to 75% in 6 years post-operation, so it is considered a significant problem[20]. Most baseline variable data in the two groups were convergent, although there were some differences that may reverberate the route each surgical technique was selected for patients. Patients with obesity who had LGS (37.1 ± 7.09) were lesser in age than patients who had SASI surgery (39.1 ± 6.84); younger patients may be more likely to regain weight after the operation. Because re-weighting after LGS enable facilely managed with re-sleeve or switching to bypass surgery, this may elucidate the expansion of LGS in younger patients with obesity[21]. The LGS group had a slightly higher body mass index than) 46.37±4.45 (SASI patients (44.82±5.37). This is consistent with a previous study by Otto et al. in 2016, which demonstrated that SG surgery is efficient in patients with a mean BMI of about 55 kg/m^2 [22]. The proportions of patients who underwent the two surgeries, whether SASI or LGS, were almost similar in terms of their suffering from comorbidities, as no statistically significant difference was recorded. Both surgeries carried out noteworthy weighing loss and BMI with a raise in % EWL after six and twelve months post-operatively. The variance between the two surgical techniques in terms of weighing loss outcomes after six months was not significant, but after twelve months, bypassing SASI proved to be significantly better than LGS. Weight loss after the first six months of surgery is based on a restrictive effect during this initial period, followed by a significant onset of the effect of hormonal changes[23,24]. After SASI, losing weight is primarily caused by a neuroendocrine response resulting from the early receipt of nutrients in the distal gut, prompting the secretion of the distal gastrointestinal hormone and inducing a sense of satiety[13,25]. The two procedures had similar proportions of amelioration in hypertension, hyperlipidemia, and obstructive sleep apnea.

Table V: Complications after two surgeries.

Complications	Surgical Techniques			P-value
	Total	SASI	LGS	
Bleeding	3 (3.8%)	1 (1.3%)	2 (2.5%)	
Obstruction	2 (2.5%)	1 (1.3%)	1 (1.3%)	0.70
Leakage	1 (1.3%)	0 (0.0%)	1 (1.3%)	
	Clavien- Dindo classification			
Class	SASI		LGS	
I	0		0	
II	1		2	
III	1		2	
IV	0		0	

SASI medical procedure accomplished all the more measurably more noteworthy improvement in diabetes mellitus/type 2 as well as GERD contrasted with LGS. This huge improvement in diabetes is through a few systems, for example, limitation of capability followed by a noticeable diminishing in caloric admission, a bipartition approach that permits expedient passage of somewhat processed food (chyme) to enhance the dietary feeling of the distal digestive tract, and crossing of a negligible piece of the feast out of the duodenum to decrease excitement unnecessary food admission of the proximal digestive tract[14,16]. In a recent study by Wu et al. (2022) to compare the outcomes of SASI and SG surgeries using a rodent model with diabetes, they concluded that the SASI procedure is a better alternative because it has perfect outcomes in the treatment of obesity and metabolism with a lower risk of hypoalbuminemia[26]. In another review, Romero et al. assessed the results and attainability of their SASI strategy for 43 patients who finished a year after a medical procedure. Among the 25 patients, a reduction from diabetes happened in 95.8% of them[27]. Concerning the improvement in gastroesophageal reflux illness in the wake of bypassing SASI, which came to 80%[16]. In a recent systematic review of the short-term outcome of SASI in the treatment of morbid obesity, which was conducted in 10 studies including 941 patients, the crude percentages of patients with GERD reached 92%[28]. When comparing the complication rates of both surgical techniques, there was no clear significant difference (0.70), which means that both are safe with little risk[29,30,31]. One of the limitations of the current study is that the valuation of the results was short-term, about one year after each operation. Although, the follow-up of patients after the operation for a longer period of more than several years is also required. In addition, the necessary nutritional parameters, such as some proteins, minerals, and vitamins, were not regularly evaluated after each procedure.

Conclusions

Accurately chosen of the bariatric procedure according to every obese patient's condition has the most important role in achieving the best possible outcomes. There was no clear difference between the outcomes of both procedures at six months after the operation. But at twelve months after SASI bypass, a greater decrease in body weighing and BMI, increased % EWL, and better improvement in diabetes/type 2 and GERD were observed compared to LGS. The study recommends conducting another study to estimate the long-term outcomes of both surgical procedures, as well as other prospective studies comparing SASI with obesity surgery techniques

Conflict of Interest
The authors declare that there is no conflict of interest.

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ORIGINAL

A Meta-analysis and Systematic Review of the Antimicrobial Activities of Calcium Hydroxide Paste Mixed with Different Metallic Salts, Polymers, and Metallic Nanoparticles

Un metaanálisis y revisión sistemática de las actividades antimicrobianas de la pasta de hidróxido de calcio mezclada con diferentes sales metálicas, polímeros y nanopartículas metálicas

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Abstract

Objective: the present study were conducted to evaluate the antimicrobial activity of calcium hydroxide paste mixed with different metallic salts, polymers, and metallic nanoparticles.

Material and methods: A search of all international databases was conducted between January 2013 and May 2023 using keywords related to the study's objectives, including PubMed, Scopus, Science Direct, ISI, Web of Knowledge, and Embase. For the current study, related articles were found by using the PRISMA 2020 checklist and Google Scholar search engine. Inverse-variance method and the fixed effect model were used to calculate the 95% confidence interval for mean differences. The meta-analysis was conducted using Stata/MP v.17 software.

Results: A total of 183 abstracts were reviewed in the initial review, which removed duplicate studies. A total of 41 studies were reviewed by two authors, and ten studies were chosen for further study. The mean differences of antibacterial effect on E. faecalis between CHX + CH and CH were 0.75 (MD, 0.75 95% CI 0.67, 0.83; p=0.00). Mean differences of antibacterial effect on E. faecalis between CHT+ CH and CH were 2 (MD, 2 95% CI -5.46, 9.46; p=0.60).

Conclusion: Based on the findings of the present meta-analysis, a mixture of CH and CHX, silver nanoparticles, copper nanoparticles, and zinc nanoparticles can lead to eradicating E. faecalis as an intracanal medicine. The use of CHT as an antimicrobial adjuvant for CH-based drugs was not supported.

Key words: Nanoparticles, biofilms, root canal obturation, metal nanoparticles, chlorhexidine.

Resumen

Objetivos: el presente estudio se realizó para evaluar la actividad antimicrobiana de la pasta de hidróxido de calcio mezclada con diferentes sales metálicas, polímeros y nanopartículas metálicas.

Métodos: se realizó una búsqueda en todas las bases de datos internacionales entre enero de 2013 y mayo de 2023 utilizando palabras clave relacionadas con los objetivos del estudio, incluidas PubMed, Scopus, Science Direct, ISI, Web of Knowledge y Embase. Para el estudio actual, se encontraron artículos relacionados utilizando la lista de verificación PRISMA 2020 y el motor de búsqueda Google Scholar. Se utilizó el método de varianza inversa y el modelo de efectos fijos para calcular el intervalo de confianza del 95% para las diferencias de medias. El metanálisis se realizó utilizando el software Stata/MP v.17.

Resultados: Se revisó un total de 183 resúmenes en la revisión inicial, que eliminó los estudios duplicados. Dos autores revisaron un total de 41 estudios y se eligieron diez estudios para realizar estudios adicionales. Las diferencias medias del efecto antibacteriano sobre E. faecalis entre CHX + CH y CH fueron 0,75 (DM, 0,75; IC del 95 %: 0,67 a 0,83; p = 0,00). Las diferencias medias del efecto antibacteriano sobre E. faecalis entre CHT+ CH y CH fueron 2 (DM, 2 IC del 95%: -5,46; 9,46; p=0,60).

Conclusión: Según los hallazgos del presente metanálisis, una mezcla de CH y CHX, nanopartículas de plata, nanopartículas de cobre y nanopartículas de zinc puede conducir a la erradicación de E. faecalis como medicamento intracanal. No se apoyó el uso de CHT como adyuvante antimicrobiano para medicamentos a base de CH.

Palabras clave: Nanopartículas, biopelículas, obturación del canal radicular, nanopartículas metálicas, clorhexidina.

Introduction

As a result of persistent microbial infection in the root canal system and surrounding radicular tissues, apical periodontitis develops, which is considered an inflammatory disorder[1]. The basis of root canal treatment is to destroy microorganisms and prevent re-infection[2]. However, for some reasons, including the anatomical complications of the root canal system, apical periodontitis may remain[3,4]. Therefore, it is recommended to use the supplement of antimicrobial drugs[5-7]. One widely used drug is Calcium hydroxide (CH) paste, which studies have reported its antimicrobial effect. CH paste creates a very alkaline environment that usually microorganisms cannot survive[8]. However, studies have reported that the effectiveness of CH paste can be limited, or some microbial species have become resistant to it[4]. It has been reported that Enterococcus faecalis (E. faecalis) and Candida albicans (C. albicans) are among the species resistant to CH paste treatment and cause root canal treatment to fail. Apical periodontitis remains[9,10]. These bacteria can tolerate high pH and have the ability to penetrate dentin[11]. Studies have tried to increase its antimicrobial activity by adding auxiliary antimicrobial substances to CH paste[12]. One of these substances is Chlorhexidine (CHX), Gram-positive and Gram-negative bacteria have been shown to be susceptible to this antimicrobial agent. This material is biocompatible and can be absorbed into dental tissues, increasing the treatment level[13]. Many studies have investigated the advantage of mixing CH with CHX. According to the studies, CHX is much more effective at killing bacteria than CH alone. However, other studies also observe contradictory findings[14-16]. Some studies have shown that using metallic nanoparticles (MNPs) can effectively control oral infections[17-19]. Studies have suggested that MNPs can be promising alternatives to traditional antimicrobial agents[20,21].

Silver, copper and zinc nanowires are among the MNPs whose antimicrobial properties have been reported by many studies[22]. Polymeric nanoparticles (PNPs) have recently been introduced as complex carriers for drug delivery[23,24]. The advantages of PNPs include biocompatibility, improved stability, biodegradability, drug release profiles, and ease of use[25]. Metallic nanoparticles have also been successfully synthesized in aqueous solutions using chitosan (CHT) as a reducing and stabilizing agent[26]. One of the advantages of CHT is that they are biocompatible and biodegradable. Studies have indicated that CHT is hemostatic, antimicrobial and analgesic[23]. A study has reported promising results in using CHT/CDP/metallic nanoparticles[27]. An investigation of the antimicrobial activity of CH paste mixed with different metallic salts and metallic nanoparticles, PMNPs, has been conducted in the present study. Therefore, the present study evaluated the antimicrobial activity of calcium hydroxide paste mixed with different metallic salts, polymers, and metallic nanoparticles.

Methods

Search strategy

A search was conducted in all international databases, PubMed, Scopus, Science Direct, ISI, Web of Knowledge and Embase, based on keywords related to the study's objectives, between January 2013 and May 2023. A PRISMA 2020 checklist[28] was used to guide the current study, and related articles were also found by using Google Scholar. Keywords and the MeSH terms:

(((((((((("Periapical Periodontitis"[Mesh]) AND ("Anti-Infective Agents"[Mesh] OR "Antimicrobial Stewardship"[Mesh] OR "Biofilms"[Mesh])) AND "Candida albicans"[Mesh]) AND ("Root Canal Obturation"[Mesh] OR "Dental Pulp Diseases"[Mesh])) AND "Metal Nanoparticles"[Mesh]) OR "Silver"[Mesh]) OR "Copper"[Mesh]) OR "Zinc Oxide"[Mesh]) AND "Chlorhexidine"[Mesh]) AND ("Microbiology"[Mesh] OR "microbiology" [Subheading] OR "Microbiological Techniques"[Mesh]).

Process of data collection, data selection, and data items

A checklist that included seven items was used to extract sample specifications from the selected studies: author's name, publication year, sample size, study design, Nanoparticle type, number of control groups, assessment of the antimicrobial properties and Bacterial strain. Additionally, the findings of the studies were used to extract the data required for the meta-analysis, including the antimicrobial performance. Each record was reviewed independently by two reviewers, and each report was retrieved. According to inclusion and exclusion criteria, all studies were selected.

Eligibility criteria

Inclusion criteria: Articles published in English, in-vitro studies and studies assessing the antibacterial effect.
Exclusion criteria: Review papers, case studies, and case reports. Studies without full-text access.

Critical appraisal

A modified version of the CONSORT Criteria (Guidelines for reporting pre-clinical in vitro studies on dental materials) was used to evaluate the quality of the study[29]. The parameters were answered yes or no for each study in a review with 14 items. These items were:

A structured description of the methods, results, and conclusion of the trial; an explanation of the scientific context; specific objectives or hypotheses; and sufficient details about the intervention, including when and how it was administered, for replication. An outcome measure that is fully defined, predetermined, and includes how and when it is evaluated, how the sample size is calculated, how the random allocation sequence is generated, how it is implemented, who is responsible for creating the random allocation sequence, and who becomes blind

after the intervention is administered. Statistics used to compare the groups, results from each group, estimation of effect size and precision, trial limitations, identifying potential biases and imprecisions, and where the full trial protocol can be found, including multiple analyses, funding sources and other support sources. This tool was adapted and modified from the Cochrane risk of bias tool. This tool assigned scores of 2, 1, or 0 to each item. A low bias risk score is 0 to 3, a moderate bias risk score is 4 to 7, and a high bias risk score is 8 to 10. The tool produced the lowest score of 0 and the highest score of 10[30].

Data analysis

According to the I^2 coefficient, low heterogeneity can be determined with values less than 50%, moderate heterogeneity can be determined with values between 50% and 75%, and high heterogeneity can be determined with values over 75%. The fixed effects model and inverse variance method were used to calculate 95% confidence intervals for mean differences. STATA/MP. V17 software was used to conduct the meta-analysis.

Result

Study selection

All references were entered into EndNote X8 software after the initial search for articles using keywords revealed 198 articles. Six articles were duplicates, three articles were due to records marked as ineligible by automation tools, and six articles were removed for other reasons. After reviewing 183 abstracts, 142 articles that did not meet inclusion criteria were removed. The full texts of 41 articles were reviewed by two blinded observers. Ten articles were selected (**Figure 1**) after excluding 31 incomplete articles without data inconsistency with the objectives of the study.

Study characteristics

In the present study, 536 human teeth were examined in vitro; two studies did not report the sample size. Other extracted data are reported in **table I**.

Bias assessment

Four studies received a score of 3, which indicates a low risk of bias; Three studies received a score of 4, which indicated a moderate risk of bias; and three studies received a score of 8, which indicated a high risk of bias. Two studies were low quality in the sample size section, and two were low quality in the Assessment methods section. In three methodological studies, the studies were very poorly written (**Tables II** and **III**).

Antibacterial activity

AgNPs+ CH

Mean differences of antibacterial effect on E. faecalis between AgNPs+ CH and CH were -0.39 (MD, -8.39 95% CI -8.56, -8.21; p=0.00) with high heterogeneity (I^2=99.93%; p =0.00). The results significantly reduced the E. faecalis with AgNPs+ CH than the control group (**Figure 2**).

CuNPs+ CH

Mean differences of antibacterial effect on E. faecalis between CuNPs+ CH and CH were -1.49 (MD, -1.49 95% CI -2.36, -0.62; p=0.00) with high heterogeneity (I^2=98.59%; p =0.00). The results significantly reduced the E. faecalis with CuNPs+ CH than the control group (**Figure 3**).

ZnNPs+ CH

Mean differences of antibacterial effect on E. faecalis between ZnNPs+ CH and CH were -2.54 (MD, -2.54 95% CI -3.39, -1.68; p=0.00) with high heterogeneity (I^2=96.52%; p =0.00). The results significantly reduced the E. faecalis with ZnNPs+ CH than the control group (**Figure 4**).

CHX + CH

Mean differences of antibacterial effect on E. faecalis between CHX + CH and CH were 0.75 (MD, 0.75 95% CI 0.67, 0.83; p=0.00) with high heterogeneity (I^2=99.50%; p =0.00). The results significantly reduced the E. faecalis with CHX + CH than the control group (**Figure 5**).

CHT+ CH

Mean differences of antibacterial effect on E. faecalis between CHT+ CH and CH were 2 (MD, 2 95% CI -5.46, 9.46; p=0.60). The results showed no statistically significant differences in reducing the E. faecalis between groups (**Figure 6**). The mixture of CH and AgNPs was the most effective medicament against E. faecalis bacteria, and CHX displayed the best efficacy at the lowest concentrations against E. faecalis.

Figure 1: PRISMA 2020 Checklist.

Identification of studies via databases and registers

Identification

Records identified from*:
Databases
(n=198)

Records removed before the screening:
Duplicate records removed (n = 6)
Records marked as ineligible by automation tools (n = 3)
Records removed for other reasons (n = 6)

Screening

Records screened (n=183)

Records excluded** (n = 142)

Reports sought for retrieval (n =0)

Reports not retrieved (n = 0)

Reports assessed for eligibility (n =41)

Reports excluded: (n = 31)

Included

Reports of included studies (n =10)

Table I: Summary of study data.

N	Study. Years	Study design	Sample size	Teeth	Intervention group (n)	Number of control group	Bacterial strain
1	Rôças et al., 2023[31]	In-vitro	90	necrotic root canals of teeth	2% CHX + CH	CH	bacterial
2	Afkhami et al., 2022[32]	In-vitro	60	single-rooted, sound human teeth with mature apices	2% CHX (10) CH paste (10) CH/CHX: Mixture of CH and 2% CHX gel in 1:1 ratio (10) Group TAP: Metronidazole, ciprofloxacin and minocycline; 0.5 mg of each antibiotic was mixed with 1 mL of saline (10) Group DAP: Metronidazole and ciprofloxacin; 0.5 mg of each antibiotic was mixed with 1 mL of saline (10) CH and AgNPs suspension were mixed in a 1:1 ratio (10) 1: No drug therapy (5) 2: Saline (5)		*E. faecalis* (ATCC 29212)
3	Raza et al., 2022[33]	In-vitro	60	human premolar teeth have a single root	AgNPs + CH (30)	Unmodified CH (30)	*E. faecalis*
4	Tülü et al., 2021[34]	In-vitro	29	Human single-rooted mandibular premola's	AgNPs + CH CHX + CH	saline solution, CH	*Enterococcus faecalis, Streptococcus mutans, Lactobacillus acidophilus*
5	Sy et al., 2021[35]	In-vitro	NR	NR	AgNPs+ CH, CuNPs+ CH, ZnNPs + CH, CHX + CH, CHT	CH alone	*E. faecalis* and *C. albicans*
6	Hegazi et al., 2019[36]	In-vitro	45	human single-rooted teeth	CH+ AgNPs	CH	*E. faecalis*
7	Samiei et al., 2018[22]	In-vitro	132	single root teeth	CH+ ZnNPs, CHX + CH, CH+ AgNPs	normal saline	*E. faecalis*
8	Yousefshahi et al., 2018[20]	In-vitro	NR	NR	CH+ AgNPs, CH +CuNPs, CH +ZnNPs	CH alone	*E. faecalis*
9	Afkhami et al., 2015[17]	In-vitro	54	single-root teeth	CH+ AgNPs, CHX + CH	CH alone (6)	*E. faecalis*
10	Javidi et al., 2014[37]	In-vitro	66	human single-rooted teeth	CH+ AgNPs	CH alone	E. faecalis

AgNPs: silver nanoparticle; CHX: Chlorhexidine; CH: Calcium hydroxide paste; CuNPs: Copper Nanoparticle; ZnNPs: zinc nanoparticles; CHT: chitosan.

Table II: Quality of the included studies.

Study. Years	Item grade													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Rôças et al., 2023[31]	√	√	×	×	×	×	×	×	×	√	×	×	×	×
Afkhami et al., 2022[32]	√	√	√	√	√	√	√	×	×	√	√	√	×	×
Raza et al., 2022[33]	√	√	√	√	×	√	×	×	×	√	√	√	×	×
Tülü et al., 2021[34]	√	√	√	√	√	√	√	×	×	√	√	√	×	×
Sy et al., 2021[35]	×	×	×	×	×	×	×	×	×	√	√	√	×	×
Hegazi et al., 2019[36]	√	√	×	×	×	×	×	×	×	√	×	√	×	×
Samiei et al., 2018[22]	√	√	√	√	√	√	√	×	×	√	√	√	×	×
Yousefshahi et al., 2018[20]	×	×	×	×	×	√	×	×	×	√	√	√	×	×
Afkhami et al., 2015[17]	√	√	√	√	√	√	√	×	×	√	√	√	×	×
Javidi et al., 2014[37]	√	√	×	√	×	×	×	×	×	√	√	√	×	×

Yes: √; No: ×

Table III: Risk assessment.

Study. Years	Allocation concealment	Sample size	Blinding	Assessment methods	Selective outcome reporting	Score	Risk of bias
Rôças et al., 2023[31]	1	0	2	0	0	3	Low
Afkhami et al., 2022[32]	1	0	2	0	0	3	Low
Raza et al., 2022[33]	1	1	2	0	0	4	Moderate
Tülü et al., 2021[34]	1	0	2	0	0	3	Low
Sy et al., 2021[35]	2	2	2	2	0	8	High
Hegazi et al., 2019[36]	1	1	2	2	1	8	High
Samiei et al., 2018[22]	1	1	2	0	0	4	Moderate
Yousefshahi et al., 2018[20]	2	2	2	1	1	8	High
Afkhami et al., 2015[17]	1	1	2	0	0	4	Moderate
Javidi et al., 2014[37]	1	0	2	0	0	3	Low

Figure 2: The forest plot showed a reduction of bacterial load after AgNPs+ CH and CH.

Study	AgNPs + CH			Control			Mean diff. with 95% CI	Weight (%)
	N	Mean	SD	N	Mean	SD		
Afkhami et al., 2022	10	2.8	9.8	10	17	2.4	-14.20 [-20.45, -7.95]	0.08
Raza et al., 2022	30	9.63	3	30	20	2	-10.37 [-11.66, -9.08]	1.93
Tülü et al., 2021	5	7.7	1	5	8.9	.82	-1.20 [-2.33, -0.07]	2.50
Sy et al., 2021	10	51	8	10	61	9	-10.00 [-17.46, -2.54]	0.06
Hegazi et al., 2019	15	3	.4	15	5	.2	-2.00 [-2.23, -1.77]	62.79
Samiei et al., 2018	33	67.73	20	33	84	10.7	-16.27 [-24.01, -8.53]	0.05
Yousefshahi et al., 2018	10	10	1	10	12	1	-2.00 [-2.88, -1.12]	4.19
Afkhami et al., 2015	16	71	7	6	100	10	-29.00 [-36.37, -21.63]	0.06
Javidi et al., 2014	22	5.8	.1	22	29.7	.8	-23.90 [-24.24, -23.56]	28.34
Overall							-8.39 [-8.56, -8.21]	

Heterogeneity: I^2 = 99.93%, H^2 = 1451.21

Test of $\theta_i = \theta_j$: Q(8) = 11609.70, p = 0.00

Test of θ = 0: z = -91.65, p = 0.00

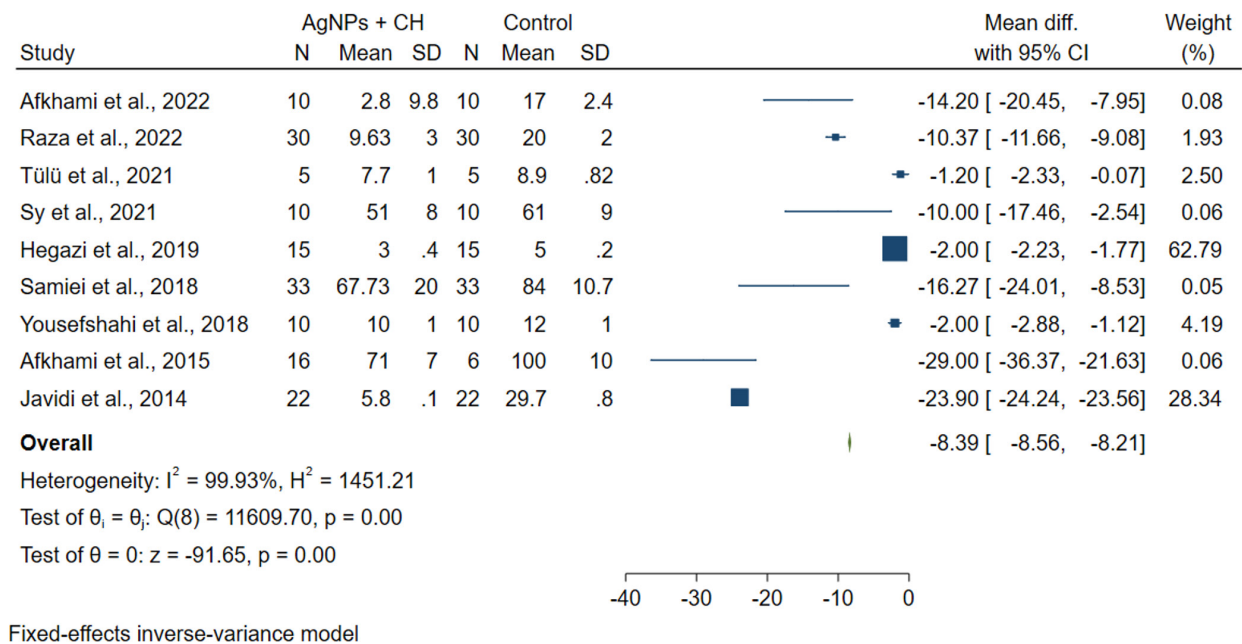-40 -30 -20 -10 0

Fixed-effects inverse-variance model

Figure 3: The forest plot showed the Mean colony count in the groups after CuNPs+ CH and CH.

Study	CuNPs+ CH			Control			Mean diff. with 95% CI	Weight (%)
	N	Mean	SD	N	Mean	SD		
Sy et al., 2021	10	31	6	10	61	9	-30.00 [-36.70, -23.30]	1.68
Yousefshahi et al., 2018	10	11	1	10	12	1	-1.00 [-1.88, -0.12]	98.32
Overall							-1.49 [-2.36, -0.62]	

Heterogeneity: I^2 = 98.59%, H^2 = 70.67

Test of $\theta_i = \theta_j$: Q(1) = 70.67, p = 0.00

Test of θ = 0: z = -3.35, p = 0.00

-40 -30 -20 -10 0
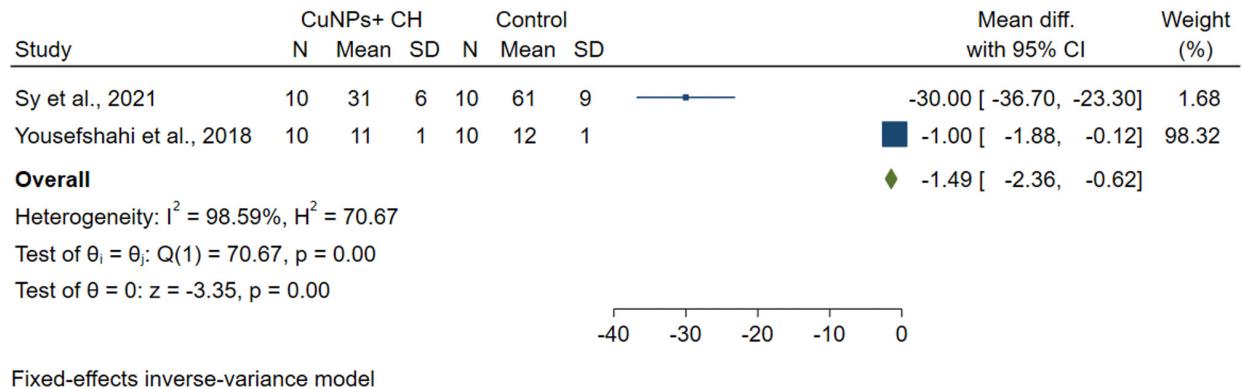
Fixed-effects inverse-variance model

Figure 4: The forest plot showed the Mean colony count in the groups after ZnNPs+ CH + CH and CH.

Study	CH+ ZnNPs			Control			Mean diff. with 95% CI	Weight (%)
	N	Mean	SD	N	Mean	SD		
Sy et al., 2021	10	32	7	10	61	9	-29.00 [-36.07, -21.93]	1.46
Samiei et al., 2018	33	83	8	33	89	10.7	-6.00 [-10.56, -1.44]	3.51
Yousefshahi et al., 2018	10	10	1	10	12	1	-2.00 [-2.88, -1.12]	95.02
Overall							-2.54 [-3.39, -1.68]	

Heterogeneity: I^2 = 96.52%, H^2 = 28.76

Test of $\theta_i = \theta_j$: Q(2) = 57.53, p = 0.00

Test of θ = 0: z = -5.82, p = 0.00
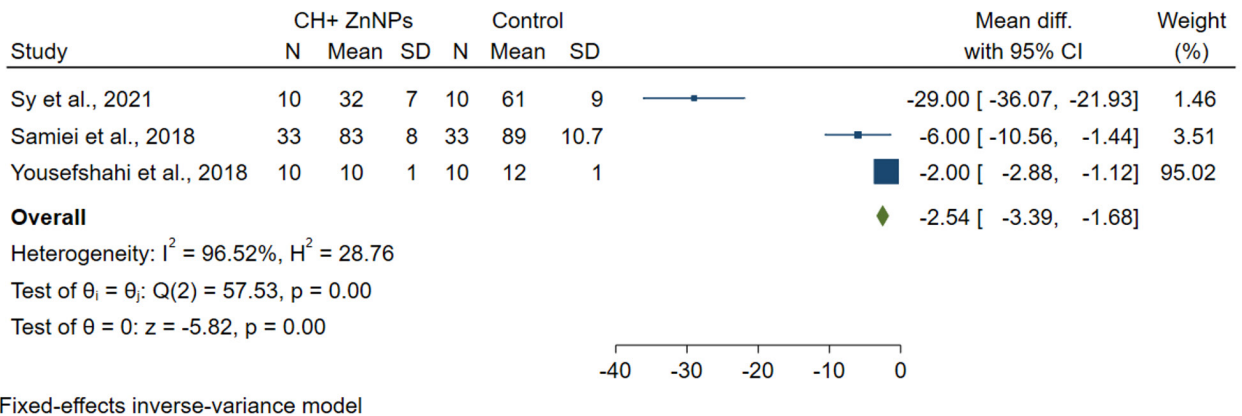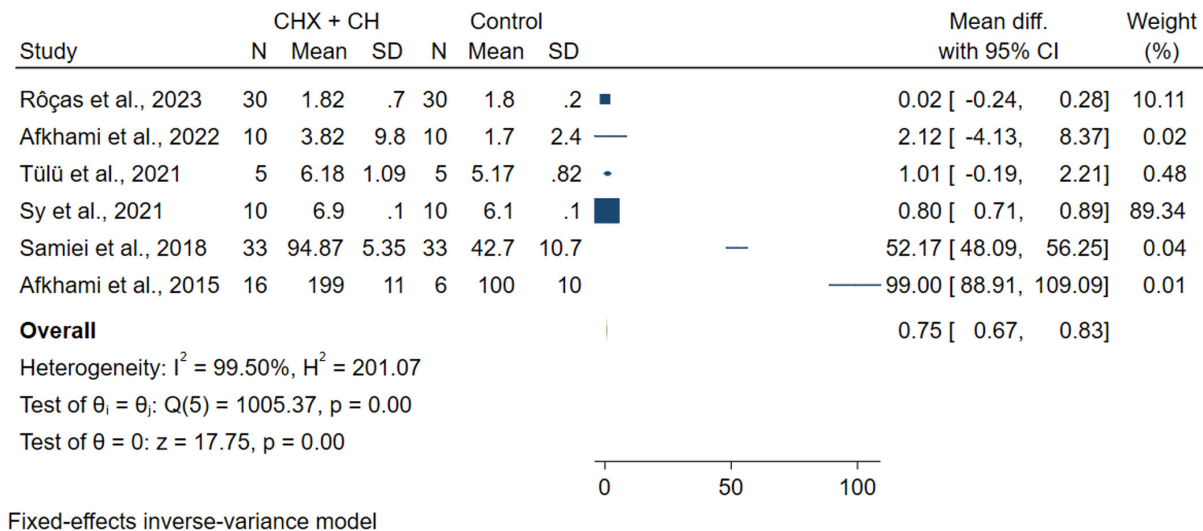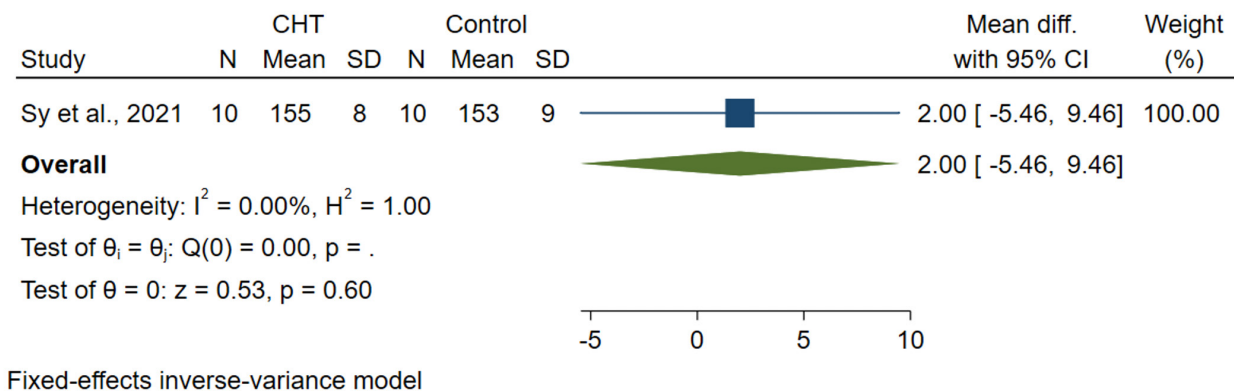
-40 -30 -20 -10 0

Fixed-effects inverse-variance model

Figure 5: The forest plot showed the Mean colony count in the groups after ZnNPs+ CH + CH and CH.

Figure 6: Forest plots showed a reduction of bacterial load after CHT+ CH and CH.

Discussion

The present study investigated the antimicrobial activity of CH mixed with metallic nanoparticles, CHT and CHX compared to CH alone. In the present study, an attempt was made to investigate studies that had performed antibacterial activity in the eradication of E.faecalis in a laboratory manner Because studies have shown that E. faecalis, which is associated with root canal infections, is resistant to CH[4,38]. One of the goals of the present study was to investigate CH paste mixed with different metallic salts (Ag2SO4, CuSO4, ZnCl2). However, due to the existence of very few studies in this field and contradictory results, it was not possible to conduct a meta-analysis. A study showed that zinc oxide has no antimicrobial effect on E. faecalis[39]. Contradictory findings have also been reported with similar metals for other bacteria found in the mouth[40,41]. Based on the findings of the present study, the combination of silver nanoparticles with CH showed an antibacterial effect compared to CH alone. The findings of most studies are in line with the study of the esophagus, while some studies could not show this advantage[17]. A high heterogeneity was found between studies, which can be attributed to differences in methodology or characteristics of nanoparticles and concentrations used. Studies have shown that the size of AgNPs less than 10 nm can increase antimicrobial activity; however, higher toxicity has also been reported[42-45]. According to the available evidence, the antibacterial activity of AgNP may also depend on the shape[46]. According to the present meta-analysis, CH + CHX is more effective at reducing the number of E. faecalis bacteria than CH paste alone. A systematic review and meta-analysis of nine studies found many findings that matched those of the present study[47], A significant difference was not observed between CH + CHX and CH alone in their effects on E. faecalis. The difference in findings can be attributed to the selection of newer studies.

Newer studies published in the last ten years can provide better results; however, high heterogeneity was observed, which could be related to the cognitive methodology of the studies. Based on the present meta-analysis, it was observed that the combination of CuNPs + CH ZnNPs + CH is effective in reducing the number of E. faecalis bacteria compared to CH paste alone. However, according to the present meta-analysis, the combination of CHT + CH was not different compared to CH paste alone. Therefore, the present study does not support using CHT metal nanoparticles as an antimicrobial adjuvant for CH-based drugs. The current study had limitations: the sample size of the studies was small, which requires more studies with a larger sample size. Also, high heterogeneity between studies was observed, which can be related to the cognitive methodology of the studies. Consequently, interpreting the results of this study should be done with caution. Also, all studies were in vitro, making it possible to approximate only a number of parameters involved in vivo. Only in most studies, the antimicrobial activity against E. faecalis was investigated. A multimicrobial biofilm consists of root pathogens, each of which is sensitive to different antimicrobial agents in vivo. These results need to be confirmed and correlated with clinical outcomes in future studies.

Conclusion

Based on the findings of the present meta-analysis, it was observed that a mixture of CH and CHX can lead to the eradication of E. faecalis as an intracanal medicine. Also, silver, copper, and zinc nanoparticles showed antimicrobial activity. The use of CHT as an antimicrobial adjuvant for CH-based drugs was not supported. Further studies are needed to confirm the results of the present study, and further studies are needed to optimize the antimicrobial activity of CHT/CDP metal nanoparticles before using them as an adjunct to endodontic therapy.

Conflict of Interest

The authors declare that there is no conflict of interest.

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ORIGINAL

Tumor infiltrating lymphocytes density as the chemoresistance and relapse factor for advanced breast cancer patients

Densidad de linfocitos infiltrantes tumorales como factor de quimiorresistencia y recaída en pacientes con cáncer de mama avanzado

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Abstract

Introduction: Recent studies on more reliable predictors, such as TIL density and spatial localization, are associated with clinical and pathological features.

Aim: - to improve comprehensive treatment of advanced breast cancer patients by focusing on tumor infiltrating lymphocytes density.

Methods: We examined TILs in 150 advanced breast cancer (ABC) and non-ABC patients, focusing on their spatial distribution in the tumor.

Results: TIL decline following neo-adjuvant chemotherapy (NC) is associated with the ABC (OR: 0.25, 95% CI: 0.013-0.56, p = 0.018). The difference in peripheral immunological markers between ABC and non-ABC was not statistically significant. 75 individuals had remaining status after NC. In this group, having a low number of TIL before NC (HR: 0.23, 95% CI: 0.05-1.02, p = 0.05) was associated with a longer OS, whereas having a high number of TIL after NC (HR: 0.29, 95% CI: 0.10-0.97, p = 0.047) and a low answer of cancer cell to therapy (HR: 0.20, 95% CI: 0.11-0.98, p = 0.044) (RFS), that leaded to chemoresistance and relapses.

Conclusions: ABC patients with a higher number of TIL following NC associated with a poor outcome. The quantity of TIL was considerably decreased following NC in both groups.

Key words: Breast cancer, tumor-infiltrating lymphocytes, chemoresistance, recurrence.

Resumen

Introducción: Estudios recientes sobre predictores más fiables, como la densidad de TIL y la localización espacial, se asocian con características clínicas y patológicas.

Objetivo: mejorar el tratamiento integral de las pacientes con cáncer de mama avanzado centrándose en la densidad de linfocitos infiltrantes tumorales.

Metodología: Examinamos los TIL en 150 pacientes con cáncer de mama avanzado (ABC) y no ABC, centrándonos en su distribución espacial en el tumor.

Resultados: La disminución de TIL tras la quimioterapia neoadyuvante (NC) está asociada al ABC (OR: 0,25; IC 95%: 0,013-0,56; p = 0,018). La diferencia en los marcadores inmunológicos periféricos entre ABC y no ABC no fue estadísticamente significativa. 75 individuos tenían estado remanente después de NC. En este grupo, tener un número bajo de TIL antes de la NC (HR: 0,23; IC 95%: 0,05-1,02; p = 0,05) se asoció con una SG más larga, mientras que tener un número alto de TIL después de la NC (HR: 0,29; IC 95%: 0,10-0,97; p = 0,047) y una baja respuesta de las células cancerosas a la terapia (HR: 0,20; IC 95%: 0,11-0,98; p = 0,044) (RFS), que condujo a quimiorresistencia y recaídas.

Conclusiones: Los pacientes con ABC con un mayor número de TIL tras la NC se asociaron a un mal pronóstico. La cantidad de TIL disminuyó considerablemente tras la NC en ambos grupos.

Palabras clave: Cáncer de mama, linfocitos infiltrantes de tumores, quimiorresistencia, recurrencia.

Introduction

Although the clinical outcomes of most breast cancer subtype have improved, the prognosis for advanced breast cancer (ABC) remains poor, with a 5-year overall survival rate of 39%[1] and recurrence-free survival 21% and chemoresistance rate about 34 %[2].

Current treatment guidelines for stage III ABC recommend preoperative chemotherapy followed by surgical resection and adjuvant radiation therapy[3]. Currently, the National Cancer Network (NCCN) guidelines recommend that patients who respond appropriately to neo-adjuvant chemotherapy (NC) undergo total mastectomy with level I/II axillary lymph node dissection[4]. ABC patients have an approximate 43% increased risk of death compared to those with non-ABC[5]. There is increasing evidence that the tumor microenvironment (TME) is of paramount importance in ABC pathological biology. However, despite this well-documented association, the composition of ABC TME is very poorly described, especially when compared to other types of breast cancer. Histologically, ABC tumors show extensive involvement of lymph and blood vessels, cancer-related fibroblasts and their associated extracellular matrix, and invasive immune cells[6].

This suggests that ABC clinical and research studies need to consider TIL in addition to stage. This results in better results for patients with high TIL, than for patients with low TIL. Is an immune checkpoint molecule that is more abundant in both ABC tumor cells and TIL than non-ABC and is a potential predictive biomarker for immunotherapy[7].

Previous studies have shown that high numbers of tumor-infiltrating lymphocytes (TILs) do not consistently guarantee good results in all ABC patients. In Luminal HER2-negative patients, high TIL numbers are considered a prognostic factor that is detrimental to survival. TIL ought to be considered from an unused viewpoint in arrange to comprehensively get it the tumor microenvironment[8]. Recent studies on more reliable predictors, such as TIL density and spatial localization, are associated with clinical and pathological features. However, the association between clinical pathological features and para-neoplastic infiltrating lymphocytes (PIL) in the lobular region of para-neoplasm remains unclear[9].

Like other cancers, the immune infiltrate of the ABC TME appears to be heterogeneous. However, immune-related gene expression in ABC appears to be distinct from non-ABC tumors, independent of molecular subtype. To date, most studies have focused on the resident lymphocytes of ABC tumors. For instance, it has been reported that up to 41% of ABC tumors harbor dense aggregates of CD8+ cytotoxic T-lymphocytes. This was paralleled by a recent, larger study of 150 treatment naïve ABC patients, which reported that, on average, tumor infiltrating lymphocytes (TILs) comprise roughly 18% of the tumor stroma. Tumors with stroma composed of more than 10% leukocytes had a significant life-prolonging effect. This study also looked at molecular subtypes and investigated the status of hormone receptors and HER2. There was no significant difference in TIL infiltration between ABC and non-ABC tumors in the luminal and triple negative subgroup, but HER2-positive ABC tumors had TIL compared to HER2-positive non-ABC tumors[10].

Here we summarize the clinical evidence that explains the potential role of TIL in the pathological biology of ABC and past and present attempts to improve the treatment of ABC. Discuss the current status of ABC TME, where increased presence of TIL is associated with better response to chemotherapy. This decisively suggests TIL density as an important prognostic factor.

Materials and methods

The SNE "National Cancer Institute of Ukraine's" institutional Ethics Committee authorized this study (Minutes No. 221 of December 23, 2020).

We presented findings from a study of ABC patients who were diagnosed and treated at the SNE "National Cancer Institute of Ukraine" between December 31, 2020, and December 31, 2022. In this study, we looked at all stage patients (n = 150) - the first group (75 patients) had ABC; the second group (75 patients) with non-ABC. Examine the progression of TIL between ABC and non-ABC. Anthracycline/taxane-based neo-adjuvant chemotherapy (NC) followed by a lumpectomy or mastectomy was also required for participation. Trastuzumab was given to HER2 positive individuals (n = 26 non-ABC/31 ABC).

Results based on clinical data, biomarker data, and surgical and resected tissue discoveries.

The estimated 2-year overall survival (OS) and recurrence-free survival (RFS) values are reported, with statistical confidence intervals (CI). TILs were evaluated for prognostic significance in patients with ABC who were treated with chemotherapy in the neo-adjuvant context using the technique for reading TILs (as per International Immune-Oncology Biomarker Working Group criteria)[11].

Three distinct researchers scored the TIL following NC on hematoxylin and eosin stained 5-mm slices of formalin-fixed paraffin-embedded tumor tissue. The International TILs Working Group's precise guidelines for rating TIL in remaining tumor tissue following neo-adjuvant treatment were followed[12]. With hematoxylyn and eosin slides containing the most invasive tumors surviving, a semi-quantitative evaluation of the fraction of stromal compartments impacted by TIL in all locations harboring invasive tumor cells was done. TIL was also assessed in the tumor bed for all ABC patients with pCR.

TIL had an interclass correlation coefficient (ICC) of 0.827 (95% CI: 0.776-0.882, p < 0.001), indicating high agreement. The mean was computed and utilized as a continuous and categorical variable: 10% (category 1), 10%-40% (category 2), and 40% (category 3). After speaking with additional pathologists, a consensus score was produced if the results differed. Cell counts were reported: the proportion of remaining tumor beds occupied by invasive cancer cells following microscopic examination of slides containing the greatest number of remaining tumors and also analyzed by TIL. Estrogen (ER) and progesterone receptor (PR) expression were measured using approved immune-histo-chemical techniques and were considered positive if the Alfred score was 3/8 or higher. When a fluorescence in situ hybridization (FISH) test revealed amplification, tumor samples were designated HER2-positive.

Statistical Analysis
A Mann-Whitney U test for continuous parameters was used to compare the two ABC and non-ABC groups. A Paired Wilcoxon signed-rank test was used to compare the evolution of the parameters before and after neo-adjuvant chemotherapy. A multivariate logistic regression model was built using significant parameters from univariate analysis. The median value was utilized for distribution, and two survival endpoints were measured: The time between pathological diagnosis and cancer recurrence is defined as recurrence-free survival (RFS), while the interval between pathological diagnosis and death is defined as overall survival (OS). Patients who had not relapsed or died at the time of analysis were censored at the date of their final follow-up visit, with the survival data last updated on December 31st 2022.

The log-rank test was used to compare survival curves computed by Kaplan-Meier. A multivariate analysis proportional hazard model was used to assess the impact of all important clinical and pathological variables on survival. When p-values were less than 0.05, they were considered statistically significant.

Overall survival curves of advanced breast cancer patients treated with neo-adjuvant chemotherapy, according on pathological prognostic stage and TILs.

Results

Tumor samples were considered HER2-positive (+) when a fluorescence in situ hybridization (FISH) test documented amplification. Systemic therapy altered over the research period, however the majority of HER2+ patients (n = 26 non-ABC/31 ABC) received target therapy. The absence of carcinoma in the resected breast material and all collected regional lymph nodes following completion of neo-adjuvant chemotherapy was classified as partial or complete response (PCR).

Table I describes the tumor features. The majority of the ABC patients had a hormone receptor (HR) positive malignancy (n = 39, 52.3%), and 50 exhibited PCR following neo-adjuvant treatment (75.0%). Aside from having more poorly differentiated tumors (p = 0.001) and a higher stage (p < 0.001), which are inherent to the classification of ABC, no significant clinical and pathological changes were detected between the ABC and non-ABC cohorts.

Evolution of TIL after neo-adjuvant chemotherapy
Following neo-adjuvant chemotherapy, the amount of TIL was reduced in both the ABC (median TIL: 11%, p = 0.002) and non-ABC (median TIL: 12.5%, p = 0.007) groups, however the decline was considerably greater in the ABC cohort (p = 0.039). **Figure 1**.

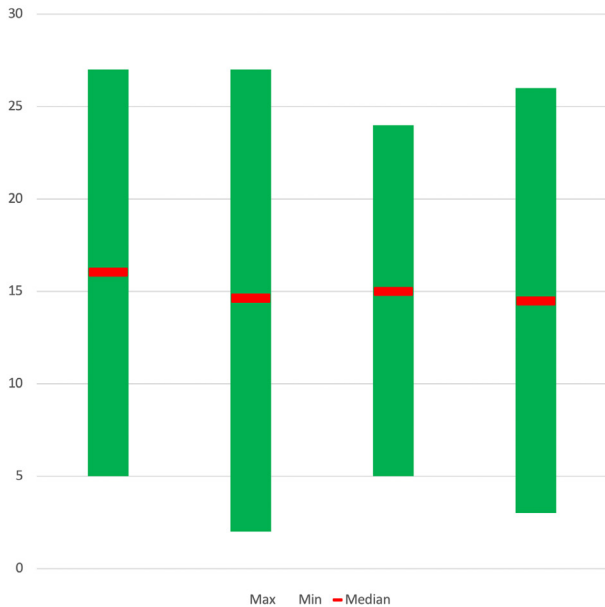**Table I:** Clinical and Pathological indicators non-ABC and ABC patients.

Indicators	non-ABC	ABC	p
Hormonal receptor status			**0.48**
Negative	34	31	
Positive	41	46	
HER2 status			0.89
Negative	49	44	
Positive	26	31	
Neo-adjuvant chemotherapy response			0.78
RS	26	25	
PCR	49	50	
Before neo-adjuvant chemotherapy TIL			0.24
<12.5%	32	27	
≥12.5%	43	48	
After neo-adjuvant chemotherapy TIL in RS (%)			0.52
<5%	42	54	
≥5%	33	21	
Difference in TIL before and after neo-adjuvant chemotherapy			0.022
Increase (>5%)	6	7	
No change	60	50	
Decrease (<5%)	9	18	

non-ABC-non-advanced breast cancer, ABC - advanced breast cancer, RS – remaining status, pCR – complete (partial) pathological response. Bold values denote statistical significance at the p < 0.05 level.
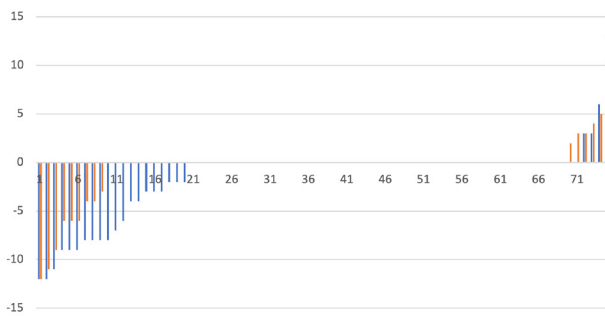
ABC patients showed a larger decline in TILs following NC (OR: 0.24, 95% CI: 0.21-0.66, p = 0.016) in a multivariate model containing all patients. A higher decline in TIL was related with a high number of TIL before to NC (OR: 0.029, 95% CI: 0.0018-0.175, p = 0.002) and a low number of TIL after NC (OR: 23.12, 95% CI: 3.57-489.76, p = 0.008) in a model including just ABC patients – **Table II**.

In the overall cohort (including both ABC and non-ABC patients) the number of TIL after NC seemed to largely depend on the number of TIL (OR: 2.023, 95% CI: 1.18–3.125, p = 0.04) and the remaining cancer cell count (OR: 2.05, 95% CI: 1.60-6.98, p = 0.004) -**Table II**.

In the ABC cohort, the number of TIL after neo-adjuvant chemotherapy was only significantly associated with higher remaining cancer cell count (OR: 12.64, 95% CI: 4.88-15.65, p < 0.001) - **Picture 1a** and **1b** and worse clinical outcome (RECIST 1.1 – stabilization (without regression) after NC – **Picture 2**.

TIL decline following NC is associated with the ABC (OR: 0.25, 95% CI: 0.013-0.56, p = 0.018).

The difference in peripheral immunological markers between ABC and non-ABC was not statistically significant. 75 individuals had remaining status after NC. In this group, having a low number of TIL before NC (HR: 0.23, 95% CI: 0.05-1.02, p = 0.05) was associated with a longer OS, whereas having a high number of TIL after NC (HR: 0.29, 95% CI: 0.10-0.97, p = 0.047) and a low answer of cancer cell to therapy (HR: 0.20, 95% CI: 0.11-0.98, p = 0.044) (RFS) - **Figure 2a**; **b**.

Figure 1: Evolution of TIL after neo-adjuvant chemotherapy.

Figure 1 (A): Boxplot graph of the evolution of TIL after neo-adjuvant chemotherapy: In both ABC (median TIL: 11%, p < 0.001) and non-ABC (median TIL: 12,5%, p = 0.06) the number of TIL are lower after neo-adjuvant chemotherapy.

Figure 1 (B): ABC Non-ABC

Picture 1a: Cell counts were reported: the proportion of remaining tumor beds occupied by invasive cancer cells following microscopic examination of slides containing the greatest number of remaining tumors and also analyzed by TILs before neo-adjuvant chemotherapy.
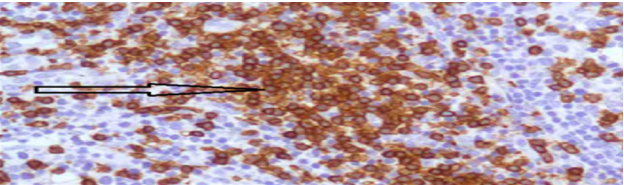
Picture 1b: Cell counts were reported: the proportion of remaining tumor beds occupied by invasive cancer cells following microscopic examination of slides containing the greatest number of remaining tumors and also analyzed by TILs after neo-adjuvant treatment and a low answer of cancer cell to therapy..
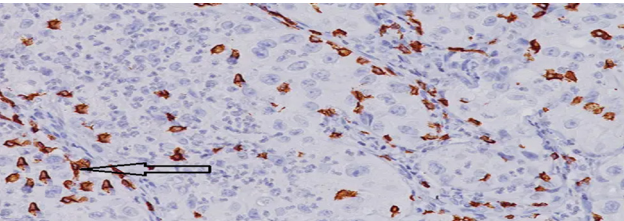

Table II: Uni- and multivariate analysis for decrease of TIL after neo-adjuvant chemotherapy HR - hormone receptor status, Bold values denote statistical significance at the p < 0.05 level.

Indicators	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value
Non-ABC opposite ABC	0.22 (0.162–0.583)	**<0.001**	0.235 (0.0217–0.759)	**0.02**
TIL before neo-adjuvant chemotherapy: <12.5% opposite ≥12.5%	0.079 (0.047–0.232)	**<0.003**	0.028 (0.014–0.087)	**<0.001**
TIL after neo-adjuvant chemotherapy: <5% opposite ≥5%	2.023 (1.18–3.125)	**0.04**	12.64 (4.88–15.65)	**<0.001**
Remaining cancer cell count: <20% opposite >20%	2.021 (1.60–4.31)	0.065		

Boxplot depicting the evolution of median TIL after neo-adjuvant chemotherapy in individual ABC patients and nom-ABC patients: Out of 75 patients, 7 had an increase, 50 had no change and 18 patients had a decrease; non-ABC, out of 75, 6 had an increase, 60 had no change and 9 patients had a decrease.

Picture 2: Spiral computer scan left breast gland: a – skin edema and umbilication, tumor 3 cm, before neo-adjuvant chemotherapy; b – remaining skin edema and umbilication, tumor 2 cm, after neo-adjuvant chemotherapy.
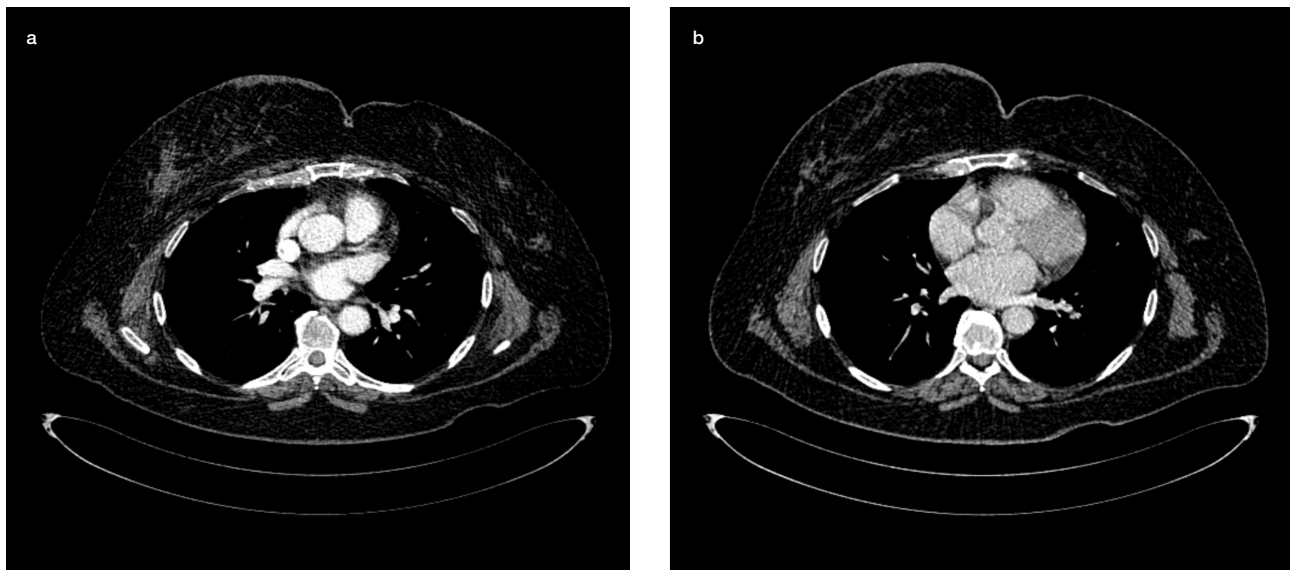
Figure 2: Kaplan–Meier curves for RFS.
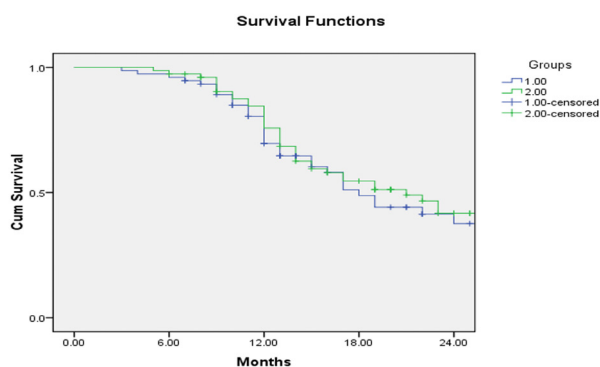
A. Patients with ≥4% sTIL after neo-adjuvant chemotherapy have a significant shorter RFS: Median survival of 18.0 months (95% CI: 15.1–20.9) opposite 20.9 months (95% CI: 15.7–26.3), p = 0.002.
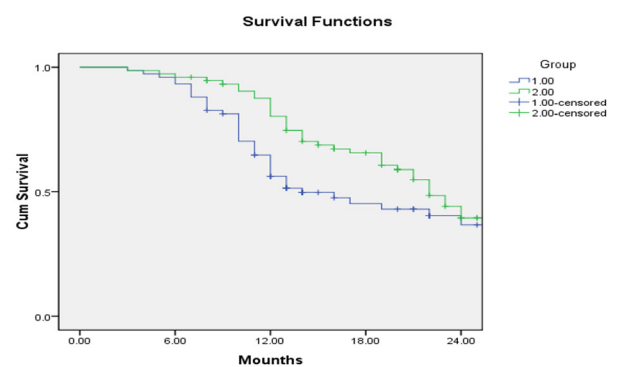
B.A higher remaining cell count (≥17.5%) in the tumor bed is associated with a shorter RFS: Median survival of 14,3 months (95% CI: 7.7–20.3) opposite21.8 months (95% CI: 19.4–24.6), p < 0.001.

In the ABC population, HR and HER2 status had no effect on OS or RFS.

A low TIL score before NC (p = 0.028) remained a significant predictor of longer OS in the HR+ group, while a larger remaining cancer cell count (p = 0.018) and a rise in TIL after NC (p = 0.033) were associated with shorter RFS. In the HER-positive group, an increase in TIL after NC was related with a lower RFS (p = 0.048), but only a lower pre-neo-adjuvant chemotherapy TIL was associated with a longer OS (p = 0.028) in the TN patients - **Table III**.

Table III: Uni- and multivariate analysis for RFS in the group of ABC patients without pCR after neo-adjuvant chemotherapy. pCR – complete (partial) pathological response.

Indicators	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p	HR (95% CI)	p
HR negative opposite HR positive	0.35 (0.24–1.14)	0.06		
HER2 negative opposite HER2positive	1.15 (0.53–1.85)	0.07		
TIL before neo-adjuvant chemotherapy: <10% opposite ≥10%	1.32 (0.74–1.91)	0.09		
TIL after neo-adjuvant chemotherapy: <4% opposite ≥4%	0.33 (0.15–0.98)	**0.003**	0.33 (0.15–0.98)	**0.003**
Remaining cell count: <17.5% opposite ≥17.5%	0.12 (0.05–0.29)	**<0.002**	0.24 (0.12–0.56)	**<0.002**
Change: increase opposite decrease	2.11 (0.93–3.23)	0.03	2.15 (0.85–4.23)	0.11

Discussion

Similarly, to the Ochi T study[13], we discovered that following neo-adjuvant treatment, TIL decreased in more patients. This was true in both the ABC (median TIL: 11%, p< 0.001) and non-ABC groups, although the median decline in the ABC cohort was larger (OR: 0.24, 95% CI: 0.21-0.66, p = 0.016). Following NC, a high number of TIL was associated with a high number of residual cancer cells in our ABC cohort, indicating that more surviving tumor cells may attract more infiltrating immune cells.

According to Vagia E[14], a larger number of TIL following neo-adjuvant treatment correlates with decreased tumor burden as measured by tumor size and nodal status. This might explain why, in several studies, a larger number of TIL was linked to a better prognosis, like Van Berckelaer C[15], notwithstanding our findings. Indeed, a greater number of TIL following NC was associated with a shorter OS (HR: 0.24, 95% CI: 0.04-1.12, p < 0.05) and RFS (HR: 0.33, 95% CI: 0.11-0.98, p = 0.046) in our ABC population.

While we found a link between cancer cell count and TIL count following neo-adjuvant treatment, both were independent prognostic indicators in the multivariate model. As a result, it appears that the predictive effect of TIL in our ABC cohort is more than just a reflection of tumor burden. The number of remaining tumor cells is not the only indicator of remaining tumor burden or response to neo-adjuvant chemotherapy, but chemoresistance and following relapses. According to Murthy R et al., a combination of RCB (residual cancer burden) and TIL is a more sensitive predictor of RFS than TIL alone[16].

TIL following NC had no effect on RFS in HER2+ BC, but had a borderline significant effect in TNBC, according to other researchers, so the HR state has an influence on the number of TIL - Zhang H[17], however in univariate analysis, we only found a relationship between HR status and a more TIL. Even though the patient numbers for the different genetic subtypes were limited in our study, an increase in TIL was related with a shorter RFS in both the HR+ and HER2+ ABC cohorts, but not in the TN ABC cohort. The immune response to the tumor is influenced by the composition of the immune infiltrate as well as the functional state of immune cells. According to Loi S et al [8] a large number of CD8+ cells is advantageous in terms of both chemotherapeutic response and survival.

Rufell et al.[18] demonstrated, for example, an increase in CD8+ cells and a decrease in CD20+ lymphocytes after chemotherapy. In the study of Gracia-Martinez et al.[19], patients with high TIL after neo-adjuvant chemotherapy had a worse RFS, which was partially explained by the presence of many CD68+ macrophages that have been associated with tumor progression[20]. The unfavorable predictive effect of TIL following neo-adjuvant chemotherapy, as well as the greater decline in TIL in ABC, might thus be explained by a distinct immune infiltrate composition in ABC compared to non-ABC illness. It is critical to do more study to investigate the makeup and role of the various immune cells in ABC[21].

The timing of surgery and the time since the previous chemotherapy session may alter the amount and composition of immune infiltrates, and hence the prognostic effect. In this study, we managed to explore the evolution of TIL ABC and compare this with a molecular subtype-matched cohort of non-ABC patients.

We showed that a low number of TIL after neo-adjuvant chemotherapy was associated with a longer RFS and that TIL tended to decrease in ABC compared to non-ABC.

There was neither significant difference in TIL score between ABC and non-ABC, nor the quantity of TIL was considerably decreased following NC in both groups.

Despite recent breakthroughs in other types of breast cancer, ABC continues to pose a considerable clinical challenge and is frequently resistant to standard therapy. Though immunotherapy has transformed the treatment paradigm for a variety of malignancies, such methods have yet to demonstrate significant therapeutic benefit in ABC. As previously stated, the reasons for immunotherapy's greater failure in ABC are unknown. Many of the same hurdles to treatment success that have hampered immune therapy in other breast tumors exist in ABC; nevertheless, there have been relatively few investigations investigating ABC's intrinsic resistance to such techniques. Furthermore, the immunological milieu of the ABC TME is still being explored, with several results that are very context-specific and even inconsistent.

This is an important and relatively unexplored area of breast cancer research that deserves more investigation, especially given that ABC has a far poorer prognosis than stage-matched non-ABC breast cancer[22].

Conclusions

ABC is linked with a considerably lower TIL following neo-adjuvant chemotherapy. In ABC patients with a higher number of TIL following neo-adjuvant treatment associated with a poor outcome.

There was no significant difference in TIL score between ABC and non-ABC, and the quantity of TIL was considerably decreased following neo-adjuvant chemotherapy in both groups.

Conflict of Interest
None

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Relación de los índices de adiposidad visceral (VAI) y disfuncional (DAI) con riesgo de enfermedad de hígado graso no alcohólico

Visceral adiposity index (VAI) and dysfunctional adiposity index (DAI). Relationship with non-alcoholic fatty liver disease

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Resumen

Introducción y objetivo: Estimar en población laboral española la relación de los índices de adiposidad visceral (DAI) y adiposidad disfuncional (VAI) con riesgo de desarrollar hígado graso no alcohólico (NAFLD: Non-Alcoholic Fatty Liver Disease).

Métodos: análisis descriptivo en 418.343 trabajadores durante la vigilancia de la salud en sus empresas. Se calcularon VAI y DAI con sus ecuaciones y el riesgo de NAFLD con las escalas Fatty liver index (FLI), Hepatic Steatosis index (HSI), Zhejiang University (ZJU), Lipid accumulation Product (LAP) mediante curvas ROC- área bajo la curva (AUC). Se utilizó el programa estadístico SPSS 27.0, considerando significación estadística p< 0,05.

Resultados: Los porcentajes de riesgo de HGNA son más elevados en hombres que en mujeres (p<0.0001). Los valores medios de VAI y DAI son más elevados en hombres (p<0.0001). En el análisis de las curvas ROC- área bajo la curva (AUC), los índices VAI y DAI para riesgo de NAFLD muestran una alta fortaleza de asociación en ambos sexos AUC>0,8 con FLI y, especialmente, con LAP. Los valores obtenidos con ZIU solo muestran moderada fortaleza de asociación con VAI en hombres y con VAI y DAI en mujeres (AUC >0,7). HSI muestra baja fortaleza de asociación en ambos sexos (AUC <0,7).

Conclusión: VAI y DAI muestran alta fortaleza de asociación con el riesgo de desarrollar NAFLD calculado con FLI y LAP, en población laboral, moderada con ZIU y baja con HSI y se consideran métodos útiles de prevención primaria de NAFLD en salud laboral.

Palabras clave: Hígado graso no alcohólico, índice de adiposidad visceral, índice de adiposidad disfuncional, salud laboral.

Abstract

Introduction and objective: To estimate the relationship between visceral adiposity index (DAI) and dysfunctional adiposity (VAI) and the risk of developing Non-Alcoholic Fatty Liver Disease (NAFLD) in the Spanish working population.

Methods: descriptive analysis in 418,343 workers during health surveillance in their companies. VAI and DAI with their equations and the risk of NAFLD with the Fatty liver index (FLI), Hepatic Steatosis index (HSI), Zhejiang University (ZJU), Lipid accumulation Product (LAP) scales were calculated using ROC curves - area under the curve (AUC). SPSS 27.0 statistical software was used, considering statistical significance p<0.05.

Results: The percentages of HGNA risk are higher in men than in women (p<0.0001). Mean VAI and DAI values are higher in men (p<0.0001). In the analysis of the ROC curves - area under the curve (AUC), the VAI and DAI indices for NAFLD risk show, in both sexes a high strength in the association AUC>0.8 with FLI and especially with LAP. Values obtained with ZIU only show moderate strength in the association with VAI in men and with VAI and DAI in women (AUC >0.7). HSI shows low strength in the association in both sexes (AUC <0.7).

Conclusion: VAI and DAI show high strength in the association with the risk of developing NAFLD calculated with FLI and LAP, moderate with ZIU and low with HSI and are considered useful methods of primary prevention of NAFLD in occupational health.

Key words: Non-alcoholic fatty liver disease, visceral adiposity index, dysfunctional adiposity index, occupational health.

Introducción y objetivo

La enfermedad del hígado graso no alcohólico (NAFLD), tiene una prevalencia mundial de alrededor del 25%. La incidencia está aumentando de forma similar al aumento de los niveles de obesidad, sujeto con diabetes tipo 2 y síndrome metabólico, y se prevé que se convierta en la principal causa de cirrosis que requiera trasplante de hígado en la próxima década. Sin embargo, la enfermedad cardiovascular es la causa más común de muerte en la población y, entre ellos solo una minoría desarrollará fibrosis y complicaciones relacionadas con el hígado. Por lo tanto, es imperativo identificar el riesgo de forma precoz o temprana para actuar en las primeras etapas y evitar la evolución hacia estadios graves[1].

Actualmente (NAFLD) es la enfermedad hepática más común en el mundo y su presentación varía desde la esteatosis simple hasta la esteatohepatitis no alcohólica (EHNA) fibrosis, cirrosis, carcinoma hepatocelular, etc. Se trata de una manifestación hepática del síndrome metabólico, que incluye obesidad abdominal central junto con otros componentes. Hasta el 80% de los pacientes con NAFLD son obesos, definidos como un índice de masa corporal (IMC) > 30 kg/m². Sin embargo, la distribución del tejido graso juega un papel más importante que el IMC. La gran cantidad de tejido adiposo visceral (VAT) en individuos con obesidad mórbida (IMC>40 kg/m²) contribuye a una alta prevalencia de NAFLD. Se considera que el exceso de ácidos grasos libres y la inflamación crónica de bajo grado por VAT son dos de los factores más importantes que contribuyen a la progresión de la lesión hepática. La mayoría de los pacientes con NAFLD son asintomáticos clínicamente, aunque algunos pueden presentar síntomas de sospecha: fatiga, dispepsia, dolor sordo en el hígado y hepato-esplenomegalia. El mejor tratamiento para su prevención es la reducción de peso, dada la estrecha relación entre la grasa visceral y la del hígado y la resistencia a la insulina[2].

El objetivo de este trabajo fue estimar la prevalencia de riesgo de desarrollar NAFLD utilizando herramientas no invasivas: Fatty liver index (FLI), Hepatic Steatosis index (HSI), Zhejiang University (ZJU), Lipid accumulation Product (LAP) y estimar la fortaleza de asociación de los índices de adiposidad visceral (VAI) y adiposidad disfuncional (DAI) con el riesgo de desarrollar NAFLD en la población laboral objeto de estudio.

Material y método

Estudio transversal realizado en 418.343 trabajadores de diferentes comunidades autónomas de España (Baleares, Andalucía, Canarias, Comunidad Valenciana, Cataluña, Madrid, Castilla La Mancha, Castilla León, País Vasco) y con diversas ocupaciones laborales (hostelería, construcción, comercio, sanidad, administración pública, transporte, educación, industria y limpieza),

durante el periodo comprendido entre enero de 2019 hasta septiembre de 2021. La población de estudio se obtuvo de la base de datos anonimizada de trabajadores depositada en el repositorio de la escuela universitaria ADEMA-UIB (Universidad de las Islas Baleares). Esta base de datos procede de los reconocimientos médicos laborales realizados en los últimos 5 años en diversos servicios de prevención de riesgos laborales de toda España[3]. El sistema de anonimización de ADEMA no permite a los investigadores conocer la identidad de los trabajadores. Son criterios de inclusión: edad entre 18 y 67 años, ser trabajador en activo y aceptación voluntaria de participación en el estudio.

Las medidas antropométricas de talla y peso, clínicas y analíticas, fueron realizadas por el personal sanitario de las diferentes unidades de salud laboral participantes en el estudio, previa homogeneización de las técnicas de medición.

Para el cálculo de NAFLD se han utilizado cuatro escalas:

- Fatty liver index[4] FLI, que utiliza para su cálculo las variables: triglicéridos (mg/dL), Índice de Masa Corporal (IMC) (kg/m²), Circunferencia Cintura (cm), Enzima GGT (U/L) y se calcula a partir de la siguiente fórmula:
FLI=(e0,953*loge (triglicéridos)+0,139*IMC+0,718*loge (GGT)+0,053* perímetro abdominal−15745)/(1+e0,953*loge (triglicéridos)+0,139*IMC+0,718*loge (GGT)+0,053* perímetro abdominal−15.745)*100.
Estableciendo: Si FLI<30 indica no riesgo de HGNA; FLI≥60 indica riesgo de HGNA; FLI entre 30-60, riesgo indeterminado.

- Hepatic Steatosis index – HSI[5], que utiliza para su cálculo las variables: Índice de Masa Corporal (IMC) (kg/m²) y la relación de las enzimas aspartato aminotransferasa (AST) y alanina aminotransferasa (ALT) en sangre y se calcula a partir de la siguiente fórmula:
Índice de esteatosis hepática (HSI) = 8 × (relación ALT/AST) + IMC (+2, si era mujer; +2, si era paciente con diabetes).

- Zhejiang University – ZJU[6]. Incluye como variables: índice de masa corporal (IMC), glucosa plasmática en ayunas (FPG), triglicéridos (TG) y la proporción de alanina aminotransferasa (ALT) sérica y aspartato aminotransferasa sérica (AST). Fórmula:
IMC (Kg/m²)+FPG(mmol/l)+TG(mmol/l)+3xALT(IU/L)/AST(IU/L) ratio (+2, si es mujer).

- Lipid accumulation Product – LAP[7]. Incluye como variables el perímetro abdominal y los triglicéridos y se calcula mediante la fórmula:
LAP para hombres= (circunferencia de cintura-65) x triglicéridos.
LAP para mujeres= (circunferencia de cintura-58) x triglicéridos.

Valores de LAP en hombres <4 y en mujeres <4,4 indican no HGNA.

Valores de LAP en hombres ≥4 y en mujeres≥4,4 indicarían HGNA.

Para el cálculo de VAI y DAI se han utilizado las siguientes fórmulas[8,9].

$VAI = (Cintura (cm)/(39.68 + (1.88*IMC)))*(triglicéridos/1.03)*(1.31/HDL)$ para hombres y $(Cintura (cm) / (36.58+(1.89*IMC)))*(triglicéridos /0.81)*(1.52/HDL)$ para mujeres.

$DAI=[Cintura/[22.79+[2.68*IMC]]]*[triglicéridos (mmol/L)/1.37]*[1.19/(HDL, mmol/L)]$, para hombres y $[Cintura/[24.02+[2.37*IMC]]]*[triglicéridos (mmol/L)/1.32]*[1.43/HDL(mmol/L)]$, para mujeres.

Análisis estadístico: Para el estudio estadístico se realizó un análisis descriptivo de las variables categóricas, calculando la frecuencia y la distribución de las respuestas en cada variable. En el caso de las variables cuantitativas, se calcularon la media y la desviación típica. Para evaluar la normalidad de la muestra se aplicó la prueba de Kolmogorov-Smirnov. Para valorar la utilidad de los diferentes métodos en la asociación del riesgo de desarrollar hígado graso no alcohólico (NAFLD) con los cuatro métodos, se realizaron curvas ROC y se determinó el área bajo la curva (AUC). El análisis estadístico se realizó con el programa SPSS 27.0, siendo el nivel de significación estadística aceptado de p<0,05.

Consideraciones éticas: Se solicitó a los pacientes el consentimiento informado para participar en la investigación descrita. La investigación cumple con la normativa vigente en investigación bioética y fue aprobado por el Comité Ético de Investigación Clínica del Área de Salud de Baleares (IB 4383/20).

Los autores declaran que este artículo no contiene información personal que permita identificar a los pacientes participantes en este estudio.

Resultados

Se realiza este estudio transversal en 418.343 trabajadores, edad media 40 años, con un porcentaje de hombres del 58,82% y 41,18% mujeres; IMC medio de 26,1; perímetro de cintura medio 81,5cm; valores de presión arterial: sistólica 123,7 y diastólica 75,6; valores

medios de lípidos: Col. Total 191,8, col HDL 53,0, col LDL 117,2 y triglicéridos 109,5; valor medio de glucemia 91,0; valores de transaminasas GOT 21,73, GPT 26,64 y GGT 29,56. Todos los valores están más altos en hombres que en mujeres. Tanto hombres como mujeres se encuadran mayoritariamente en la clase social III y en el tipo de trabajo manual y son mayoritariamente no fumadores. El 9,58% de las mujeres y el 16,85% de los hombres presentaban criterios de Sindrome metabólico ATP-III y el 9,35% de las mujeres y el 18,25% de los hombres criterios de Síndrome metabólico IDF. En todos los casos los resultados son estadísticamente significativos (p<0,001)[10].

Los valores porcentuales más altos en estimación de riesgo de NAFLD, tanto en hombres (49,50%) como en mujeres (44,73%), se obtienen con HSI y los porcentajes más bajos con FLI, en hombres (24,80%) y en mujeres (7,73%). Con los 4 métodos empleados, los valores porcentuales altos de riesgo de NAFLD son más elevados en los hombres que en las mujeres (p<0.0001) (**Tabla I**).

Los valores medios de VAI son más elevados que los de DAI y superiores en los hombres (p<0.0001). Los valores más altos de VAI y DAI en NAFLD, tanto en hombres como en mujeres se obtienen con el método LAP: VAI mujeres 4,37 (dt 2,27) VAI hombres 12,45 (dt 8,20) y con FLI: VAI en mujeres 4.99 (dt 3.05), VAI en hombres 13.79 (dt 9.33) (**Tabla II**).

En el análisis de las curvas ROC - área bajo la curva (AUC), los índices VAI y DAI para riesgo de NAFLD con los 4 métodos empleados muestran diferencias, encontrando una elevada capacidad asociativa en ambos sexos (AUC>0,8) en relación con FLI: Mujeres, AUC en VAI = 0,847 (IC95% 0,844-0,851), en DAI= 0,826 (IC95% 0,822-0,829) y hombres AUC VAI 0,885 (IC95% 0,883-0,886) DAI 0,835 (IC95% 0,834-0,837); y, especialmente, con LAP: Mujeres, AUC en VAI= 0,905 (IC95% 0,903-0,906), en DAI= 0,890 (IC95% 0,888-0,891) y hombres, AUC en VAI=0,949 (IC95% 0,948-0,950) y en DAI= 0,920 (IC95% 0,919-0,921). Son siempre más altos los valores con VAI que con DAI. Con ZIU solo se obtiene moderada capacidad asociativa con VAI en hombres [AUC en VAI= 0,704 (IC95% 0,700-0,708)], siendo baja (AUC<0,7) con DAI en hombres y con VAI y DAI en mujeres. Con el método HSI se observa baja capacidad asociativa de riesgo de NAFLD, ya que los valores de AUC no superan 0,6, ni hombres ni mujeres, tanto con VAI como con DAI (**Figuras 1, 2, 3** y **4**).

Table I: Distribución Porcentual de la estimación de NAFLD según método utilizado y según sexo.

Método	Mujeres						Hombres						p
	Bajo		Medio		Alto		Bajo		Medio		Alto		
	n	%	n	%	n	%	n	%	n	%	n	%	
FLI	138.694	80,5	20.273	11,77	13.316	7,73	121.116	49,22	65.406	26,58	59.539	24,8	<0,0001
HSI	40.028	16,26	67.207	39,01	65.047	44,73	32.505	13,21	91.756	37,29	12.1800	49,5	<0,0001
ZIU	111.139	64,51		–	61.143	35,49	151.893	61,73		–	94.168	38,27	<0.0001
LAP	130.056	75,49			42.226	24,51	156.323	63,53			89.738	36,47	

Se considera significativo p<0, 05. Fatty liver index (FLI), Hepatic Steatosis index (HSI), Zhejiang University (ZJU), Lipid accumulation Product (LAP).

Table II: Valores Medios de VAI y DAI por sexo según escalas de riesgo de hígado graso (FLI, HSI, ZJU, LAP).

Método de Valoración		Mujeres					Hombres				
			VAI		DAI			VAI		DAI	
		n	media (dt)	p	media (dt)	p	n	media (dt)	p	media (dt)	p
FLI	bajo medio alto	138.694 20.273 13.316	2,29 (1,04) 3,81 (1,80) 4.99 (3.05)	<0.0001	0,59 (0,27) 0,95 (0,46) 1.22 (0.76)	<0.0001	121.116 65.406 59.539	4,13 (1,92) 7,39 (3,58) 13.79 (9.33)	<0.0001	0,58 (0,27) 0,93 (0,48) 1.54 (1.06)	<0.0001
HSI	bajo medio alto	28.020 67.209 77.054	2,26 (1,15) 2,47 (1,34) 3,32 (1,92)	<0.0001	0,60 (0,30) 0,64 (0,34) 0,83 (0,47)	<0.0001	32.511 91.747 121.803	4,60 (2,97) 5,99 (4,18) 9,10 (6,57)	<0.0001	0,68 (0,43) 0,80 (0,54) 1,05 (0,73)	<0.0001
ZJU	normal alto	111.145 61.137	2,38 (1,12) 3,61 (2,14)	<0.0001	0,62 (0,29) 0,89 (0,53)	<0.0001	151.901 94.160	5,39 (3,07) 10,51 (7,28)	<0.0001	0,73 (0,41) 1,19 (0,83)	<0.0001
LAP	normal alto	130.058 42.224	2,17 (0,86) 4,37 (2,27)	<0.0001	0,56 (0,22) 1,09 (0,57)	<0.0001	156.332 89.729	4,49 (2,10) 12,45 (8,20)	<0.0001	0,60 (0,28) 1,45 (0,93)	<0.0001

dt= desviación típica. Índice de adiposidad visceral (VAI) Índice de adiposidad disfuncional (DAI).Se considera significativo p<0,05. Fatty liver index (FLI), Hepatic Steatosis index (HSI), Zhejiang University (ZJU), Lipid accumulation Product (LAP).
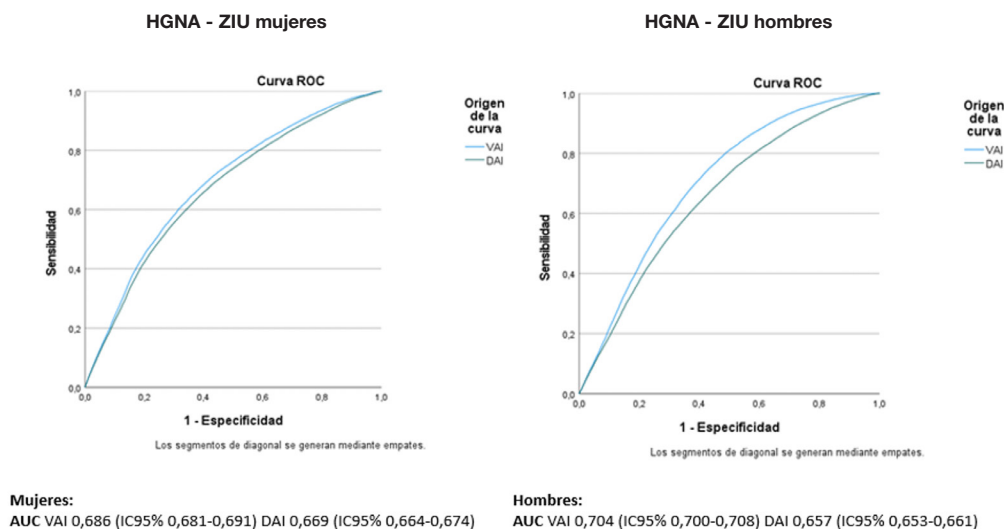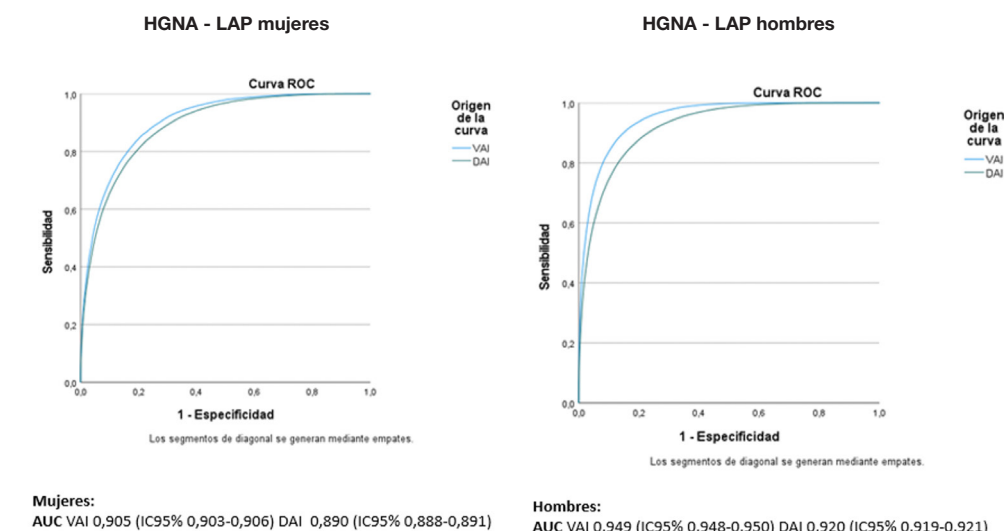
Figura 1: Valoración de la fortaleza de asociación del índice de adiposidad visceral (VAI) e índice de adiposidad disfuncional (DAI) en Riesgo de Hígado Graso No Alcohólico Fatty liver index (FLI) según sexo.

HGNA - FLI mujeres

HGNA - FLI hombres

Mujeres:
AUC VAI 0,847 (IC95% 0,844-0,851) DAI 0,826 (IC95% 0,822-0,829)

Hombres:
AUC VAI 0,885 (IC95% 0,883-0,886) DAI 0,835 (IC95% 0,834-0,837)
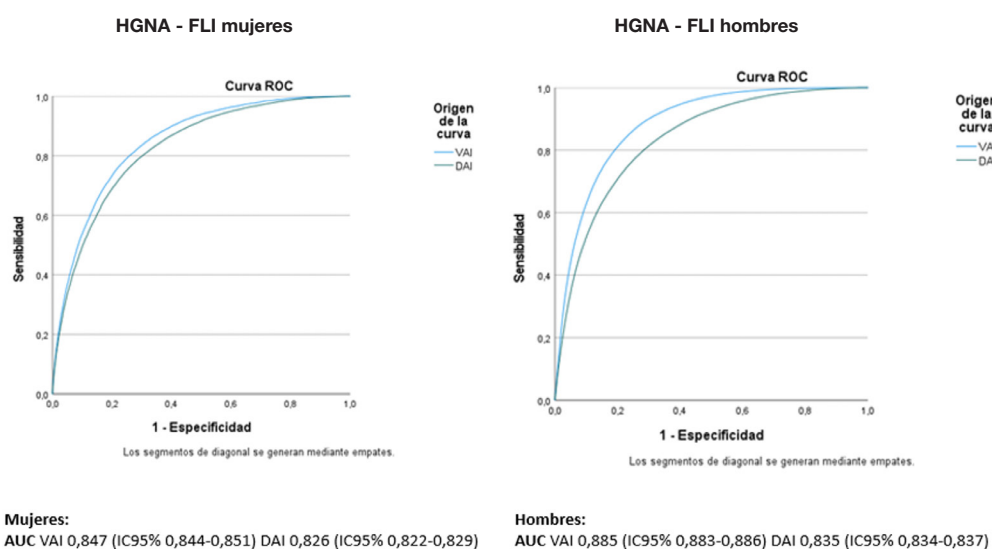
Figura 2: Valoración la fortaleza de asociación del índice de adiposidad visceral (VAI) e índice de adiposidad disfuncional (DAI) en Riesgo de Hígado Graso No Alcohólico Hepatic Steatosis index (HSI) según sexo.

HGNA - HSI mujeres

HGNA - HSI hombre

Mujeres:
AUC VAI 0,639 (IC95% 0,634-0,643) DAI 0,624 (IC95% 0,619-0,629)

Hombres:
AUC VAI 0,634 (IC95% 0,631-0,638) DAI 0,597 (IC95% 0,594-0,601)
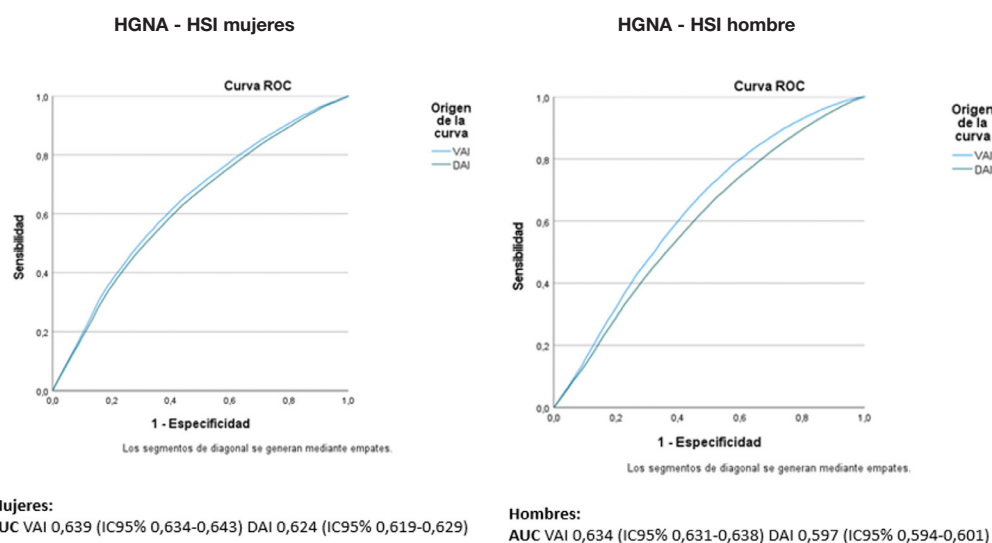
Figura 3: Valoración la fortaleza de asociación del índice de adiposidad visceral (VAI) e índice de adiposidad disfuncional (DAI) en Riesgo de Hígado Graso No Alcohólico Zhejiang University (ZJU) según sexo.

HGNA - ZIU mujeres

HGNA - ZIU hombres

Mujeres:
AUC VAI 0,686 (IC95% 0,681-0,691) DAI 0,669 (IC95% 0,664-0,674)

Hombres:
AUC VAI 0,704 (IC95% 0,700-0,708) DAI 0,657 (IC95% 0,653-0,661)

Figura 4: Valoración de la fortaleza de asociación del índice de adiposidad visceral (VAI) e índice de adiposidad disfuncional (DAI) en Riesgo de Hígado Graso No Alcohólico Lipid accumulation Product (LAP) según sexo

HGNA - LAP mujeres

HGNA - LAP hombres

Mujeres:
AUC VAI 0,905 (IC95% 0,903-0,906) DAI 0,890 (IC95% 0,888-0,891)

Hombres:
AUC VAI 0,949 (IC95% 0,948-0,950) DAI 0,920 (IC95% 0,919-0,921)

Discusión

La NAFLD se ha convertido en un problema de salud pública, con un impacto negativo para la salud pero también socioeconómico, y con repercusión en el sistema sanitario. Por ello, la detección temprana y el cribado sistemático es cada vez más importante, especialmente si se tiene en cuenta que es una complicación de patologías metabólicas como la DM2, la obesidad y el síndrome metabólico pero que, con frecuencia no se valorar ni diagnostica o cuando se hace es en formas tardías con la enfermedad hepática ya avanzada[11]. Esto es de especial relevancia en Salud Laboral, donde la actividad preventiva se fundamenta en la prevención primaria, anticipándose a la aparición del daño, en este caso el desarrollo posterior de NAFLD.

El uso de la biopsia hepática para el diagnóstico de NAFLD es sin duda el patrón de referencia pero no accesible en la clínica diaria por su coste y las complicaciones que conlleva, sin embargo este procedimiento, al igual que la ecografía hepática, los ultrasonidos, el fibroScan o la medición mediante *controlled attenuation parameter* (CAP) no son accesibles para los servicios de medicina del trabajo. Es por ello que se recurre a métodos no invasivos que han demostrado ser relativamente efectivos, económicamente accesibles y útiles en un entorno como el de atención primaria y en salud laboral[12].

El aumento del tejido adiposo visceral incrementa el riesgo de desarrollar enfermedad del hígado graso no

alcohólico (NAFLD) y se relaciona con complicaciones crónicas, especialmente con sujetos con diabetes[13]. Por este motivo realizamos en nuestro estudio una estimación para relacionar el tejido graso visceral y disfuncional (VAI y DAI) con el riesgo de desarrollar NAFLD y poder actuar en prevención desde la esfera laboral y en población aparentemente sana.

El índice de adiposidad visceral (IVA), calculado con el índice de masa corporal, el colesterol unido a lipoproteínas de alta densidad, los triglicéridos y la circunferencia de la cintura, ha mostrado ser un factor que se asocia con el riesgo de NAFLD incidente en trabajos previos al nuestro[14] coincidiendo con nuestros resultados, que muestran valores de asociación en las curvas ROC >0,8 y, especialmente con las estimaciones de FLI y LAP. En algunos trabajos se afirma que en pacientes con NAFLD el VAI es una expresión cualitativa y cuantitativa de la disfunción del tejido adiposo y que, junto con la resistencia a la insulina, se correlaciona de forma independiente con una fibrosis hepática significativa[15]. Sin embargo, en otros trabajos la puntuación VAI no se asoció con la gravedad de la inflamación o fibrosis hepática y no se recomienda como factor que se relacione con cambios histológicos hepáticos en pacientes con NAFLD[16].

En lo que respecta al DAI, ha mostrado su utilidad como parámetro de asociación en NAFLD en algunos estudios anteriores al nuestro y asociado con otras complicaciones metabólicas y cardiovasculares como: diabetes, aterosclerosis subclínica e hipertensión[17].

Tanto el DAI como el VAI son fáciles de obtener utilizando parámetros accesibles, por lo que pueden incorporarse a la práctica clínica para la identificación temprana de anomalías del tejido graso en sujetos aparentemente sanos y prevenir posteriores complicaciones[18].

Los resultados comparativos de nuestro trabajo con los 4 métodos destacan la fortaleza de asociación de FLI y LAP y coinciden con los obtenidos en otros trabajos en lo que respecta a FLI, siendo menores con LAP. Con HSI, al igual que en nuestro trabajo, los resultados de Lind y cols no tuvieron fortaleza de asociación, a pesar de que en este trabajo de referencia la población fue mayor que la de nuestro estudio (>50 años) y en personas con riesgo metabólico (pacientes con un índice de masa corporal > 25 kg/m², triglicéridos plasmáticos altos o sujetos con diabetes tipo 2). En nuestro trabajo, al contrario, se trata de una población más joven, laboralmente activa y aparentemente sana, lo que dificulta establecer una comparativa entre ambos estudios[19].

Queda así abierto un campo a futuras investigaciones, asumiendo las aportaciones del VAI y DAI como marcadores de la distribución y disfunción de la grasa visceral, y su fortaleza asociativa con el riesgo cardiovascular y cerebrovascular, al que se añade la evidencia clínica del fuerte vínculo con el riesgo de desarrollar NAFLD. Sin embargo, la patogenia de la esteatosis y fibrosis hepática son diferentes de la aterogénesis y los futuros estudios podrán confirmar si VAI y DAI pueden actuar con rigor asociativo de la fibrosis hepática en diferentes poblaciones, asumiendo las diferencias intersexo y en grandes cohortes de pacientes, antes de poder aplicarlo en la práctica clínica diaria[20].

Se considera fortaleza de este trabajo su tamaño muestral, el uso de índices específicos de adiposidad como el VAI y el DAI en la capacidad de asociación con el riesgo de desarrollar NAFLD, junto con la comparativa realizada con los distintos métodos de valoración y parámetros utilizados. La mayor debilidad es no tener un comparativo por sectores laborales en esta muestra de población tan extensa, ser un estudio transversal, no poder extrapolar ni generalizar los resultados y no disponer en ámbito laboral de herramientas más potentes para definir el HGNA, .como: ultrasonido, FibroScan o la medición mediante *controlled attenuation parameter* (CAP) que se ha propuesto como un método no invasivo para la detección y medición simultánea de esteatosis hepática[21,22].

Conclusiones

La prevalencia más elevada de riesgo de NAFLD en ambos sexos se obtiene con HSI y la más baja con FLI. Con los 4 métodos empleados, el riesgo de NAFLD es más elevado en los hombres.

Los índices VAI y DAI muestran alta fortaleza de asociación con el riesgo de desarrollar hígado graso no alcohólico calculado con FLI y LAP en población laboral, moderada fortaleza con ZIU y baja con HSI. Se consideran métodos útiles de prevención primaria, anticipándose a la aparición de hígado graso no alcohólico en salud laboral.

Financiación

Conflicto de intereses
Durante el desarrollo de esta investigación no se presentó ningún caso de conflicto de interés.

María Teófila Vicente-Herrero et al.

Relación de los índices de adiposidad visceral (VAI) y disfuncional (DAI) con riesgo de enfermedad de hígado graso no alcohólico

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ORIGINAL

Frequency and risk factors for the development of ventricular arrhythmias after acute myocardial infarction –cross-sectional study

Frecuencia y factores de riesgo para el desarrollo de arritmias ventriculares después del infarto agudo de miocardio – estudio transversal

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Abstract

Objectives: Ventricular arrhythmias (VA) are the most common cause of sudden cardiac death in the period after an acute myocardial infarction (AMI), i.e. due to myocardial ischemia. The aim of this study was to analyze the frequency of ventricular tachycardia (VT) and ventricular fibrillation (VF) in patients treated for AMI, as well as to determine which factors increase the risk of these arrhythmias.

Methods: This is a retrospective of cross-sectional study. The data used here are from the database of the Clinical Information System from Clinic for Cardiology, University Clinical Centre of the Republic of Srpska, from 2020. Patients with a diagnosis of AMI were taken into account, and data on the occurrence of ventricular arrhythmias, percentage of ejection fraction, Killip class, comorbidities, socio-epidemiological data, and complications within the one year that the patients were under observation were taken from the medical records.

Results: During hospitalization, VT was significantly more common in overweight patients, in patients with a low ejection fraction (EF%) and a Killip class higher than 1. The results were similar during the one-year observation of the patients, with the exception that in the period of observation it was found that both older patients and those with multivessel heart disease are statistically significantly more prone to developing ventricular arrhythmias. AMI of the posterior wall showed a higher risk for developing complications.

Conclusions: The results showed that the frequency of VA after AMI is 11.26% and age, posterior localization of infarction, obesity, left ventricular function and Killip class significantly determine the tendency for patients to develop malignant arrhythmias immediately after AMI and during one year of observation.

Key words: Ventricular arrhythmias, ventricular tachycardia, acute myocardial infarction, risk factors, ventricular fibrillation.

Resumen

Objetivos: Las arritmias ventriculares (AV) son la causa más común de muerte súbita cardíaca en el período posterior a un infarto agudo de miocardio (IAM), es decir, debido a isquemia miocárdica. El objetivo de este estudio fue analizar la frecuencia de taquicardia ventricular (TV) y fibrilación ventricular (FV) en pacientes tratados por IAM, así como determinar qué factores aumentan el riesgo de estas arritmias.

Métodos: Se trata de un estudio retrospectivo de corte transversal. Los datos utilizados aquí provienen de la base de datos del Sistema de Información Clínica de la Clínica de Cardiología, Centro Clínico Universitario de la República de Srpska, de 2020. Se tuvieron en cuenta los pacientes con diagnóstico de IAM y los datos sobre la aparición de arritmias ventriculares. De las historias clínicas se extrajeron porcentaje de fracción de eyección, clase Killip, comorbilidades, datos socioepidemiológicos y complicaciones dentro del año que los pacientes estuvieron en observación.

Resultados: Durante la hospitalización, la TV fue significativamente más común en pacientes con sobrepeso, en pacientes con una fracción de eyección (FE%) baja y una clase Killip superior a 1. Los resultados fueron similares durante el año de observación de los pacientes, con la excepción que durante el período de observación se encontró que tanto los pacientes de mayor edad como aquellos con enfermedad cardíaca multivaso son estadísticamente significativamente más propensos a desarrollar arritmias ventriculares. El IAM de la pared posterior mostró un mayor riesgo de desarrollar complicaciones.

Conclusiones: Los resultados mostraron que la frecuencia de AV después del IAM es del 11,26% y la edad, la localización posterior del infarto, la obesidad, la función ventricular izquierda y la clase Killip determinan significativamente la tendencia de los pacientes a desarrollar arritmias malignas inmediatamente después del IAM y durante un año de observación.

Palabras clave: Arritmias ventriculares, taquicardia ventricular, infarto agudo de miocardio, factores de riesgo, fibrilación ventricular.

Introduction

One of the biggest risks that medical employees face when it comes to working with patients who have had a heart attack is the possibility of developing malignant arrhythmias. The most common cause of cardiac arrest in this population is ventricular arrhythmias - ventricular tachycardia (VT) and ventricular fibrillation (VF).

Myocardial infarction represents necrosis of the heart muscle in the field of ischemia caused by changes and narrowing of the coronary blood vessels, which lead to reduced oxygenation and nutrition of the myocardium. Myocardial ischemia represents the single greatest risk for the development of malignant arrhythmias[1].

Ventricular arrhythmias are related to myocardial ischemia, and therefore, patients with coronary heart disease (CHD) and/or low ejection fraction are the most common substrate for these rhythm disorders. They are divided into sustained and non-sustained ventricular arrhythmias, depending on the duration and nature of the arrhythmia. Nowadays, when medication or mechanical revascularization of the myocardium is performed even earlier, their lethal impact in the period of hospitalization decreases, but they still remain the most common cause of post-infarction death before and during transport to the coronary unit. These rhythm disturbances often occur in the first few minutes after the development of myocardial necrosis, often even before the patient has a contact with the medical staff. The onset of VF is sudden and unpredictable, and there are only a limited number of studies that attempt to explain the nature of the onset of these arrhythmias[2-4].

A greater number of studies on acute myocardial infarction (AMI) were conducted on the topic of ischemia and correction of the effect of ischemia on the myocardium, while an insufficient number of studies looked at its arrhythmogenic effect. In practice, there is a need to monitor patients with myocardial ischemia and predict the occurrence of malignant arrhythmias, as well as how to introduce the adequate antiarrhythmics in time[2,3,5].

A larger number of studies were conducted with patients who underwent primary percutaneous coronary intervention with reperfusion of artery affected by stenosis (PPCI). These studies have shown unclear conclusions[6-8].

It is considered that the main trigger for VA is the appearance of autonomy in borderline zones of ischemia, where there is an overload of the intracellular milieu with calcium ions and hyperkalemia extracellularly. Further maintenance of VA takes place according to the type of re-entry arrhythmias around the focus of ischemia and later around the scar tissue[7,8].

The aim of this study was to determine the frequency of VT/VF in patients who were treated at the University Clinical Centre of the Republic of Srpska (UCC RS) in 2020 for AMI, as well as to investigate which factors increase the risk of these arrhythmias.

Methods

A retrospective cross-sectional study was performed. Data were collected from all patients who were hospitalized at the Coronary Unit of the Clinic of Cardiology, UCC RS in 2020. The study was approved by the Local Ethics Committee (decision No: 01-17367-2/21). Data were collected from electronic database – Clinical Informational System. Patients with incomplete documentation were not included in the analysis.

Basic sociodemographic data (sex, age) were collected, as well as the presence of comorbidities and risk factors: tobacco smoking, obesity, diabetes mellitus, hypertension, dyslipidemia. The clinical picture and tests performed were also recorded: how much time passed from the onset of pain to first contact with the doctor, whether the symptoms were typical for ACS, maximal troponin values, lipid and electrocardiogram (ECG) on admission. The ECG recorded whether it was STEMI / NSTEMI, as well as the localization of the infarction. Complications during hospitalization were recorded and analyzed: arrhythmias, VT (as well as whether it was sustained /unsustained), VF, AF, necessity for reanimation, death. Complications were observed and recorded for one year after the onset of ACS: reinfarction, angina, episodes of VT, VF, cardiac decompensation, death.

Data were analyzed using IBM SPSS for Windows v. 16.0 software. The normality of data distribution was determined using the Kolmogorov-Smirnov test and appropriate parametric / nonparametric statistic tests were applied. Descriptive statistics consisted of expressing the data as a mean with its standard deviation (SD) and a 95% confidence interval (CI). Categorical variables were compared using the Chi-square test (Fisher exact test if one of the categories had less than 5 variables). Comparison of continual variables was performed using Student's t-test for two categories and One-way analysis of variance for several categories for parametric data, and Man–Whitney U-test, or Kruskal–Wallis test for non-parametric data. Two continuous variables were analyzed using correlations – Pearson's for parametric and Spearman's for nonparametric variables. Statistical significance was set at $p < 0.05$.

Results

The mean age of the patients was 64.45 ± 10.50 years (range: 28-90). Of the 222 patients, 154 (69.37%) were men and 68 (30.63%) were women (**Table I**). Women were slightly older than men (66.31: 63.63, respectively), but without significant difference (F: 0.114, p = 0.736). The presence of comorbidities are shown in **table I**.

There were equal distribution of risk factors and comorbidities related to age and sex. There were slightly more smokers among men, but not significantly (p = 0.286). Symptoms, clinical picture and performed test results of patients with ACS are shown in **table II**.

(**Table II** near here)
In-hospital complications were not significantly related to localization of the infarction. Frequency of arrythmias occurrence, AF, reanimation and death, were not related to localization of the infarction (x^2 = 6.153, p = 0.725; x^2 = 4.324, p = 0.889; x^2 = 8.364, p = 0.498; and x^2 = 11.967, p = 0.215, respectively). VT and VF occurred in 11.26% of patients treated for AMI. Occurrence of VT was influenced with localization of the infarction (x^2 = 33.027, p = 0.017), VT was somewhat more common in patients with posterior AIM (x^2 = 5.259, p = 0.072) (Data not shown).

Complications during one-year follow-up in relation to the localization of the infarction are shown in **Figure 1**.

Posterior wall myocardial infarction was associated with more frequent complications within one year after infarction. Ventricular arrhythmias (x^2 = 8.089, p = 0.010), angina (x^2 = 11.983, p = 0.001) and heart failure (x^2 = 6.656, p = 0.015) were more common in these patients. On the other hand, anterior wall infarction was associated with rarer complications. Within a year, ventricular arrhythmias (x^2 = 10.646, p = 0.001), angina (x^2 = 6.405, p = 0.017) and heart failure (x^2 = 7.836, p = 0.006) were less common. Reinfarction and death within a year after infarction were not related to localization of the infarction (data not shown).

The frequency of VT / VF in relation to relevant risk factors, symptoms and clinical parameters during hospitalization and during one-year follow-up are shown in **Figures 2** and **3**.

Table I: Sociodemographic parameters and comorbidities in patients with acute myocardial infarction.

Parameter		Total	
		N	%
Sex			
	Male	154	69.37
	Female	68	30.63
Age			
	Mean ± SD	64.45 ± 10.50	
Hypertension			
	Yes	174	78.38
	No	48	21.62
Diabetes mellitus			
	Yes	63	28.38
	No	159	71.62
Obesity			
	Yes	21	10.40
	No	181	89.60
Tobacco smoking			
	Yes	81	36.49
	No	88	39.64
	Missing	53	23.87
Total		222	100.00

*Obesity: body mass index more than 30 kg/m²;

Table II: Symptoms, clinical picture and results of tests performed in patients with acute myocardial infarction.

| Parameter	N	%
Onset time		
Up to 1 h	70	31.53
1-2 h	28	12.61
2-3 h	15	6.76
3-4 h	10	4.50
More than 4 h	89	40.09
Missing	10	4.50
Symptoms		
Typical	196	88.29
Atypical	26	11.71
ECG		
STEMI	186	83.78
NSTEMI	35	15.77
Infarction localization		
Inferior	56	25.23
Inferoposterior	34	15.32
Inferolateral	5	2.25
Right-inferior	2	0.90
Posterior	7	3.15
Posterolateral	6	2.70
Anterior	69	31.08
Anterolateral	31	13.96
Lateral	4	1.80
Extended	4	1.80
Missing	4	1.80
hsTnT		
Mean ± SD	3078.04 ± 5052.45	
Range	0-37574	
Interquartile Range	3417.5	
LDL		
Mean ± SD	1.76 ± 1.89	
Range	0-7.10	
Interquartile Range	3.6	
Coronography		
No stenosis	10	4.50
One vessel	101	45.50
Two vessels	73	32.88
Three vessels	38	17.12
ECHO – EF (%)		
Mean ± SD	41.85 ± 10.99	
Range	5-65	
Interquartile Range	15	
Killip class		
1	169	76.13
2	29	13.06
3	18	8.11
4	1	0.45
Missing	5	2.25

Onset time: period from first manifestation of symptoms until first contact with doctors; hsTnT: high-sensitive troponin T, normal value: < 15 pg/mL; LDL: low-density lipoprotein, normal value: 2.6 - 3.3 mmol/L; EF: ejection fraction.

Figure 1: Complications during one-year follow-up period in patients with acute coronary syndrome in relation to the localization of the infarction.
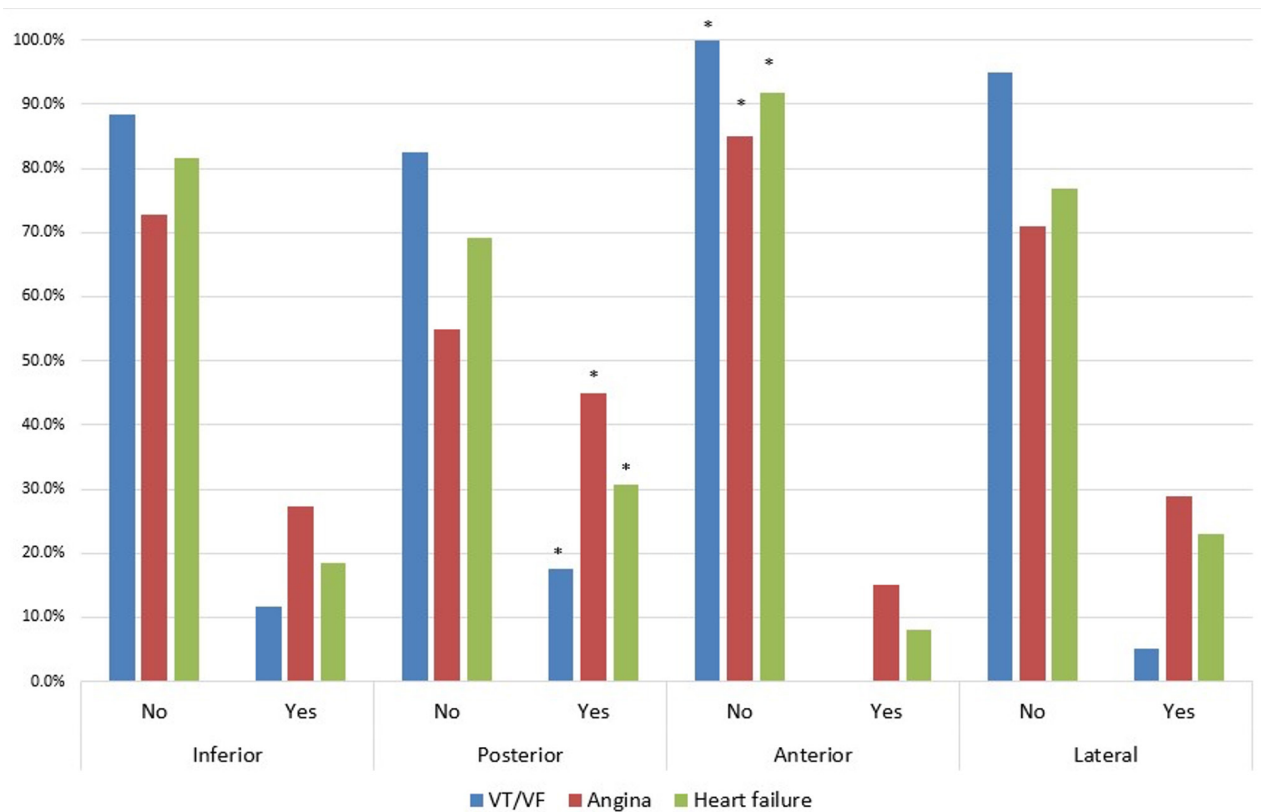

*Statistical significance: Ventricular arrhythmias (χ^2 = 8.089, p = 0.010), angina (χ^2 = 11.983, p = 0.001) and heart failure (χ^2 = 6.656, p = 0.015) were more common in patients with posterior wall infarction, and less common in patients with anterior wall infarction (χ^2 = 10.646, p = 0.001), (χ^2 = 6.405, p = 0.017) and (χ^2 = 7.836, p = 0.006), respectively.

Figure 2: The frequency of VT / VF in relation to obesity, EF and Killip class during hospitalization.
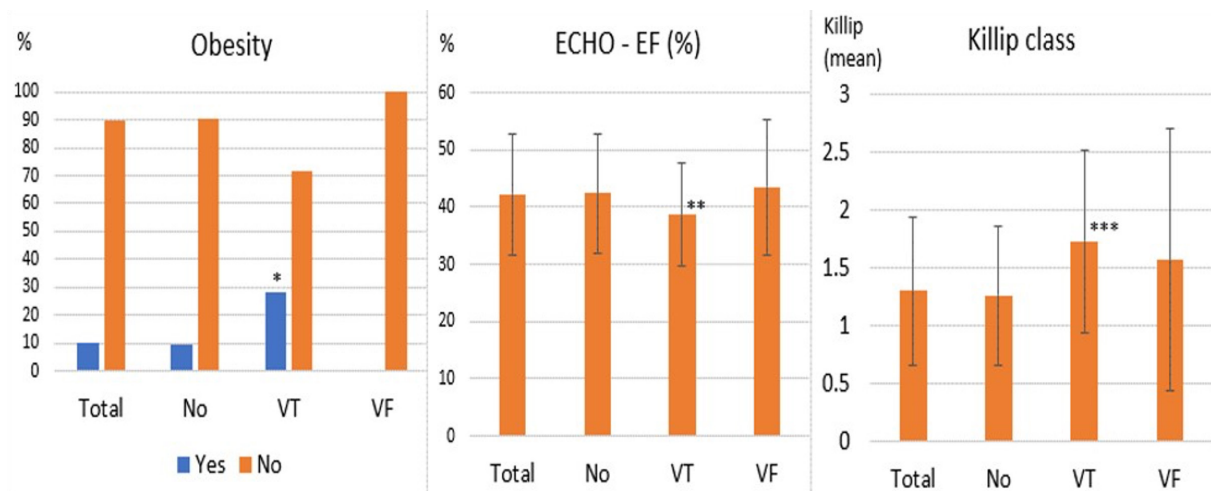
* Obese patients were significantly more likely to have VT (χ^2 = 6.068, p = 0.048). **VT was more common in individuals who had lower EF on ultrasonography. *** VT was more common in patients with higher Killip class score.

Although VT was slightly more common in men and older and VF in women and older, the difference was not statistically significant. Obese patients were significantly more likely to have VT (χ^2 = 6.068, p = 0.048). Other risk factors (hypertension, diabetes mellitus, smokers) did not influence frequency of VT.

VT was more common in individuals who had lower ejection fraction (EF%) on ultrasonography (Kruskal-Wallis test: χ^2 = 7.751, p = 0.021) as well as higher Killip class score (χ^2 = 15.880, p < 0.001). Symptoms, onset time, ECG and hsTnT were not related to frequency of VT occurrence.

Figure 3: The frequency of VT / VF in relation to obesity, coronary angiography findings, EF and Killip class during one-year follow-up.
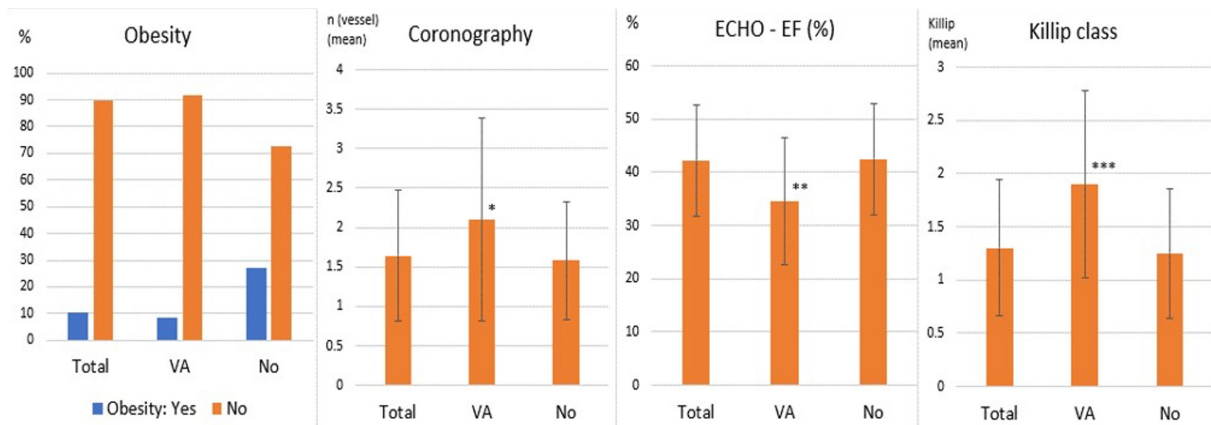
*VT / VF were more common in subjects with lower EF values on ultrasonography (Man-Whitney U = 408.000, p = 0.029), higher Killip scores (U = 606.000, p = 0.005) and the presence of occlusion of multiple blood vessels on coronary angiography (U = 572.500, p = 0.017).

During one-year follow-up, the elderly were more likely to have ventricular arrhythmias (Student t-test t = 2.232, p = 0.027). VT / VF were more common in subjects with lower EF% values on ultrasonography (Man-Whitney U = 408.000, p = 0.029), higher Killip scores (U = 606.000, p = 0.005) and the presence of occlusion of multiple blood vessels on coronary angiography (U = 572.500, p = 0.017). Other parameters were without significant difference.

Discussion

Among the data collected from 222 patients in 2020, from the Clinical Information System of the UCC RS, it was found that VT and VF occurred in 11.26% of patients treated for AMI, which is in accordance with the data obtained by experts from other world centres[6-8].

The study indicated that VT/VF in hospital conditions, i.e. in the first 48 hours after the AMI itself, occur most often in cardiac arrest with posterior localization. The majority of world studies have shown that the greatest risk for early VT/VF is cardiac arrests affecting the posterior segment of the lower wall, especially the part of the myocardium around the annulus, which leads to circular movement of depolarization currents in unclear manner. In this study, there was no statistical significance in the number of sustained and unsustained VT[9-11].

According to these data, patients with a lower EF% are more liable to AMI complications, especially ventricular arrhythmias. This has also been confirmed in international studies as the main factor in assessing the risk of ventricular arrhythmias post-infarction. The MADIT study (The multicenter automatic defibrillator implantation trial) proved a 5.6% reduction in mortality in patients who had an AMI, and who were preventively implanted with an ICD; the observation period was 27 months. However,

the MUSTT study indicated that EF% should not be the only argument for VA risk assessment. According to this study, other parameters should be included, such as age, degree of myocardial functionality, history of heart failure, conduction abnormalities, AF and others[12-14].

When we observe the Killip class at admission, a Killip class higher than 1 represents an additional risk of developing VA. This makes sense, given that the Killip classification was introduced as a tool for rapid risk assessment in patients with AMI. This classification has proven to be an extremely useful tool, especially in countries with less developed methods and diagnostics when it comes to the health system[15-17].

The estimated risk for VA according to gender showed no statistically significant difference, although VT was slightly more common in men, while VF was more common in women. International studies, as well, have not shown that gender plays a significant role as a risk factor in these arrhythmias after myocardial infarction.

Ventricular tachycardias, according to research data, more often affected the elderly population and obese patients. These data are consistent with the data obtained in some foreign studies. The MADIT II study linked overweight with an increased risk of myocardial arrhythmogenicity after AMI. However, some other studies strongly point to the so-called "obesity-paradox", where a higher body-mass index (BMI) is associated with a protective role when complications of certain chronic diseases come in question. This applies mostly to patients with low EF% and patients with AMI. It is not clear why in this particular case a higher BMI indicates a lower risk of VA, but some possible solutions have been suggested - inadequate sample, obesity is more common in younger people, more obese patients are more often on more rigorous therapeutic regimens, adipose metaplasia of coronary blood vessels, absence of ischemic cachexia[18-20]…

While observing the patients over a period of one year, it was shown that patients with AMI of the posterior wall were more liable to complications in terms of ventricular arrhythmias, angina pectoris and heart failure, while in patients with anterior localization of infarction, a lower risk of developing complications related to AMI. Not enough studies have been done worldwide to confirm or contradict the results of this study.

Research has showed that the degree of affected coronary blood vessels (multivessel coronary disease) represents a risk for the development of ventricular arrhythmias in the observation period of one year after hospitalization. These results are consistent with research results from around the world. This makes sense if it is known that the degree of affected myocardium and left ventricular dysfunction determine the risk for ventricular arrhythmias. Multivessel coronary disease leads to chronic ischemia of a large part of the myocardium, and to cardiac remodeling. This weakens the EF%, and increases the risk of VA[2,13,15].

Conclusion

The main risk factor for VT is ischemia that occurs during myocardial infarction, or chronic ischemia in coronary disease, where ejection function of the myocardium is lowered significantly. The study confirmed these findings. This research indicated that patients with posterior wall infarction, higher Killip class, obese and older patients were more susceptible to ventricular arrhythmias. Creating clear list of risk factors for developing ventricular arrhythmias is still the subject of continuing research.

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Pain assessment tools for non-verbal adult ICU patients: systematic review

Herramientas de evaluación del dolor no verbales para pacientes adultos en UCI: revisión sistemática

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Abstract

Aim: determine valid and reliable pain assessment tools for ICU patients who are unable to self-report their pain and discomfort. Design: Systematic review based on PRISMA Checklist 2020 "Preferred Reporting Items for Systematic Reviews and Meta-Analyses". This study is still in the registration process in PROSPERO.

Methods: We have collected data from December 20th, 2022 to March 28th, 2023, in the following databases: PubMed, Google Scholar, NIH Library, Cochrane central register, and Medscape. We've collected 789 studies. They were all screened "title and abstract and full-text screening" by the two researchers independently. The total number of included studies is 25.

Results: Twenty-five (n=25) studies were included and seven hundred sixty-four studies (n=764) were excluded. Quality appraisal of included studies was done by the two researchers using the CASP checklist. Eighteen (n=18) studies discussed CPOT, sixteen (n=16) studies discussed about BPS, three (n=3) studies discussed BPS-NI, three (n=3) studies discussed NPAT, six (n=6) studies discussed ONVPS, nine (n=9) studies discussed RNVPS, four (n=4) studies discussed PAINAD and two (n=2) studies discussed DPS. CPOT, BPS, BPS-NI, RNVPS, and PAINAD were all valid and reliable instruments to be used among the non-verbal adult ICU population. The CPOT is to be preferred since it showed nearly perfect properties. ONVPS, DPS, and NPAT showed low evidence of psychometric properties..

Key words: Pain assessment tool, pain scale, non-verbal ICU patients, adult ICU population, valid and reliable pain assessment tools.

Resumen

Objetivo: Determinar herramientas de evaluación del dolor válidas y fiables para pacientes en UCI que no pueden comunicar su dolor e incomodidad. Diseño: Revisión sistemática de la literatura basada en la Lista de verificación PRISMA 2020 "Ítems de Reporte Preferidos para Revisiones Sistemáticas y Metaanálisis". Este estudio se encuentra aún en proceso de registro en PROSPERO.

Métodos: Recopilamos datos desde el 20 de diciembre de 2022 hasta el 28 de marzo de 2023, en las siguientes bases de datos: PubMed, Google Scholar, Biblioteca NIH, Registro central Cochrane y Medscape. Hemos recopilado 789 estudios. Todos fueron evaluados "por título y resumen y revisión de texto completo" por los dos investigadores de manera independiente. El número total de estudios incluidos es 25.

Resultados: Se incluyeron veinticinco (n=25) estudios y se excluyeron setecientos sesenta y cuatro (n=764) estudios. La evaluación de calidad de los estudios incluidos fue realizada por los dos investigadores utilizando la lista de verificación CASP. Dieciocho (n=18) estudios discutieron sobre CPOT, dieciséis (n=16) estudios discutieron sobre BPS, tres (n=3) estudios discutieron sobre BPS-NI, tres (n=3) estudios discutieron sobre NPAT, seis (n=6) estudios discutieron sobre ONVPS, nueve (n=9) estudios discutieron sobre RNVPS, cuatro (n=4) estudios discutieron sobre PAINAD y dos (n=2) estudios discutieron sobre DPS. CPOT, BPS, BPS-NI, RNVPS y PAINAD fueron todos instrumentos válidos y fiables para ser utilizados en la población de adultos no verbales en UCI. El CPOT es preferible ya que mostró propiedades casi perfectas. ONVPS, DPS y NPAT mostraron baja evidencia de propiedades psicométricas.

Palabras clave: Herramienta de evaluación del dolor, escala de dolor, pacientes no verbales en UCI, población de adultos en UCI, herramientas de evaluación del dolor válidas y fiables.

Introduction

Intensive care unit (ICU) services are a source of many aggressions for patients, who must undergo the application of heavy and often invasive support techniques. And because of the technicality of the care and the imperatives of security and surveillance, they create an extremely difficult living environment for them[1]. According to some authors, almost 30% of patients experience pain at rest and 50% during various nursing interventions. The majority of patients discharged from an ICU identify the pain experienced as a huge source of stress[2].

Pain takes on subjective dimensions; in other words, its description is based upon the patient's own description of pain, which is not always possible: the intensive care patients have a diminished ability to communicate, and it causes that the patient may experience pain without being able to reveal it in a way that intensive care personnel understand. Thus, it becomes necessary to take into consideration the case of patients who are unable to formulate and express their experience of discomfort.

A lack of the ability to communicate pain verbally does not eliminate patient's potential for experiencing pain. However, the inability to communicate pain verbally remains a significant ethical and medical challenge, to recognize this pain as well as to choose an appropriate treatment. For this reason, this systematic review conducted conforming to PRISMA 2020 checklist aims to determine valid and reliable pain assessment tools to be used among this ICU population.

Methods

Study design
This study is designed in accordance with systematic review criteria which is conducted conforming to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. The protocol of this systematic review is still in the registration process in PROSPERO (ID: 431148).

Eligibility criteria
Inclusion criteria
- Grey literature and published full text studies in English, Italian and French.
- Studies that address nonverbal pain assessment tools.
- Selection of ICU (every type of intensive care units) adult (aged 18 years or older) population who have impaired ability to communicate their pain experience.

Exclusion criteria
- Transcultural adaptation and summarized articles.
- Repetitive papers

Information sources and search strategy
the study was performed from December 20th 2022 to March 28th 2023, in the following databases: Pub med, Google scholar, NIH library, Cochrane central register, Medscape, using the following keywords: pain assessment tool, pain scale, non-verbal ICU patients, adult ICU population, valid and reliable pain assessment tools. These keywords addressed the different elements of the search question in order to select all possible studies. Multiple combinations of search keywords were done using Boolean connectors including: AND, OR, such as: pain scale OR pain assessment tool – pain scale AND non-verbal ICU patient. This strategy generated 789 studies.

Selection and data collection process
The articles that were found in the search were screened by two independent authors, who assessed whether titles, abstracts and full-text studies respected the inclusion criteria. the articles that respected inclusion criteria were selected for data analysis. Conflicts were resolved by at least two researchers.

Data collection concerned: title, author/authors, year, country in which the study was conducted, aim of study, study design, start date/end date, population description, age, outcome, pain scale, tool description, reliability, validity, clinical utility and feasibility, sensitivity and specificity, limitations.

Quality appraisal
To assess the quality of the included studies we used CASP check lists.

Figure 1: Flow Diagram.
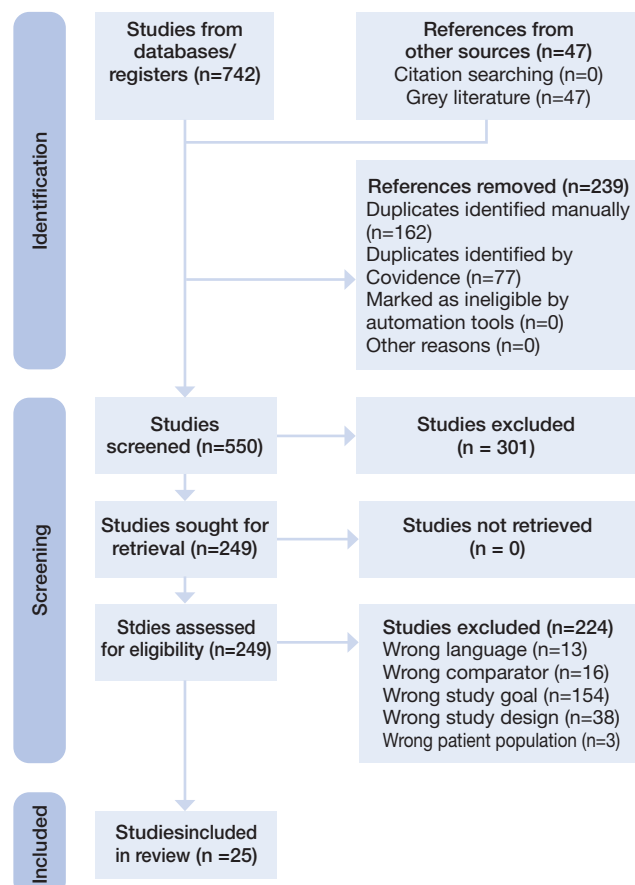
Results

Summary of studies in accordance with variable properties

Table I: Summary of studies in accordance with variable properties.

Studies	TOOL Psychometric properties	CPOT	BPS	BPS-NI	ONVPS	RNVPS	NPAT	PAINAD	DPS
(Al Darwish et al., 2016)	Reliability Validity	✗ ✗	✗ ✗			✗ ✗			
(Azevedo-Santos & DeSantana, 2018)	Reliability Validity	✗ ✗	✗ ✗		✗ ✗		✗ ✗		
(Birkedal et al., 2021)	Reliability Validity	✗ ✗	✗ ✗						
(Cade, 2008)	Reliability Validity	✗ ✗	✗ ✗		✗ ✗				
(Chanques et al., 2009)	Reliability Validity		✗ ✗	✗ ✗					
(Chanques et al., 2014)	Reliability Validity	✗ ✗	✗ ✗	✗ ✗		✗ ✗			
(Chatelle et al., 2008)	Reliability Validity		 ✗					 ✗	 ✗
(Creek 2019)	Reliability Validity	✗ ✗	✗ ✗	✗ ✗	✗ ✗	✗ ✗	✗ ✗	✗ ✗	
(Dorji 2019)	Reliability Validity	✗ ✗							
(Favaretto et Carraro 2015)	Reliability Validity	✗ ✗	✗ ✗			✗ ✗			
(Goe, 2018)	Reliability Validity								
(Juarez et al., 2010)	Reliability Validity		✗ ✗			✗ ✗			
(Kabes et al., 2009)	Reliability Validity				✗ ✗	✗ ✗			
(Keane, 2013)	Reliability Validity	✗ ✗							
(Li et al., 2008)	Reliability Validity	✗ ✗	✗ ✗		✗ ✗				
(Paulson-Conger et al., 2011)	Reliability Validity	✗						✗	
(Pereira, 2016)	Reliability Validity	✗ ✗				✗ ✗			
(Ross et al., 2016)	Reliability Validity	✗ ✗							
(Salamat et al., 2021)	Reliability Validity	✗ ✗	✗ ✗			✗ ✗			
(Severgnini et al., 2016)	Reliability Validity	 ✗	 ✗						
(Stites, 2013)	Reliability Validity	✗ ✗	✗ ✗		✗ ✗	✗ ✗	✗ ✗		
(Tapp et al., 2019)	Reliability Validity	✗ ✗						 ✗	
(Val et al., 2009)	Reliability Validity								✗ ✗
(Weldon, 2017)	Reliability Validity	✗	✗						
(Young et al., 2006)	Reliability Validity		✗ ✗						

This table showed that from the 25 included studies:
- 68% discussed reliability of CPOT and 64% its validity.
- 56% treated reliability of BPS and 60% its validity.
- 12% focused on reliability of BPS-NI and 12% its validity.
- 24% examined reliability of ONVPS and 24% its validity.
- 62% reviewed reliability of RNVPS and 36% its validity.
- 12% discussed reliability of NPAT and 12% its validity.
- 8% referred to reliability of PAINAD and 12% referred to its validity.
- 4% of studies brough up DPS's reliability and 8% discussed its validity.

Summary of included studies

Table II: Summary of included studies.

Reference	title	country	design	RESULTS
(Al Darwish et al., 2016)	Evaluation of Pain Assessment Tools in Patients Receiving Mechanical Ventilation	KSA	Descriptive cohort study	In this study, all 3 nonverbal pain scales were reliable and valid: • **BPS** - Reliability: (r)=0.90 - Validity: Cronbach (α)= 0.95 • **CPOT** - Reliability: (r)=0.93 - Validity: Cronbach (α)= 0.95 • **RNVPS** - Reliability (r)=0.86 - Validity: Cronbach (α)= 0.86
(Azevedo-Santos & DeSantana, 2018)	Pain measurement techniques: spotlight on mechanically ventilated patients	Brazil	Systematic review of literature	• **CPOT**: this tool is valid in the following languages "French, English, Turkish, Chinese, Polish, Korean, Swedish, Finish, Dutch, Italian, Danish and Spanish". It was validated in the following simples "post operative heart surgery, neurosurgery, surgical wards, patients with brain injury, burned and delirium patients. The inter-rater reliability in both the English and Swedish version was greater than 0,80 (ICC). As for the French and Spanish versions weighted Kappa varied from [0,52-1]. For the internal consistency Cronbach (α) coefficients vary from 0.31 to 0.81. • **BPS**: it's valid in different languages "French, English, Chinese, Swedish, Polish, Finnish, Dutch, Portuguese and Spanish". This tool was found acceptable in the "Non-intubated Traumatic brain injury". The internal consistency Cronbach (α) coefficient ranged from 0.63 to 0.72 The inter-rater reliability Kappa coefficient ranged from 0.67 to 0.83. • **NPAT**: many limitations were reported in the validation study of this tool. Samples were from Cardiothoracic surgery, cardiology, medical and surgical patients. The studies were in English. • **ONVPS:** It was validated in English, Iranian and finish in post cardiac surgery, trauma, burned and neurological ICU. The NVPS has good inter-rater agreement and discriminant validity (Cronbach α coefficients ranged from 0.36 to 0.75 and ICC ranged from 0.60 to 0.76)
(Birkedal et al., 2021)	Comparison of two behavioral pain scales for the assessment of procedural pain: A systematic review	Norway	Systematic review	• **Inter-rater reliability**: was validated in 8 studies. 4 of these 8 studies used weighted kappa. BPS kappa varied from [0,73 to 0,94] as for CPOT it changes from [0,70 to 0,96]. • **Internal consistency:** 7 studies used Cronbach (α) BPS [0,74-0,90] and CPOT [0,70-0,93]. • **Discriminant validity** :6 studies used different analyses method • **Criterion Validity**: it was cited in 3 studies. In 1 of them BPS and CPOT were associate to self-reported pain and (p ⟨ 0,5)
(Cade, 2008)	Clinical tools for the assessment of pain in sedated critically ill adults	UK	Systematic review	• **BPS:** reliability and validity were discussed in 3 studies They showed that this tool's construct validity was higher during painful procedures. For internal consistency 2 studies calculated Cronbach(α) and it was greater than 0,64. • **CPOT:** In one study, construct validity (paired t-test) demonstrates this tool scores increased during positioning. For the inter-rater reliability, weighted Kappa coefficient changed from 0,52 to 0,88 during various procedures. • **ONVPS:** one study showed that inter-rater reliability Coefficient (α) =0,78. There was no information about internal consistency. For criterion validity, a correlation between FLACC and NVPS was calculated "Pearson's correlation = 0,86") (p <0,05).
.(Chanques et al., 2009)	Assessing pain in non-intubated critically ill patients unable to self-report: an adaptation of the Behavioral Pain Scale	France	Observational psychometric study	• **BPS-NI:** - Internal consistency Cronbach (α) = 0.79 - Inter-rater reliability weighted Kappa coefficient varies from 0,82 to 0,89 - Discriminant validity: high scores were observed during painful procedures. There wasn't any change in scores in non-painful procedures.

(Chanques et al., 2014)	Psychometric comparison of three behavioural scales for the assessment of pain in critically ill patients unable to self-report	USA	Descriptive cohort study	• **BPS and BPS-NI:**
				  - Internal consistency: Cronbach (α)=0,80
				  - Discriminant validation: the score was higher during procedures.
				• **CPOT:**
				  - Internal consistency: Cronbach (α)=0,81
				  - Discriminant validation: the score was higher during procedures.
				• **ONVPS:**
				  - Internal consistency: Cronbach (α)=0,76
				  - Discriminant validation: the score was higher during procedures.

(Chatelle et al., 2008)	Mesurer la douleur chez le patient non communicant	Belgium	Systematic review	• **PAINAD:** was developed to assess pain in patients with advanced dementia. • **BPS:** is a validated pain assessment tool. It includes the following items body movements and respiratory rate. • **DPS:** still in the validation stage. This pain scale evaluates face, respiratory rate and tears.

(Creek, 2019)	Pain assessment tools for the non-verbal critical care adult : an integrative review of the literature	USA	Integrative review of the literature	• **BPS:**
				  - Discriminant validity: remarkable increase during nociceptive periods
				  - Construct validity: 4 studies showed that there was a big difference between scores in rest and painful procedures
				  - Criterion validity: 2 studies showed that there was a correlation between BPS and self-report
				  - Internal consistency: In 8 studies, Cronbach(α) varies from 0,70 to 0,95
				  - Inter-rater reliability: 4 studies showed good agreement
				• **BPS-NI:**
				  - Internal consistency: 1 study showed internal consistency >0,70
				  - Inter-rater reliability: Kappa > 0,60
				  - Validity: low
				• **CPOT:**
				  - Construct validity: high during painful procedures
				  - Discriminant validity: 5 studies showed that it was high during nociceptive periods
				  - Criterion validity: average correlation to self-report (r=0,419, p<0,01)
				  - Internal consistency: Cronbach (α) changes from 0,70 to 0,95
				  - Inter-rater reliability: it was found to be moderate to good
				• **ONVPS:**
				  - Discriminant validity: it was supported by 6 studies
				  - Criterion validity: it was low in physiology item
				  - Inter-rater reliability: 2 studies showed that Kappa varies between 0,71 and 0,80.
				• **RNVPS:**
				  - Criterion validity: these items were high during self-reporting pain "physiology 1: (19,8%)" and "physiology2: (40%)"
				  - Discriminant validity: high in painful procedures
				  - Internal consistency: Cronbach (α)> 0,70
				  - Inter-rater reliability: good
				• **PAINAD:**
				  - Inter-rater reliability: ICC=0,80
				• **NPAT:**
				  - Validity: moderate
				  - Internal consistency: Cronbach (α)>0,70

(Dorji, 2019)	Implementation and Evaluation of Critical Care Pain Observation Implementation and Evaluation of Critical Care Pain Observation Tool (CPOT)	USA	descriptive study	• **Inter-rater reliability:** agreement of 93,3%. • **Validity:** 97,95% of nurses agreed that CPOT is a valid tool.

(Favaretto & Carraro, 2015)	Gli strumenti di valutazione del dolore per il paziente critico non comunicante in terapia intensiva. Revisione di litteratura	Italy	systematic review	• **BPS:**
				  - Inter-rater reliability: good
				  - Discriminant validity: valid
				• **CPOT:**
				  - Inter-rater reliability: good
				  - Discriminant validity: most valid
				• **RNVPS:**
				  - Inter-rater reliability: low
				  - Discriminant validity: valid

(Goe, 2018)	Evaluation of a Critical-Care Pain Observation Tool Quality Evaluation of a Critical-Care Pain Observation Tool Quality Initiative	USA	Retrospective pre and post design	• The frequency of pain assessment documentation by nurses was higher after the implementation of CPOT. • No difference was found in the use of analgesic and sedatives in the pre and post implementation groups. • There wasn't any remarkable change in patient's outcome.

(Juarez et al., 2010)	Comparison of Two Pain Scales for the Assessment of Pain in the Ventilated Adult Patient	USA	Study expanded upon a pilot study	• **BPS:**
				  - Reliability: Cronbach (α)=0,70
				• **RNVPS:**
				  - Reliability: Cronbach (α)=0,75
				• Scores were higher in surgical patients than medical patients.
				• Scores were higher during turning compared to rest in both pain scales.

(Kabes et al., 2009)	Further Validation of the Nonverbal Pain Scale in Intensive Care Patients	USA	Nonexperimental and methodological. Observational	• **ONVPS:**
				  - Inter-rater reliability: 94.7% agreement.
				  - Internal consistency: Cronbach (α) was high during procedures and after 0,62. Before procedures (α)= 0,36
				  - Validity: Valid
				• **RNVPS:**
				  - Inter-rater reliability: 90.8% agreement.
				  - Internal consistency: before procedures Cronbach (α)=0,36 during (α) =0,72 and after (α)=0,71
				  - Validity: valid. Mean rank is high during procedures.

(Keane, 2013)	Validity and reliability of the Critical Care Pain Observation Tool: A Validity and reliability of the Critical Care Pain Observation Tool: A replication study	USA	Cohort study	• **Inter-rater reliability**: weighted Kappa varies from 0,34 to 1,0 • **Discriminant validity:** The score was higher during nociceptive periods

(Li et al., 2008)	A Review of Objective Pain Measures for Use with Critical Care Adult Patients Unable to Self-Report	USA	Critical review	• **BPS:**
				  - Construct validity: the score was high during painful procedure P .01
				  - Internal consistency: Cronbach's 0.6444; 0.721)
				  - Inter-rater reliability: It was not consistent between 3 studies
				• **CPOT:**
				  - Criterion validity: not confirmed
				  - Internal consistency: no data
				  - Inter-rater reliability: good agreement,
				• **ONVPS:**
				  - Construct validity:
				  - Internal consistency: good coefficient of 0.78.
				  - Inter-rater reliability: no information.

(Paulson-Conger et al., 2011)	Comparison of Two Pain Assessment Tools in Nonverbal Critical Care Patients	USA	Descriptive, comparative, prospective design	• **Internal consistency:**
				  - CPOT: 0,76.
				  - PAINAD: 0,80.
				• The correlation between the PAINAD and CPOT was 0.86 (p < 0,01).
				• The correlation between the average of the two scores and their difference was 0.27 (p < 0 .05).

(Pereira, 2016)	Acute Pain Symptom Assessment and Management in Nonverbal Puerto Rican Patients in the Early Postoperative Period	USA	Cohort study	• CPOT and RNVPS are positively correlated:
				  - Upon arrival to PACU: correlation coefficient r=0,88.
				  - After 120 minutes r=0,89.

(Ross et al., 2016)	Validation of the Critical-Care Pain Observation Tool with Seriously Ill Patients	Canada	Prospective cohort study	• **Inter-rater reliability:** ICC > 0,75 "all procedures nociceptive and non-nociceptive". • **Discriminant validity:** non difference in scores before, during and after gentle touch, it was different during turning procedures "Friedman test".
(Salamat et al., 2021)	A Systematic Review of Pain Assessment in	Iran	Systematic Review	• **CPOT**

	Mechanically Ventilated Patients			- The internal consistency: Cronbach (α) varies between 0.56 and 0.94 - Inter-rater reliability: (Intraclass Correlation Coefficient) ICC = 0.56 in one study, but it was good in three studies (ICC ≥ 0.91) • **BPS** - The internal consistency: Cronbach (α) > 0.7 in six studies and < 0.70 in two studies, also it was cited in two studies that (α)=0.950 - Inter-rater reliability: (Intraclass Correlation Coefficient) ICC > 0.86 • **RNVPS** - The internal consistency: Cronbach (α) > 0.70 - Inter-rater reliability: (Intraclass Correlation Coefficient) ICC > 0.68 in two studies.
(Severgnini et al., 2016)	Accuracy of Critical Care Pain Observation Tool and Behavioral Pain Scale to assess pain in critically ill conscious and unconscious patients: prospective, observational study	Italy	Prospective, observational study	• CPOT and BPS showed a good criterion and discriminant validity (p < 0.0001). • BPS is more specific (91.7 %) than CPOT (70.8 %), but less sensitive (BPS 62.7 %, CPOT 76.5%). • COPT and BPS scores were significantly correlated with VAS (p < 0.0001).
(Stites, 2013)	Observational Pain Scales in Critically Ill Adults	USA	Review of the Literature	• **CPOT**: - Criterion validity: the score was low in patients that denies pain - Discriminate validity: the scores were high during stimulus. - Inter-rater reliability: In two studies Kappa varies between 0,52 and 0,88. • **BPS**: - Discriminant validity: the score was high during painful stimulation - Construct validity: there was a correlation between BPS and NRS - Inter-rater reliability: Cronbach (α)=0,94 - Internal consistency: Cronbach (α)> 0,63
				• **NVPS**: - Discriminant validity: no data - Construct validity: correlation of NVPS and NRS poor, 0.38. - Inter-rater reliability: in both the ONVPS and RNVPS, the score levels were high during painful periods. - Internal consistency: Cronbach (α)= 0.80 • **NPAT**: - Validity: weak - Inter-rater reliability: concordance coefficient=0.72; 95% confidence interval
(Tapp et al., 2019)	Observational Pain Assessment Instruments for Use with Nonverbal Patients at the End-of-life: A Systematic Review	Canada	Systematic Review	• **CPOT**: It was invented by Gelinas et al in 2007. • **PAINAD**: - Good agreement in the following domains: facial expression, vocalization and body language. - Good indicator: physical item - Less good indicators: were the following categories: breathing, consolability, behavioural and physiological changes.
(Val et al., 2009)	Evaluation de la douleur chez le patient non communicant en Unité de Soins Intensifs	Belgium	Cohort	• **Internal consistency** : [0,559 - 0,637]
(Weldon, 2017)	Comparison of the Behavioral Pain Scale and the Critical-Care Pain Observation Tool in Assessing Pain in Ventilated Critical Care Patients	USA	Non-experimental, correlational, comparative design	• **CPOT**: Cronbach (α) =0,921 • **BPS**: Cronbach (α) =0.95 • CPOT and BPS scores were higher during turning.
(Young et al., 2006)	Use of a Behavioural Pain Scale to assess pain in ventilated, unconscious and/or sedated patients	Australia	Prospective, descriptive repeated measures study design	• **Internal consistency**: The Cronbach's alpha value for the BPS was 0.64, indicating moderate to good reliability • **Inter-rater reliability:** - Before procedures: good agreement (82% to 91%) - After procedures: low agreement "eye care range between 64% and 73%" and "after repositioning: ranging between 36% and 46%."

Quality assessment

Table III: Quality appraisal of included studies.

Reference	1	2	3	4	5	6	7	8	9	10	11	12	total
(Al Darwish et al., 2016)	Y	Y	Y	Y b-Y	a-Y b-C	a-Y	Y	Y	Y	Y	Y	Y C:1 N:0	Y:13
(Azevedo-Santos & DeSantana, 2018)	Y	C	Y	N	Y	Y	Y	Y	Y	Y		C:1 N:1	Y:8
(Birkedal et al., 2021)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		C:0 N:0	Y:10
(Cade, 2008)	Y	C	Y	C	Y	Y	Y	Y	Y	Y		C:2 N:0	Y:8
(Chanques et al., 2009)	Y	Y	Y	Y b-Y	a-Y b-C	a-Y	Y	Y	Y	Y	Y	Y C:1 N:0	Y:13
(Chanques et al., 2014)	Y	Y	Y	Y b-Y	a-Y b-C	a-C	Y	Y	Y	Y	Y	Y C :2 N :0	Y :12
(Chatelle et al.2008)	Y	C	N	C	Y	Y	Y	Y	Y	Y		C:2 N:1	Y:7
(Creek,2019)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y		C:0 N:1	Y:9
(Dorji, s. 2019)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		C:0 N:0	Y:10
(Favaretto & Carraro, 2015)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y		C:0 N:1	Y:9
(Goe, 2018)	Y	C	Y	Y	Y b-Y	a-Y	C	Y	Y	Y	Y	C:2 N:0	Y:10
(Juarez et al., 2010)	Y	Y	Y	Y b-Y	a-Y b-Y	a-Y	Y	Y	Y	Y	Y	Y C:0 N:0	Y:14
(Kabes et al., 2009)	Y	C	Y	Y b-C	a-C b-C	a-Y	Y	Y	Y	Y	Y	Y C:4 N:0	Y:10
(Keane, 2013)	Y	Y	Y	Y b-Y	a-Y b-Y	a-Y	Y	Y	Y	Y	Y	Y C:0 N:0	Y:14
(Li et al., 2008)	Y	C	Y	C	Y	Y	Y	Y	Y	Y		C:2 N:0	Y:8
(Paulson-Conger et al., 2011)	Y	Y	Y	Y b-Y	a-Y b-Y	a-Y	Y	Y	Y	Y	Y	Y C:0 N:0	Y:14
(Pereira,2016)	Y	Y	Y	Y b-Y	a-Y b-C	a-Y	Y	Y	Y	Y	Y	Y C:1 N:0	Y:13
(Ross et al., 2016)	Y	Y	Y	Y b-Y	a-Y b-C	a-Y	Y	Y	Y	Y	Y	Y C:1 N:0	Y:13
(Salamat et al., 2021)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		C:0 N:0	Y:10
(Severgnini et al., 2016)	Y	Y	Y	Y b-Y	a-Y b-C	a-Y	Y	Y	Y	Y	Y	Y C:1 N:0	Y:13
(Stites, 2013)	Y	N	C	N	Y	Y	Y	Y	Y	Y		C:1 N:2	Y:7
(Tapp et al., 2019)	Y	Y	N	Y	Y	Y	Y	Y	C	Y		C:1 N:1	Y:8
(Val et al., 2009)	Y	Y	Y	C a-Y	a-Y b-Y	a-C	Y	Y	Y	Y	C	Y C:3 N:0	Y:11
(Weldon,2017)	Y	Y	Y	Y	Y b-C	a-Y	C	Y	Y	Y		C:2 N:0	Y:9
(Young et al., 2006)	Y	Y	Y	Y b-Y	a-Y b-N	a-C	Y	Y	Y	Y	Y	Y C:1 N:1	Y:12

Y: yes, C: can't tell, N: no CASP checklists were used to assess the quality of included studies. Studies scored good quality are the studies that don't contain any "no" answers. Studies scored average quality, are the studies which contains 1 "no" answer. Studies scored low quality are the studies which contains 2 or more "no" answers.

Table IV: Selected assessment tools and their domains.

Pain scales	Domains	Scoring	Total scoring
BPS	Facial expressions Movements of upper limbs Compliance with ventilation	1-abr 1-abr 1-abr	3-dic
BPS-NI	Facial expressions Movements of upper limbs Vocalization	1-abr 1-abr 1-abr	3-dic
ONVPS	Face Activity Guarding Physiologic 1 Physiologic 2	0-2 0-2 0-2 0-2 0-2	0-10
RNVPS	Face Activity Guarding Physiologic Respiratory	0-2 0-2 0-2 0-2 0-2	0-10
CPOT	Facial expression Body movements Compliance with the ventilator or vocalization Muscle tension	0-2 0-2 0-2 0-2	0-8
NPAT	An affective response to a situation Change in placement and positioning of the body and extremities when not engaged in any care activities Sound cues or vocalizations other than speech Expressions on face Body responses that imply a protection of the body from contact with external touch	0-2 0-3 0-2 0-2 0-3	0-12
PAINAD	Breathing Negative vocalization Facial expression Body language Consolability	0-2 0-2 0-2 0-2 0-2	0-10
DPS	Adaptation au respirateur Expression du visage Comportement moteur Larmes	1-abr 1-abr 1-may 1-feb	abr-15

Behavioral pain scale (BPS):

According to[2], BPS pain scores increased during the painful repositioning procedure comparing to the non-painful eyecare procedure, they also made a reference to the fact that changes in BPS score during eye care is a result of autonomic responses to touch not pain since patients had not any facial trauma or facial surgery. These findings are consistent with those reported by[3-8] researches who found also that BPS scores increases significantly between painful and non-painful situations, which supports BPS discriminant validity. The research of[2] supported also the validity of BPS with logistic regression analysis, which showed that the odds of an increase in BPS score was 25 times higher for repositioning as a painful procedure compared with eye care as a non-painful procedure.

Regarding the reliability of BPS[2] revealed that due to small numbers of data, it was not realizable to conduct formal tests of reliability. Inter-rater reliability results showed that it was easier for two assessors to agree on the level of low pain but when assessing increased pain level some variance was found when using the BPS. The research of 9 showed that the BPS met the homogeneity criterion for reliability indicator. And it has shown an evident Inter-rater reliability. In the study of[4], it was found that the reliability of BPS was nearly perfect (kappa coefficient: 0.81 ± 0.03).

Behavioral pain scale non intubated (BPS-NI):

The discriminative validation was supported in the study of[4] by the significant increasing of the median BPS-NI value from rest to nociceptive procedure. The good internal consistency was supported by α Cronbach value (standardized Cronbach α = 0.79), which means that BPS-NI items were well correlated between them. The discriminant validity of this tool was supported in the study of[4] by the increasing of its median score from baseline to nociceptive procedure (p < 0.001) and a significant decrease 10 minutes after the nociceptive procedure (p < 0.001).

In the study of[4] the inter-rater reliability was evaluated by weighted kappa coefficients and it was nearly perfect for BPS. The weighted kappa coefficients for each domain were as following, for the facial domain, it was 0.75 which is considered as an excellent kappa, for the vocalization domain, it was 0.78 which is considered as an excellent kappa, and finally the upper limb domain with a good kappa of 0.61. In the study of[7], it was found that inter-rater agreement was 96% for the BPS-NI scores for both types of procedures (nociceptive and non-nociceptive) and 90% for the BPS-NI scores for painful procedures only, which is considered as a good inter-rater reliability.

Original non verbal pain scale (ONVPS):
[8]found that this ONVPS tool was not adequately tested. The developers of this tool compared the ONVPS with the FLACC as a 'gold standard', while the FLACC was not a validated tool among adult population. Which is not rational in principle. The authors[10] found that the physiologic II item was not discriminant at an acceptable level because it showed a small variation between before, during, after a nociceptive procedure. Regarding the internal consistency, it was found in the study of[4] that NVPS internal consistency was low in non-intubated non-verbal patients. Therefore, this tool was not validated for non-intubated non-verbal ICU patients.

In the study of[4], the domains of ONVPS were evaluated by weighted kappa coefficients to examine the inter-rater reliability of this tool. The essential results were as following: for the respiration and activity domain, it was 0.54 and 0,52 respectively, which is considered a moderate kappa. For the guarding domain, it was a poor kappa of 0.32, and finally the physiologic II domain which had a very poor kappa of 0.02. Generally, the ONVPS demonstrated poor to just moderate inter-rater reliability.

Revised non-verbal pain scale (RNVPS):
In the study of[11], it was found that the RNVPS showed satisfactory validity, with a Cronbach α = 0.86. The Physiology and Respiratory domains showed low psychometric properties evidence, they were not detecting pain. The studies of[4,6] showed that this tool is discriminant valid, since there was a significant difference in median scores during two similar situations which differs by the intensity and the length of the procedures.

The RNVPS was reliable according to[12], with a Cronbach α coefficient of 0.89. And this result is consistent with the findings of[11], who found a Cronbach α coefficient of 0.86. In the study of[6], it was shown that this instrument had also a good inter-rater reliability with an ICC=0.92 and ICC = 0.68 in two different surveys.

Critical care pain observation tool (CPOT):
The CPOT is the most discussed instrument in the 25 included studies. Its evidence of reliability and validity were clearly represented in the studies of[4,13]. In the study of[13], it was found that the validity of this tool was supported by the Friedman test results, which showed in the first hand that CPOT's score had negligible differences before, during and after a non-nociceptive procedure (gentle touch). While on the other hand, it showed a very significant difference in the same three times during turning procedure considered as painful situation. The study of[4] showed that CPOT's validity was supported by the significant increasing of its score from rest time to nociceptive procedure (P<0.001) and a decreasing 10 min after the procedure. And regarding the responsiveness, it was tested by the effect size coefficient which was large (>0.80). Reference must be made to the fact that in spite of all CPOT advantages,

it has some limitations, essentially: its use among traumatic brain injured patients who present different facial expressions in comparison with the other patients when experiencing pain[3]. Therefore, more studies are necessary to generalize the use of this tool in ICUs.

Inter-rater reliability of CPOT was tested in the research of[4] using the weighted kappa coefficients, and results were as following: for the facial category the coefficient was 0.81 which represents an excellent kappa, for the breathing domains, the kappa was 0.71 which is a good kappa, and finally the body movements and muscle tension domains with a moderate kappa of 0.42 and 0.43 respectively. In the study of[13], the reliability was tested with the interclass coefficient correlation (ICC), the results were as following: the highest ICC was detected before the nociceptive turning procedure, whereas the lowest ICC was observed with assessments related to gentle touch as a non-nociceptive procedure.

Nonverbal pain assessment tool (NPAT):
The authors of[3] and [14] found many limitations in their search essentially there was no information provided about the situations when patients pain were assessed by this tool. Therefore, they suggested that more studies are paramount to test NPAT validity and applicability among non-verbal ICU population. In the study of[12], it was revealed that in spite of the fact that NPAT was developed for non-verbal patients, it has never been validated in this population. Moreover, the NPAT consist of a domain of "verbal cues" which is contradictory with the principle of a nonverbal pain assessment tool.

Pain assessment in advanced dementia scale (PAINAD):
The authors[15] found that interrater reliability of the PAINAD indicated good reliability across many searches with a Pearson r range from 0.75 to 0.97, reference must be made to the fact that most Pearson r ranges over 0.80. They found also that this instrument is discriminant valid since its scores are significantly higher during painful procedures comparing with non-painful procedures. The Validity was also demonstrated by using quality improvement data. The results showed that PAINAD scores before pain medication with dosage according to this tool were 6.7 ± 1.8 and after 30 minutes of pain medication administration were 1.8 ± 2.2. Therefore, PAINAD was considered valid. For[14], this tool needs more assessing of the construct validity, discriminant validity, and internal consistency in the adult critical care setting since PAINAD was developed for a superior reason adults with cognitive impairment.

SOS Doulousi pain scale (DPS) :
This pain assessment tool was not tested enough to examine its psychometric properties evidence, it was validated only by its developer[10], using Wilcoxon test for non-parametric data. The results showed that the pain scores change in three situations differing by the intensity

of the procedure: at rest, non-nociceptive procedure, and during a nociceptive procedure. The scores seemed to increase in accordance with growing discomfort. The authors, also tested the DPS's internal consistency using Cronbach's test which varied from 0.559 to 0.637 depending on the situation[10].

Discussion

In this review, non-verbal pain assessment tools were tested for two paramount psychometric properties: validity and reliability. Some tools showed good evidence of these properties, while some did not. And some showed their evidence among a particular population.

CPOT, the most utilized instrument in the included studies, showed nearly perfect reliability and validity properties. Its validity is supported essentially by the significant increasing of its score from resting time to nociceptive procedure. Its inter-rater reliability showed also good evidence with a moderate to excellent weighted kappa coefficients of its domains. It revealed some limitations among ICU patients with traumatic brain injury, however, for the general ICU non-verbal population, it is recommended to be the first choice.

Concerning BPS, BPS-NI, RNVPS, and PAINAD, all these tools showed good validity and reliability. The BPS score was invented by Payen in 2001. This tool showed good discriminant and construct validity (scores were high during painful procedures compared to non-painful procedures like rest or eye care. For criterion validity, Creek, n.d. showed a correlation between BPS and self-report. In most studies, inter-rater reliability Kappa was higher than 0,67 and internal consistency higher than 0,64. The BPS can be used for patients with traumatic brain injury. The BPS-NI is devoted only to non-intubated patients unable to express their pain. The "compliance with ventilation" domain from BPS score was changed into "vocalization" domain. [7] study showed that BPS-ni's reliability is good (Internal consistency Cronbach (α) = 0.79 and Inter-rater reliability weighted Kappa coefficient varies between 0,82 and 0,89), also the scores were high during painful procedures and there wasn't any change in scores in non-painful procedures which indicates good validity. In the RNCVPS, the physiologic 2 item in the ONVPS was changed to respiratory item. Many authors

support the use of the Revised rather than the original version of the NVPS because it did demonstrate good evidence of psychometric properties. [10] support this score's validity because the mean rank was high during painful procedures. For the reliability, two studies showed an internal consistency Cronbach (α)> 0,70[16] and (Creek, n.d.). PAINAD was adapted from the FLACC and DS-DAT scores. It was developed to assess pain in Non-verbal patients with advanced dementia. This tool has good agreement in the following domains: facial expression, vocalization and body language and good. Inter-rater reliability of this tool was good (ICC=0,80)[17]. Each of these instruments is specific to a certain population in ICU and to generalize them among all adult non-verbal ICU population, more researches and reconstruction of these tools are certainly necessary.

Low evidence of psychometric properties was revealed in each of DPS, NPAT and ONVPS. The first was only validated by its developer, so more studies are necessary to test the validity and reliability among our population. The second tool, despite the fact that it was developed originally for this population, it was never been validated among them, therefore this tool is not recommended to be used. In the developing process of ONVPS, this tool was compared to FLACC as a gold standard, while the FLACC was never validated among our population, we can't consider this instrument valid and reliable. Also[34] study showed that Criterion validity was low in physiology item, witch mean this instrument need more testing.

Conclusion

In a nut shell, this systematic review revealed that. In the one hand, each of DPS, NPAT and ONVPS are considered neither, reliable nor valid since they showed weak evidence of psychometric properties. In the other hand, the CPOT is to be preferred among general non-verbal ICU population since it showed nearly good properties. Concerning, BPS, BPS-NI, RNVPS and PAINAD, it is recommended to use each for its specific population.

Competing interests
The authors certify that there is no conflict of interest.

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SPECIAL ARTICLE

Factores coadyuvantes del desarrollo de la red asistencial de titularidad privada y su panorama actual en las Illes Balears

Factors contributing to the development of the private healthcare network and its current situation in the Balearic Islands

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Resumen

Este estudio exploratorio tiene como objetivo principal proporcionar una visión general de los factores coadyuvantes que han impulsado el crecimiento de la red asistencial privada en las Islas Baleares. La metodología empleada se basa en la triangulación de datos obtenidos de diversas fuentes oficiales, lo que permite una comprensión más completa y contextualizada de la situación actual de la atención sanitaria en esta región. Los resultados de la investigación indican que varios factores han contribuido al desarrollo de la atención médica privada en las Illes Balears. En primer lugar, se destaca el desarrollo tardío de la infraestructura pública sanitaria en España como un factor influyente. Además, se identifica el espíritu asociativo de carácter local, que se deriva de las estructuras gremiales, como una respuesta a las necesidades esenciales de la población. Por último, se subraya el crecimiento socioeconómico resultante de la intensa actividad turística en el archipiélago como un factor clave en este desarrollo.

Palabras clave: Sanidad privada, salud, Islas Baleares, situación actual.

Abstract

This exploratory study aims to provide a comprehensive overview of the contributing factors that have driven the expansion of private healthcare services in the Balearic Islands. The methodology is grounded in the triangulation of data from various official sources, enabling a more complete and contextualized understanding of the current healthcare landscape in this region. Research findings indicate that several factors have played a significant role in the development of private medical care in the Balearic Islands. Firstly, the delayed development of the public healthcare infrastructure in Spain is identified as an influential factor. Additionally, the spirit of local associativity stemming from guild-like structures is recognized as a response to essential population needs. Finally, the socioeconomic growth resulting from the intense tourist activity in the archipelago is underscored as a key driver of this development.

Key words: Private healthcare, Balearic Islands, health, current situation.

Introducción

El archipiélago de las Illes Balears se encuentra ubicado en el Mediterráneo occidental, abarcando una extensión de 5.040 km². Está compuesto por cuatro islas principales: Mallorca, Menorca, Ibiza y Formentera. De una población total de 1.176 millones, Mallorca, la isla más grande, concentra el 78 % de la población, con una densidad de 255 hab./km² (IBESTAT, 2022). El clima es típicamente mediterráneo, con una temperatura media anual de aproximadamente 18 grados Celsius. Desde mediados del siglo XX, estas islas se han destacado por el auge turístico, consolidándose como uno de los destinos turísticos más importantes en la actualidad. En el año 2022, visitaron las islas 16.5 millones de turistas, cifra que se coloca muy cerca de las cifras previas a la pandemia de la Covid-19.

La estructura económica y productiva de las Illes Balears, a mediados del siglo XX, ha experimentado una transformación significativa, evolucionando de una economía predominantemente agraria y poco industrializada a una economía de servicios centrada en su principal industria: el turismo.

Hoy en día, esta comunidad es conocida mayoritariamente por sus atractivos paisajísticos, su clima y su infraestructura turística. No obstante, uno de sus puntos fuertes radica también en su red asistencial, tanto pública como privada. En particular, la infraestructura sanitaria de titularidad privada merece especial atención, al prestar ésta, servicios a un elevado porcentaje de la población residente y a los visitantes extranjeros, aportando un plus de seguridad al destino turístico. La infraestructura sanitaria privada ha alcanzado su apogeo a lo largo del siglo XX y continúa en expansión constante en términos de vanguardia tecnológica y profesional.

¿Cuáles son los factores que han influido para que la red de titularidad privada tenga tanta relevancia en la actividad asistencial de las Illes Balears? A lo largo de este estudio exploratorio, se busca dar respuesta a esta cuestión enumerando los factores que han propiciado e impulsado el estatus actual de la sanidad de titularidad privada en el sistema sanitario de las Illes Balears. Junto con ello, además para resaltar su importancia y dimensionamiento se acompaña de un breve acercamiento a su panorama actual.

Metodología y fuentes del estudio

La metodología empleada para esta investigación exploratoria se fundamenta en un riguroso análisis de contenido de diversas fuentes relacionadas con la materia. En primer lugar, se llevó a cabo una revisión exhaustiva de literatura y artículos científicos relacionados con el tema, con el fin de obtener una comprensión integral de los aspectos clave que influyen en el desarrollo de la red asistencial privada en la región. Posteriormente, se procedió a la recopilación de información de la hemeroteca provincial, disponible en Internet, así como informes de instituciones tanto públicas como privadas en el ámbito de la salud en las Illes Balears.

La triangulación de la información obtenida de estas diversas fuentes permitirá identificar patrones y tendencias que incidan en el desarrollo de la red asistencial privada en la comunidad, contribuyendo así a una comprensión más completa y contextualizada de la situación actual.

Factores coadyuvantes del desarrollo de la red asistencial de titularidad privada en las Illes Balears

Seguidamente, se presentan los factores que se consideran han propiciado la evolución y el crecimiento de la sanidad de titularidad privada que actúa también como palanca de seguridad del destino turístico y que han contribuido a que el peso, en actividad, y en número de población cubierta por seguro privado, sea uno de los más altos de España.

Sociedades de Socorro Mutuo y las Mutuas de Previsión Social

De acuerdo con Pons (1998), en el primer tercio del siglo XIX se fueron implantando en el territorio español asociaciones que tenían como antecedentes las *Hermandades de Socorro y los Montepíos*, y estaban esencialmente constituidas por trabajadores. Su principal interés era cubrir las necesidades relacionadas con el bienestar, principalmente enfermedad, entierro, vejez, etc., que el Estado en aquellos momentos no cubría. Las Sociedades de Socorro Mutuo tenían como objetivo principal, *"proporcionar asistencia médica a sus asociados y a sus familias. Son, por tanto, mutuas de seguro, aunque complementan este objetivo con otras actividades de entretenimiento e instrucción"* (Pons, 1998, pp.83-84). Eran entidades muy vinculadas al territorio y de carácter eminentemente local.

En las Illes Balears, en el período que va de 1887 a 1923, se pasó de 38 asociaciones de socorro mutuo a 133, es decir, en aproximadamente 40 años se incrementaron en un 250 % el número de éstas. Entre las más importantes destacan: *la Protectora, la Juventud Palmesana, la Protección Artística, la Asistencia Palmesana y la Sociedad de Socorros Mutuos* entre oficiales carpinteros, ebanistas y silleros. Todas ellas en la ciudad de Palma.

Como característica, se menciona su carácter local, cuestión que estimuló la aparición de las mismas en la *part forana*. En un primer momento, en pueblos con desarrollo vitícola, como Felanitx, Porreres y Binissalem, o industrial, como son los casos de Sóller, Llucmajor, Inca, Alaró y Lloseta. Entre las destacables de la *part forana*, estarían: la *Protectora de Felanitx* y la *Constancia de Inca*.

Una característica a destacar es que se desarrollaban en epicentros de alta actividad económica, como evidencia el hecho de que en poblaciones como Felanitx y Sóller contaran con sus respectivas instituciones financieras (*Banco de Felanitx*, fundado en 1883 y *Banco de Sóller* en 1899). Estos dos bancos perduraron hasta los años cuarenta del siglo XX.

A principios del siglo XX, estas sociedades entraron en un proceso de declive por diversas razones y fueron sustituidas por *Entidades de Previsión Social*. La participación del Estado se hizo más intensiva, apareciendo los seguros sociales obligatorios. En primera instancia, *"se creó el retiro obrero (R.D de 11 de marzo de 1919), el subsidio obligatorio de maternidad (decreto ley del 22 de marzo de 1929) y el de accidentes de trabajo de 8 de octubre de 1932"* (Pons, 1998, p.116), este último gestionado por las mutuas patronales. Sin embargo, siguieron coexistiendo las *Sociedades de Socorro Mutuo*, que se transformaron en entidades mercantiles.

Durante los años treinta del siglo XX, surgieron en las Illes Balears nuevas asociaciones que cubrían las necesidades médicas. Dichas entidades podían tener un carácter local o provincial. Por ejemplo, en la ciudad de Esporles se fundaron la *Mutualidad Quirúrgica Esporlense* en 1929 y la *Mutualidad Quirúrgica Obrera Esporlense*, que la sustituyó. Otro ejemplo, pudo ser la *Unión de Consell* para la asistencia médica, creada en 1934. En cuanto a las provinciales, mencionar la *Mutua Médica Balear*, constituida en 1935. Su cuadro asistencial estaba compuesto por profesionales médicos de reconocido prestigio, algunos de los cuales se distinguieron por estar vinculados a la creación de centros sanitarios o sociedades de seguros, o ambos a la vez (ver **tabla I**).

Tabla I: Listado de médicos de la *Mutua Médica Balear*.

Dr. Guillermo Ribas	Dr. Bartolomé Darder Hevia
Dr. Onofre Juaneda	Dr. Jaime Escalas
Dr. Sebastián Villalonga	Dr. Pedro Giménez
Dr. José Mir	Dr. Jaime Rover Motta
Dr. Enrique Cervera	Dr. Andrés Muntaner
Dr. Ramón Rotger	Dr. Juan Cervera

Fuente: Elaboración propia a partir de Pons (1998).

Las infraestructuras sanitarias entre finales del siglo XIX y principios del XX

Vilar-Rodríguez y Pons (2016) describen la evolución de la red asistencial de los centros sanitarios en el siglo XIX y primera mitad del XX en el territorio español.

Señalan las autoras que España no tenía, antes de la guerra civil española (1936-1939), una estructura hospitalaria que mantuviera cierta coherencia. La iniciativa de implementación de los centros era tanto pública como privada.

En el siglo XIX existían centros de beneficencia pública, en los que se atendía a las clases menos favorecidas, financiados primeramente, por los Ayuntamientos y

más adelante por las Diputaciones. Convivían con éstos también los hospitales militares, financiados con presupuestos estatales para atender a los oficiales y a la tropa. Financiados por fondos privados, estaban las clínicas y centros de iniciativa individual o colectiva.

A fin de constatar lo expuesto y a modo de ejemplo, en el caso de la isla de Mallorca, se postulaba como hospital de beneficencia el *Hospital General en Palma* que en 1715 a raíz de sus vicisitudes económicas, fue financiado por el Ayuntamiento. Posteriormente, en 1840, pasó gestionarse por la *Diputación Provincial de Balears.*

Un ejemplo de iniciativa privada fue la *Clínica Juaneda* fundada por el *Dr. Onofre Juaneda Salom* en 1917. Sin embargo, en 1937, pasó a manos del ejército pasándose a llamar, *Clínica Naval* e integrándose en la estructura militar. En 1958, vuelve a manos del hijo del fundador, Juan Juaneda. Como iniciativa privada también destaca en esta época, la *Clínica Planas*, fundada en 1927 por el *Dr. Vicente Planas Rosselló*.

La Guerra Civil supuso un paréntesis muy importante en muchos aspectos tanto sociales como económicos; también, como no, tuvo su lógica influencia en la evolución de la atención sanitaria y creación de sus infraestructuras. Al finalizar, España era uno de los pocos países europeos que no contaba con un seguro obligatorio de enfermedad. No fue hasta 1942 en que se publica en la *Ley de 14 de diciembre de 1942 por la que se crea el seguro obligatorio de enfermedad -SOE-* (BOE, 1942, p.10592-10597). En este sentido, la Ley, entre otros objetivos, pretendía cubrir las necesidades del colectivo al que la propia ley denominaba *"productores económicos débiles"*. Un reglamento posterior definirá del conjunto de trabajadores tanto por cuenta propia y ajena, quienes son candidatos a ser considerados como tales. El organismo asegurador, era el *Instituto Nacional de Previsión* (INP), creado en 1908, siendo presidente *Antonio Maura*. Entre otras coberturas, estaban la atención médica y la especializada. Las prestaciones podían llevarse a cabo por: La llamada *Obra 18 de Julio*, que era una entidad nacional-sindicalista creada en el 1940 para llevar a cabo la política sanitaria del momento. Por centros públicos de carácter estatal, provincial o local y por instituciones privadas (cajas de empresas, mutualidades e igualatorios médicos). A pesar de la coyuntura socioeconómica del momento, se fue tejiendo la red sanitaria pública de todo el país. Así se señala en la *Orden Ministerial de 19 de enero de 1945, en el Plan Nacional de Infraestructuras Sanitarias (PNIS)*, y en la *Orden de 5 de julio de 1945*, normativa ejecutora del PNIS (Villar-Rodríguez y Pons, 2016).

Según el *Instituto Nacional de Previsión*, el PNIS se debía ejecutar en dos etapas de cinco años cada una y supondría la construcción en la geografía española de 86 residencias de 100 a 500 camas, 149 ambulatorios completos y 110 reducidos y 73 instituciones maternales. Para ello, se trasladó personal técnico a EEUU para

conocer sus infraestructuras y posteriormente asesorar en los proyectos.

No obstante, como consecuencia de la situación económica y social del país, dos años después, el PNIS tuvo que revisarse (Villar-Rodríguez y Pons, 2016). Se pasó de las 86 residencias y 149 ambulatorios proyectados a 68 y 62, respectivamente. Y las maternidades se integraron a los centros hospitalarios, desapareciendo como entidad singular.

En las Illes Balears, bajo el PNIS, se iniciaron las siguientes obras (ver **tabla II**):

Tabla II: Proyectos del PNIS en Illes Balears.

Emplazamiento	Camas	Proyecto	Año inicio de obras	Empresa
Maó	122	Martín José Marcide	1949	Empresa Ramón Beamonte
Palma	379	Martin José Marcide	1950	Empresa Huarte y Cía.

Fuente: Elaboración propia a partir de Villar-Rodríguez y Pons (2016).

El *Hospital de Palma* fue inaugurado 16 de noviembre de 1955, con el nombre inicial de *Residencia Sanitaria Virgen de Lluc*. Finalizó su ciclo de vida en el año 2011, dando paso al nuevo hospital de referencia, el *Hospital Son Espases*.

Tuvieron que pasar más de 40 años para que se construyera un segundo hospital gestionado por el *Instituto Nacional de la Salud* (INSALUD), el Hospital Fundación de Manacor que abrió sus puertas en abril de 1997.

El *Hospital Verge del Toro* en Maó (Menorca) entró en servicio en 1955 y se mantuvo hasta 2007 en que fue sustituido por el nuevo *Hospital Mateu Orfila*.

Desde la promulgación de dicha ley, la iniciativa privada fue tejiendo, en la comunidad balear, una red de centros para cubrir las necesidades de la población residente y en un futuro inmediato se abriría también a los turistas que empezaban a visitar el destino Illes Balears.

En la **tabla III** se relacionan los centros con internamiento de iniciativa privada inaugurados en el período comprendido entre 1942 a 1955. En la misma se puede apreciar el origen de las iniciativas: Tres de carácter eminente privado como la *Clínica Mare Nostrum*, la *Clínica Femenia* y la *Clinica Rogter* y dos pertenecientes organizaciones sin ánimo de lucro, el *Hospital Cruz Roja* y el *Hospital San Juan de Dios*.

La actividad turística y el crecimiento socioeconómico

La relación entre el desarrollo turístico y el crecimiento socioeconómico de las Illes Balears es innegable. El turismo ha desempeñado un papel esencial en la economía de la región, generando un crecimiento socioeconómico palpable.

El crecimiento del turismo en las Illes Balears se ha producido en varias etapas a lo largo del siglo XX. A partir de la década de 1960, las islas se convirtieron en un destino destacado para el turismo de masas, atrayendo a visitantes nacionales e internacionales (ver **Figura 1**).

Tabla III: Centros con internamiento de iniciativa privada (1942-1955).

CENTRO	AÑO INAUGURACIÓN	FUNDADORES
Clínica Mare Nostrum	1942	Narcís Canals, Gabriel Riera, Bartomeu Planas y Lluís Palliser
Clínica Femenía	1943	Dr. Juan Femenia Perelló
Clínica Rotger	1944	Dr. Ramón Rotger
Hospital Cruz Roja	1949	Cruz Roja Española
Hospital San Juan de Dios	1955	Orden San Juan de Dios

Fuente: Elaboración propia a partir de datos de la UNIÓN BALEAR DE ENTIDADES SANITARIAS (UBES) https://www.ubes.es

Figura 1: Evolución de la demanda turística en Illes Balears.
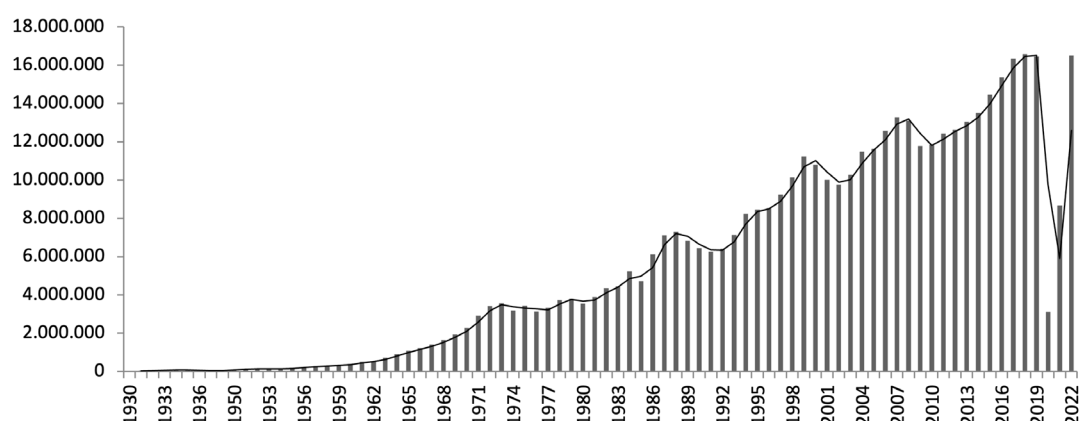
Según datos de (IMPACTUR, 2014), último informe disponible de la época pre-pandemia, cerca del 45% del PIB y uno de cada tres puestos de trabajo en las Illes Balears se generan gracias a la actividad turística. Por tanto, no es banal señalar la importancia del turismo y sus efectos multiplicadores en el ámbito socioeconómico. El turismo ha emergido como un motor económico clave en esta región y ha influido directamente en su crecimiento demográfico, lo que plantea cuestiones relevantes y desafiantes.

En la **figura 2**, se aprecia la dinámica incremental de la población de las Illes Balears. En un período de 25 años, la tasa anual compuesta de crecimiento poblacional ha sido de 1,57%, esto es, 2,24 veces superior a la española (0,70 %).

Figura 2: Comparativa tasa anual de crecimiento de población (1998-2022).
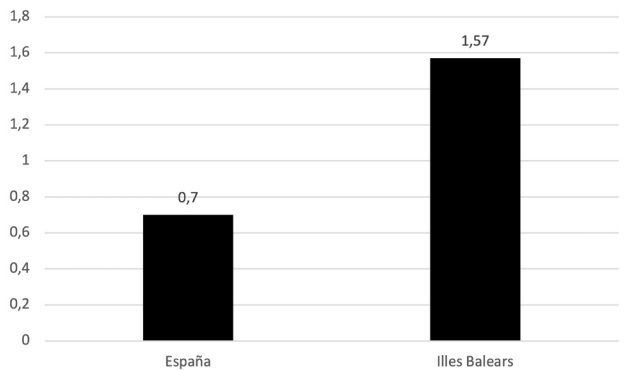
Fuente: Elaboración propia a partir de fuentes estadísticas oficiales

El aumento en la población, impulsado en gran medida por la actividad turística, ha requerido una adaptación constante de las infraestructuras, entre ellas, las sanitarias a fin de satisfacer las necesidades de la comunidad local y de los turistas. Un ejemplo de ello, se produce durante el *primer boom turístico* (Picornell y Picornell, 2002). El *primer boom turístico* en las Illes

Balears, que tuvo lugar entre 1961 y 1973, marcó un período de crecimiento espectacular en la industria del turismo en esta región de España.

Para resaltar el impacto social y económico que supuso el turismo en el período señalado por Picornell y Picornell (2002) se presenta la **tabla IV** en la cual se pueden apreciar distintas variables extraídas del trabajo de (Reig Martínez y Picazo,1998) donde se establece una comparativa de las mismas entre España e Illes Balears en dos períodos. Uno prácticamente anterior al *primer boom turístico* y el otro coincidente plenamente con el mismo.

En el período señalado en términos de tasa de crecimiento poblacional y en renta, se ve un claro despegue muy superior en las Illes Balears respecto a los datos referidos a España. El movimiento migratorio de las Illes Balears también es superior en el intervalo descrito.

El crecimiento demográfico y la expansión y mejora de la infraestructura sanitaria, especialmente de titularidad privada van parejas; coinciden en el tiempo (ver **tabla V**) en el período llamado *primer boom turístico*. Por tal motivo, es importante destacar la puesta en funcionamiento de dos centros cruciales como son la *Policlínica Miramar* en la isla de Mallorca y la *Policlínica Nuestra Señora del Rosario* en Ibiza. Ambas clínicas con una cartera de servicios orientada a residentes y a extranjeros. Señalar así mismo, el caso de la *Clínica Mutua Balear* como respuesta a la atención de contingencias derivadas de accidentes laborales relacionados con la intensiva construcción experimentada durante el auge turístico de la década.

El vínculo entre el crecimiento demográfico y la infraestructura sanitaria en las Illes Balears fue (y es) fundamental. Como se indica en el epígrafe que aparece a continuación, la red asistencial privada ha tenido (y tiene) un papel destacado, brindando servicios de salud a una parte importante de la población residente y ofreciendo seguridad a los turistas.

Tabla IV: Comparativa datos socioeconómicos.

	TASA DE CRECIMIENTO POBLACIÓN		MOVIMIENTOS MIGRATORIOS (en miles)		RENTA PER CÁPITA (media nacional)	
	1955-1964	1964-1975	1955-1964	1964-1975	1955-1964	1964-1975
España	0,94	1,04	-	-	100,00	100,00
Illes Balears	0,97	2,00	19.01	65.24	129,46	148,05

Fuente: Elaboración propia a partir de(Reig Martínez y Picazo,1998).

Tabla V: Relación centros sanitarios de titularidad privada inaugurados en el primer boom turístico.

CENTRO	AÑO INAUGURACIÓN	FUNDADORES
Policlínica Miramar	1969	AMEBA S.A.
P. Nuestra Sra. Del Rosario (Ibiza)	1969	Dr. Julián Vilas
Clínica Mutua Balear	1973	Mutua Balear

Fuente: Elaboración propia a partir de datos de la UNIÓN BALEAR DE ENTIDADES SANITARIAS (UBES) https://www.ubes.es
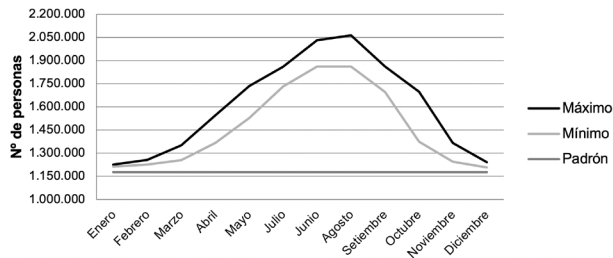Fuente: Elaboración propia a partir de datos oficiales y Picornell y Picornell (2002).

Panorámica actual de la sanidad de titularidad privada en las Illes Balears

El Índice de Presión Humana (IPH) en las Illes Balears es una métrica esencial para comprender la interacción entre el crecimiento demográfico y la estructura sanitaria en esta región española. El IPH es un indicador que refleja la presión ejercida por la población sobre los recursos y servicios disponibles en una determinada área geográfica. En el caso de las Illes Balears, este índice es de gran importancia debido al auge turístico que experimenta la región y su impacto en la infraestructura que presta servicios de salud.

Las Illes Balears son uno de los destinos turísticos más populares de España y Europa. Atraen a millones de visitantes cada año (ver **figura 1**), lo que genera un crecimiento demográfico temporal y, en algunos casos, permanente. Este aumento en la población ejerce una presión significativa sobre la estructura sanitaria.

De forma particular, en las Illes Balears, según el Instituto de Estadística de las Illes Balears (IBESTAT), se detalla el rango del IPH mensual máximo y mínimo. Durante el año 2022, la media varía entre un mínimo de 1.463 millones y un máximo de 1.603 millones. Esto indica que la población estimada se sitúa entre un 26,4% y un 36,3% por encima de la cifra oficial registrada en el censo de dicho año (registrado en 1.176 millones de habitantes).

Figura 2: Evolución del I.P.H (2022, Baleares).

Fuente: Elaboración propia a partir de fuentes estadísticas oficiales

El sistema sanitario de las Illes Balears ha tenido que adaptarse constantemente para satisfacer las necesidades de una población en constante cambio. Esto incluye la expansión de hospitales, clínicas y centros de atención médica, así como la necesidad constante de incremento de profesionales de la salud para enfrentarse a la creciente demanda, y de forma particular, del sector de la atención médica privada.

Comparativa de la infraestructura básica de la sanidad pública y de titularidad privada

El panorama de los servicios sanitarios en las Illes Balears, específicamente en el ámbito de la atención médica privada especializada, ha experimentado un notorio desarrollo y modernización. La *Conselleria de Salut i Consum*, a 31 de diciembre de 2021, tenía autorizados a un total de 15 hospitales de titularidad privada.

Desde una perspectiva geográfica, la distribución de estos hospitales privados se encuentra relacionada con el tamaño de población de las diferentes islas La mayoría de ellos, concretamente 12, se encuentran ubicados en la isla de Mallorca, mientras que 2 se sitúan en Menorca y uno en Ibiza. Este reparto geográfico demuestra el compromiso de proporcionar una cobertura adecuada y equitativa en el acceso a los servicios de atención médica privada en las distintas islas de la región.

En lo que respecta a la infraestructura tecnológica, es importante destacar que los hospitales de titularidad privada en las Islas Baleares han realizado inversiones significativas en la adquisición y puesta en marcha de tecnologías avanzadas en el ámbito de la salud. Estos dispositivos asistenciales privados se encuentran a la vanguardia de la innovación tecnológica en su sector. Esta inversión en tecnología médica se traduce en un nivel de atención a la salud de alta calidad y eficiencia, y refleja el compromiso de los hospitales privados en proporcionar servicios asistenciales de excelencia.

Tabla V: Comparativa infraestructura básica red pública vs. privada.

	TOTAL	RED PÚBLICA	RED PRIVADA	R. PRIVADA RESPECTO DE TOTAL
Camas instaladas	4.165	2.636	1.529	36,7
Sala de operaciones	137	74	63	46,0
Alta tecnología	461	352	109	23,6
TAC	24	13	11	45,8
RM	28	11	17	60,7
GAM	4	2	2	50,0
HEM	9	4	5	55,6
ASD	7	3	4	57,1
LIT	4	1	3	75,0
ALI	4	3	1	25,0
SPECT	3	2	1	33,3
PET	2	1	1	50,0
MAMOS	22	11	11	50,0
DO	12	4	8	66,7
DIAL	191	152	39	20,4
NEU	3	2	1	33,3
RVMI	148	143	5	3,4

Fuente: Elaboración propia a partir del CES (2021).

Para comprender mejor la magnitud de la infraestructura, es necesario examinar la **tabla V** que presenta información detallada sobre el número de camas instaladas y los equipos de tecnología en funcionamiento en la red pública y privada. Esta comparativa arroja luz sobre las diferencias y similitudes entre ambos sectores en términos de capacidad asistencial y dotación tecnológica, permitiendo una apreciación más precisa de la infraestructura de salud en las Illes Balears.

Los profesionales

De acuerdo con la *Memoria del Consell Econòmic i Social de les Illes Balears* correspondiente al año 2021, en la atención especializada en el sistema de salud de la región trabajan un total de 18,947 profesionales sanitarios, entre médicos, personal de enfermería y otros profesionales de la salud. De este total, un significativo porcentaje, aproximadamente el 28%, presta sus servicios en centros de atención médica de titularidad privada.

En lo que respecta a los profesionales médicos, en cuanto a su relación laboral con los centros de titularidad privada se caracteriza, en su mayoría, por ser de tipo colaborador. No obstante, es relevante observar, a lo largo del período una tendencia creciente en el número de médicos vinculados (ver **tabla VI**).

La **tabla VI** refleja de manera clara como el número de médicos que mantienen una relación laboral con los centros de titularidad privada ha experimentado un aumento progresivo durante el período de 2013 a 2021, aumentando en todo el período en un 70%. Esta tendencia al alza puede interpretarse como indicativo de un cambio de patrón contractual de relación auspiciado por los cambios en el mercado laboral que persigue exclusividad y retención de talento. Además este fuerte incremento responde a la demanda creciente de servicios médicos brindados por el sector privado en las Islas Baleares, lo que a su vez subraya la relevancia que tiene en el sistema de atención médica de la región.
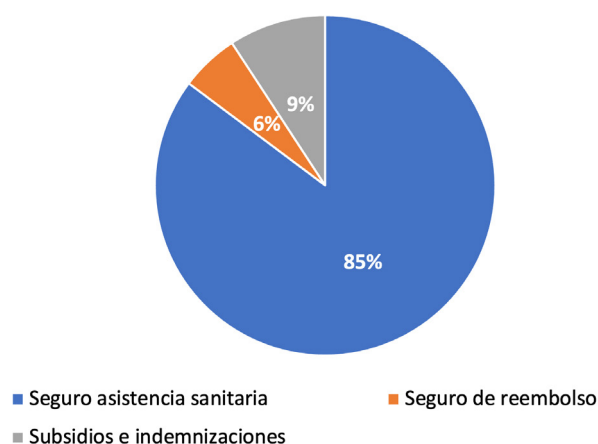
Penetración del seguro privado de salud

En el contexto de la cobertura de aseguramiento en las Islas Balears, se observa que la región mantiene un significativo grado de doble cobertura, que implica la coexistencia de sistemas protección pública y privada. Según datos disponibles, el porcentaje de penetración del seguro de salud privado en las Illes Balears se sitúa en el 33%, lo que la coloca por detrás de Madrid, con un 39%, y de Catalunya, con un 35%. Estos porcentajes reflejan la preferencia de una parte importante de la población para acceder tanto a servicios médicos públicos como privados.

El informe *"Baleares, IDIS Aportando Valor 2023"*, elaborado por la *Fundación IDIS* en 2023, indica que el número de personas aseguradas en la región superó las 350,000 en el año 2022, manteniendo una tasa anual compuesta de crecimiento del 2.3% en los últimos seis años. Además, el volumen de primas en el mismo período experimentó un crecimiento anual compuesto del 3.8%. No obstante, es relevante señalar que, en términos de crecimiento en el número de asegurados, las Islas Balears se sitúan por debajo de la media nacional, lo que podría interpretarse como un signo de madurez en el mercado de seguros de salud en la región.

De acuerdo con datos del *Instituto de Ciencias Económicas y Actuariales* (ICEA), en el año 2022, se contabilizaron 393,359 personas con seguro de salud privado en las Islas Balears, lo que representa un 33.43% de penetración en la población.

La **figura 3** presenta un desglose detallado de la distribución de los 393,359 asegurados en las Islas Balears en el año 2022 según el tipo de aseguramiento. En particular, se observa que el "Seguro de Asistencia Sanitaria" representa la opción preferida para la mayoría de los asegurados, con un notable 85% del total. Este tipo de seguro permite la cobertura de servicios médico- asistenciales adaptados al contrato establecido, normalmente con una cuota mensual y en algunos casos con un copago.

Tabla VI: Evolución del personal médico en centros privados.

	2013	2014	2015	2016	2017	2018	2019	2020	2021
Personal Médico Mir	0	0	0	0	0	0	0	1	2
Personal Médico colaborador	1.110	1.052	1.124	1.147	1205	1297	1279	1324	1117
Personal Médico Vinculado	258	328	314	359	362	369	362	393	439

Fuente: Elaboración propia a partir del CES (2021).

Tabla VII: Evolución del mercado asegurador en Baleares.

	ASEGURADOS	PRIMAS (€)	POBLACIÓN	PENETRACIÓN (%)
2018	366.651	303.416.128	1.128.908	32,48%
2019	373.099	312.725.996	1.149.460	32,46%
2020	376.489	322.736.305	1.171.543	32,14%
2021	387.029	332.439.409	1.173.008	32,99%
2022	393.359	350.524.384	1.176.659	33,43%

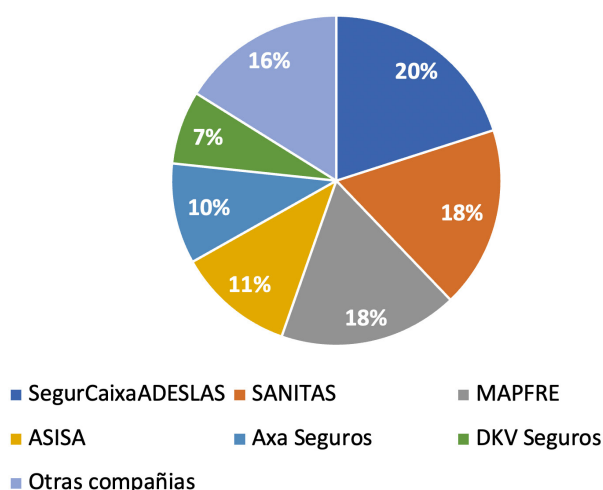Fuente: Elaboración propia a partir de datos ICEA e INE.

Figura 3: Distribución de los asegurados (2022, Illes Balears).

Fuente: Elaboración propia a partir de datos ICEA

El "Seguro de Reembolso" constituye un 6% de la distribución, lo que implica que un segmento más reducido de asegurados opta por este tipo de cobertura. Este modelo permite a los asegurados abonar directamente al prestador por los servicios médicos y luego solicitar un reembolso a su compañía de seguros.

Finalmente, "Subsidios e Indemnizaciones" representan un 9% del total. Este tipo de seguro generalmente se refiere a aquellos que ofrecen compensaciones económicas en caso de enfermedad, accidente o incapacidad. Esta opción puede ser elegida por asegurados que buscan protección financiera adicional en caso de situaciones imprevistas.

Por otro lado, la **figura 4** muestra las compañías aseguradoras con mayor cuota de mercado que operan en las Illes Balears:

Figura 4: Mercado de las compañías aseguradoras (2022, I. Balears).

Fuente: Elaboración propia a partir de datos ICEA

Estos datos proporcionan una visión detallada de la preferencia de los asegurados por tipos de cobertura y las principales compañías aseguradoras que operan en el mercado de seguros de salud en las Islas Balears. En este contexto, *"SegurCaixa ADESLAS"* lidera el mercado con una cuota de mercado del 20.05%, seguida de cerca por *"SANITAS"* con un 17.79%, y *"MAPFRE"* con un 17.53%. Estas tres compañías constituyen los principales actores en el mercado de seguros de salud de las Illes Balears.

Además, *"ASISA"* tiene una cuota del 11.45%, *"Axa Seguros"* del 9.86%, y *"DKV Seguros"* del 7.2%, lo que refleja un significativa diferencia respecto a la cuota de mercado de las tres principales enumeradas anteriormente.

Así, prácticamente el 85 % de la cuota de mercado asegurador de salud de las Illes Balears se concentra en 6 compañías.

El gasto de provisión privada

Para analizar el gasto en provisión privada de servicios de salud, se ha recurrido a estimaciones proporcionadas por el Instituto para el Desarrollo e Integración de la Sanidad (IDIS) en su informe del año 2023. La información se presenta en la **figura 5**, que muestra la distribución porcentual del gasto en el sector de la salud en las Islas Balears. Según esta estimación, el gasto privado representa el 25%, mientras que los conciertos públicos representan el 7% y el gasto público sin conciertos representa el 68% del gasto total en salud en la región.

Figura 5: Distribución del gasto público vs. Privado (2022, Illes Balears).
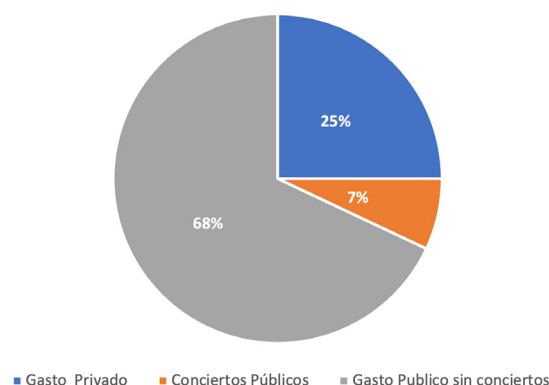
Fuente: Elaboración propia a partir de datos IDIS.

En un contexto más amplio, a nivel del Estado español, la estimación del gasto de provisión privada alcanza los 32,140 millones de euros, lo que representa un 26.7% del gasto total en salud. Comparativamente, otros países europeos como Portugal y Suiza superan esta proporción con un 35.5% y un 30.1%, respectivamente, mientras que Alemania y Francia se sitúan significativamente por debajo con un 14.9% y 15.3%, respectivamente. La media de los países miembros de la OCDE (Organización para la Cooperación y el Desarrollo Económico) se ubica en el 21.8%.

Adicionalmente, el Gasto Privado per cápita para el ejercicio 2021 en cifras absolutas se presenta en la **figura 6**, que detalla el gasto privado por habitante en diferentes comunidades autónomas de España. La Comunidad de Madrid lidera con 899 euros por persona, seguida de Cataluña con 785 euros. La Rioja, las Illes Balears y Aragón también muestran cifras notables con 774, 706 y 671 euros por habitante, respectivamente. En contraste, regiones como Extremadura y Castilla-La Mancha registran cifras más bajas con 516 y 511 euros por habitante, respectivamente, mientras que la media nacional se sitúa en 630 euros por persona.

Actividad asistencial

La importancia y la creciente implantación del aseguramiento privado en el ámbito de la sanidad en las Illes Balears tienen un impacto significativo en la actividad asistencial. De acuerdo con el informe "Análisis de la Sanidad Privada-Illes Balears" elaborado por la Alianza de la Sanidad Privada de España (ASPE) en 2022, se revela que una parte considerable de la atención médica proviene del sector privado (ver **figura 7**). A modo indicativo, del total de 2.8 millones de consultas de especialidades médicas realizadas en las Islas Balears, el 52% se generan a través de establecimientos privados. En el caso de las

intervenciones quirúrgicas, alrededor del 47% se llevan a cabo en centros privados, y de las más de 680,000 urgencias atendidas, un 44% se prestan en centros de titularidad privada. Estos porcentajes demuestran la relevancia de la sanidad de titularidad privada en la prestación de servicios asistenciales.

En el ámbito de la actividad diagnóstica, la comparativa entre la actividad pública y privada se detalla en la **figura 8**. La sanidad privada destaca por llevar a cabo el 61% de las resonancias magnéticas, el 52% de las mamografías y el 41% de los TAC de la comunidad, lo que pone de manifiesto su contribución fundamental en la realización de pruebas diagnósticas.

La colaboración entre el sector público y privado en el sistema sanitario balear es particularmente significativa y una de las más altas en comparación con otras regiones de España. Esto se refleja en la **tabla 8**, que muestra los importes destinados a conciertos por comunidad autónoma. Las Islas Balears se destacan como una de las comunidades que destinan una mayor cantidad de presupuesto per cápita a convenios de colaboración, representando el 9.2% de su gasto sanitario total.

**Figura 6:** Gasto privado *per cápita* (2021, Comunidades Autónomas).
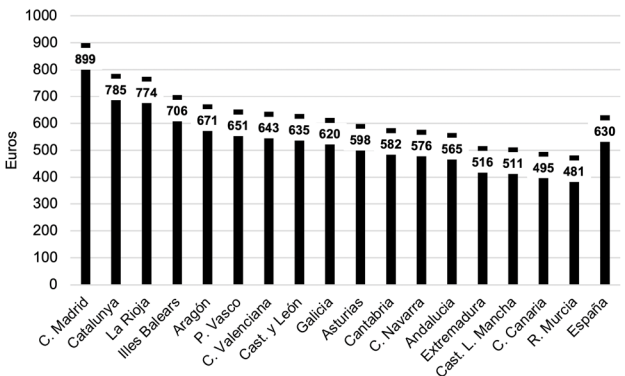
Fuente: Elaboración propia a partir de datos IDIS.

Figura 7: Actividad diagnósticada realizada en centros de atención especializada (2020, Illes Balears).
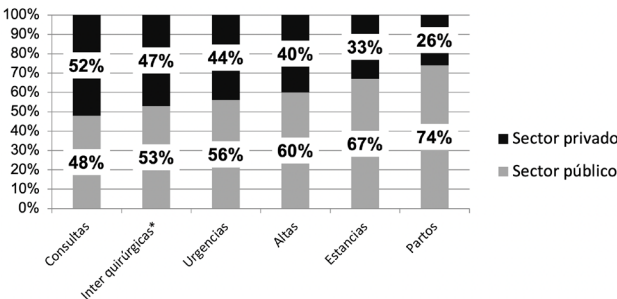
Fuente:.ASPE- Madimer (2022) *La tasa de cirugía ambulatoria es algo mayor en el sector público que en el sector privado, 39,6% del sector público frente al 31,3 % del sector privado

Figura 8: Actividad diagnósticada realizada en centros de atención especializada (2020, Baleares).
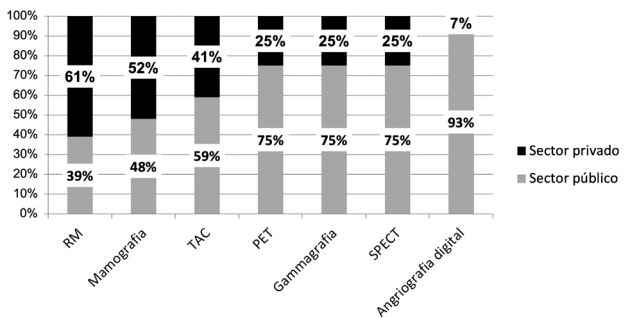
Fuente:.ASPE- Madimer (2022).

Tabla VIII: Conciertos por Comunidad Autónoma (2020).

COMUNIDAD AUTÓNOMA	IMPORTE (EN MILLONES, EUROS)	IMPORTE PER CÁPITA (EUROS)	% DEL GASTO SANITARIO
Andalucía	473	56	4,0
Aragón	97	73	4,1
Asturias	105	103	5,5
Baleares (Islas)	176	150	9,2
Canarias	256	118	7,0
Cantabria	33	56	3,1
Castilla y León	121	51	2,7
Castilla-La Mancha	152	74	4,4
Cataluña	3288	423	24,2
Comunidad Valenciana	307	61	3,8
Extremadura	75	70	4,0
Galicia	204	76	4,4
Madrid	902	133	8,9
Murcia	143	94	5,3
Navarra	80	121	6,5
País Vasco	262	118	6,1
Rioja (La)	34	106	6,7

Fuente:.ASPE- Madimer (2022).

Conclusiones

En el transcurso de este estudio, se ha llevado a cabo una reflexión exhaustiva sobre el sistema sanitario de atención especializada de titularidad privada en las Illes Balears, con el propósito de identificar los factores clave que han impulsado su desarrollo y crecimiento, además de proporcionar una visión actualizada de su importancia en el contexto actual del sector salud. Los resultados de esta investigación han permitido arrojar luz sobre varios elementos que han influido en la evolución de la sanidad de titularidad privada en la región. A grandes rasgos, los factores coadyuvantes identificados son los siguientes:

1. Espíritu asociativo local: La presencia de estructuras gremiales y asociaciones locales han desempeñado un papel crucial en la cobertura de las necesidades de atención médica en Illes Balears, evolucionando con el tiempo hacia formas mercantiles de provisión de servicios.

2. Tardía respuesta estatal: España se rezagó en la implementación de un seguro obligatorio de enfermedad, que se estableció en 1942, lo que incentivó el desarrollo del sector privado de la salud.

3. Lento despliegue de infraestructuras públicas: La limitada infraestructura sanitaria pública en su etapa inicial contribuyó a la expansión de la sanidad privada en la región.

4. Auge del turismo: El despegue de las Illes Balears como destino turístico entre 1961 y 1973 impulsó la demanda de servicios de salud, lo que favoreció el crecimiento del sector privado.

5. Cambio de modelo productivo y crecimiento poblacional: La Transición de una economía rural a una de servicios centrada en el turismo incrementa significativamente el nivel de renta. Se produce una cambio de tendencia poblacional: Se pasa de una alta emigración a ser un polo de atracción poblacional. Ello influye en el incremento de demanda de servicios de salud.

6. Emprendimiento médico: Profesionales médicos con vocación empresarial identificaron oportunidades en el sector.

En el contexto actual, la sanidad de titularidad privada en las Illes Balears juega un papel fundamental en el sistema de atención médica. Destaca por:

- Alto porcentaje de aseguramiento privado: Más del 33% de la población cuenta con seguro privado, situando a las Illes Balears entre las regiones con mayor penetración de España, quedando sólo por detrás de Madrid y Barcelona.
- Amplia actividad médico-quirúrgica: Los centros privados son responsables de una parte significativa de la atención médica, con el 52% de las consultas externas, el 47% de las intervenciones quirúrgicas y el 44% de las urgencias que se realizan en la comunidad Balear.
- Importante actividad diagnóstica: La sanidad privada realiza el 61% de las resonancias magnéticas, el 52% de las mamografías y el 41% de los TAC de la región.
- Colaboración público-privada: Las Illes Balears, en el ámbito de la salud, mantienen niveles destacados de colaboración entre el sector público y privado con una inversión per cápita significativa en convenios y una parte sustancial de su gasto sanitario destinado a este propósito.

En última instancia, es importante señalar que este estudio se ha centrado en un análisis exploratorio y por tanto, presenta ciertas limitaciones en cuanto a la exhaustividad y profundidad de la investigación. Futuros estudios podrían abordar de manera más detallada la historia y la evolución de la sanidad de titularidad privada en las Illes Balears, considerando una amplia gama de fuentes de ámbito cualitativo.

Conflicto de intereses
Ninguno para ninguno de los autores.

Antoni Miquel Fuster et al.

Factores coadyuvantes del desarrollo de la red asistencial de titularidad privada y su panorama actual en las Islas Baleares

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CASE REPORT

A rare and life-threatening bleeding into a pancreatic pseudocyst

Una hemorragia rara y potencialmente mortal en un pseudoquiste pancreático

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Abstract

Acute and chronic pancreatitis are among the most common diseases of the gastrointestinal tract. Most cases of acute pancreatitis are mild to moderate, but 15-20% of patients develop severe forms of pancreatitis that require surgery in 10.5% of cases. One of the complications of acute pancreatitis is the formation of pseudocysts. In rare cases, pseudocysts are associated with the development of pseudoaneurysms of the splenic, gastroduodenal, and pancreaticoduodenal arteries. Rupture of a pseudoaneurysm can lead to bleeding into various parts of the gastrointestinal tract, including the stomach, duodenum, pancreatic ducts, and biliary tree. The present case demonstrates bleeding from a pseudoaneurysm of the splenic artery into the gastrointestinal tract and then into the abdominal cavity. Bleeding into the ductal system of the pancreas can mimic upper gastrointestinal bleeding leading to misdiagnosis, inadequate treatment and even death.

Key words: Pancreatic pseudocyst, splenic artery pseudoaneurysm, bleeding, acute pancreatitis.

Resumen

La pancreatitis aguda y crónica es una de las enfermedades más comunes del tracto gastrointestinal. La mayoría de los casos de pancreatitis aguda son de leves a moderados, pero entre el 15 y el 20% de los pacientes desarrollan formas graves de pancreatitis que requieren cirugía en el 10,5% de los casos. Una de las complicaciones de la pancreatitis aguda es la formación de pseudoquistes. En raras ocasiones, los pseudoquistes se asocian al desarrollo de pseudoaneurismas de las arterias esplénica, gastroduodenal y pancreaticoduodenal. La rotura de un pseudoaneurisma puede provocar hemorragias en diversas partes del tracto gastrointestinal, como el estómago, el duodeno, los conductos pancreáticos y el árbol biliar. El presente caso demuestra la hemorragia de un pseudoaneurisma de la arteria esplénica en el tracto gastrointestinal y luego en la cavidad abdominal. La hemorragia en el sistema ductal del páncreas puede simular una hemorragia digestiva alta, lo que puede conducir a un diagnóstico erróneo, un tratamiento inadecuado e incluso la muerte.

Palabras clave: Pseudoquiste pancreático, pseudoaneurisma de la arteria esplénica, hemorragia, pancreatitis aguda.

Introduction

The incidence of acute pancreatitis is 5-80 cases per 100,000 people, while chronic pancreatitis is encountered 5-12 cases per 100,000[1,2]. Most cases of acute pancreatitis are mild to moderate, but 15-20% of patients develop severe forms of pancreatitis that require surgery in 10.5% of cases[3].

One of the complications of acute pancreatitis is the formation of pseudocysts – cavities containing fluid and surrounded by an inflammatory infiltrate. Pseudocysts form in 6-18.5% of cases in acute pancreatitis and in 20-40% of cases in chronic pancreatitis. Despite rare complications, pseudocysts are associated with the development of pseudoaneurysms of the splenic, gastroduodenal, and pancreaticoduodenal arteries[4,5]. Rupture of a pseudoaneurysm can lead to bleeding into various parts of the gastrointestinal tract, including the stomach, duodenum, pancreatic ducts, and biliary tree[6].

The presented clinical case describes bleeding from a pseudoaneurysm of the splenic artery into the gastrointestinal tract, and then into the abdominal cavity mimicking upper gastrointestinal bleeding. Bleeding into the ductal system of the pancreas is rare and can mimic upper gastrointestinal bleeding. In this settings the patient will undergo endoscopy to find the source of bleeding, while splenic artery embolization or ligation are the optimal treatment strategies.

Case report

A 38-year-old male, was urgently admitted to the hospital on November 20, 2019 with complaints of traces of blood in the stool. The patient considered himself ill since the summer of 2019, when for the first time after drinking alcohol he noted the appearance of girdle pain in the upper abdomen. In August he vomited blood and had black stool mixed with blood for two days. The patient was examined at the place of residence but upper gastrointestinal endoscopy and fibrocolonoscopy (FCS) did not reveal any source of bleeding. Upon admission his hemoglobin level was 79 g/l (normal reference 138-172 g/l), erythrocytes 3.3*1012 (normal reference 4.3-5.9*1012), hematocrit 25% (normal reference 41-50%). There were no other changes in laboratory tests.

Due to the clinical picture of gastrointestinal bleeding, he undergone esophagogastroduodenoscopy and FCS. During FCS, blood flow from the small intestine was noted but the source of bleeding was not visualized. The patient underwent computed tomography of the abdominal organs with intravenous contrast, which revealed a postnecrotic cyst of the pancreatic tail (**Figure 1**). At the time of the study, extravasation of the contrast agent was not detected (**Figures 1** & **2**). The patient underwent complex conservative therapy with a positive effect: the pain syndrome was relieved, laboratory parameters tended to normalize (increase in Hb level to 107 g/l). In order to search for a possible source of bleeding, the patient underwent enteroscopy, during which no data for an organic pathology of the small intestine were revealed. However, on December 8, 2019, the patient had clinical manifestations of hemorrhagic shock, clinical death and required resuscitation. An emergency ultrasound was performed and reveled free fluid in the abdominal cavity in the form of wide borders: subhepatic, parasplenic and in the pelvis (**Figure 3**). The was also a large mass with liquid (pseudocyst) that had a heterogeneous content (**Figure 4**).

**Figure 1:** CT scan of the abdomen. Splenic artery with an aneurysm (arrow).
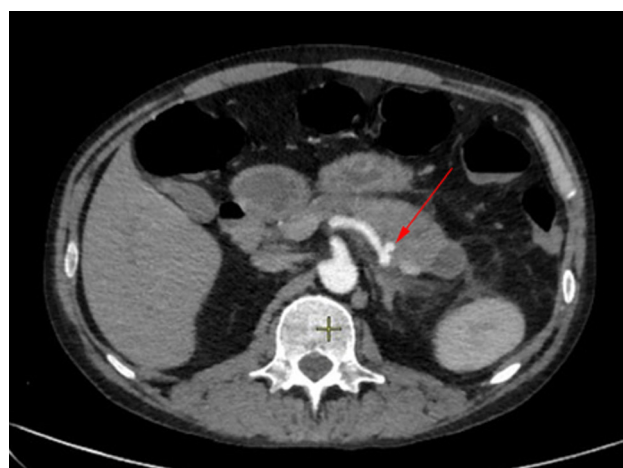
**Figure 2:** CT scan of the abdomen reconstruction. Splenic artery with an aneurysm (arrow).

The patient was resuscitated and rushed to the operating room. A median laparotomy was performed under combined endotracheal anesthesia and in aseptic conditions. During revision there was fresh blood with clots in all parts of the abdominal cavity. Blood was reinfused using Cell Saver apparatus, with intraoperative autotransfusion of 3 liters of blood. During examination there was an active flow of arterial blood from the foramen of Winslow. The omental sac was opened through the gastrocolic ligament. Through the lesser omentum a hematoma was visualized and palpated in the region of the body-tail of the pancreatic cyst. The cyst was opened and in one of the walls there was an erosive area of the splenic artery, up to 1 cm, with active bleeding. The bleeding was stopped by stitching the artery with Prolen 4.0. Taking into account the severity of the patient's condition, previous resuscitation measures and the episode of clinical death, it was decided to refrain from expanding the surgical intervention. A drain was installed on the right through the foramen of Winslow into the omental bag, brought out through the counter-opening in the right mesogastrium. One drain was installed through the gastrocolic ligament, brought out through the counter-opening in the right mesogastrium. Drainage into the pelvis was brought out through the counter-opening in the right iliac region. The wound was sutured layer-by-layer. The patient was then transferred to intensive care unit. Given the high risk of recurrent bleeding from the eroded area of the splenic artery the patient undergone upper mesentericography, celiacography, angiography, and mechanical embolization of the splenic artery on December 11, 2019 (**Figure 5**). Upon stabilization of the condition, on December 16, 2019, the patient was transferred to the surgical department, where complex conservative therapy was continued: antiulcer, antibacterial, anti-inflammatory, infusions and pain management. The drains were removed upon stabilization and the patient was discharged for supervision at the place of residence.

Figure 3: Free fluid in the abdominal cavity (A - subhepatic, a pseudocyst area is also observed in the scanning area; B - in the pelvis).
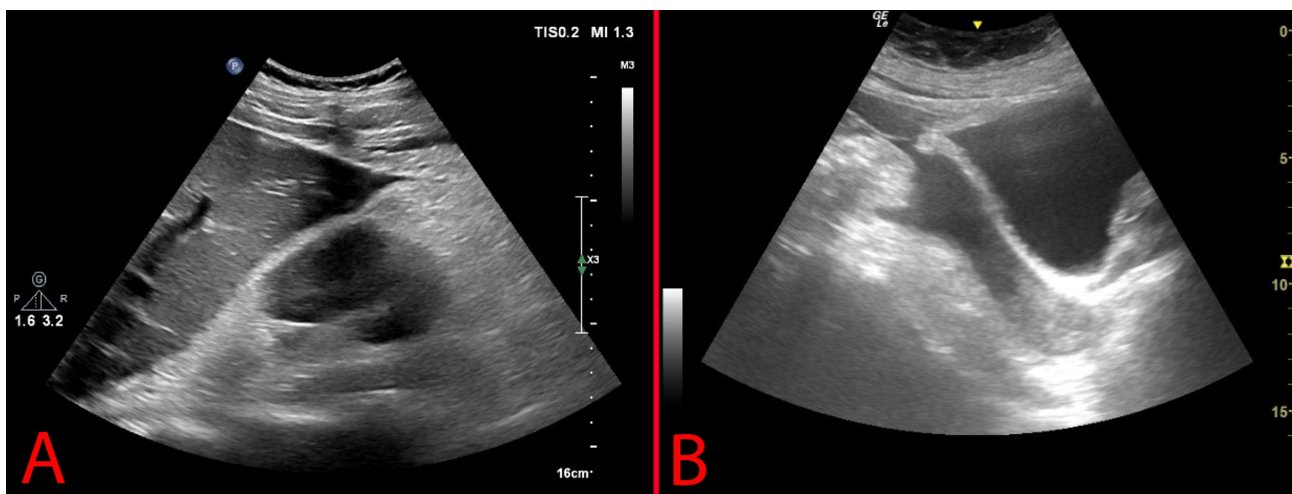
Figure 4: Pseudocyst of the pancreas with a heterogeneous component (A - transverse section in the epigastric region; B - sagittal section, the left lobe of the liver is also observed in the scanning area).
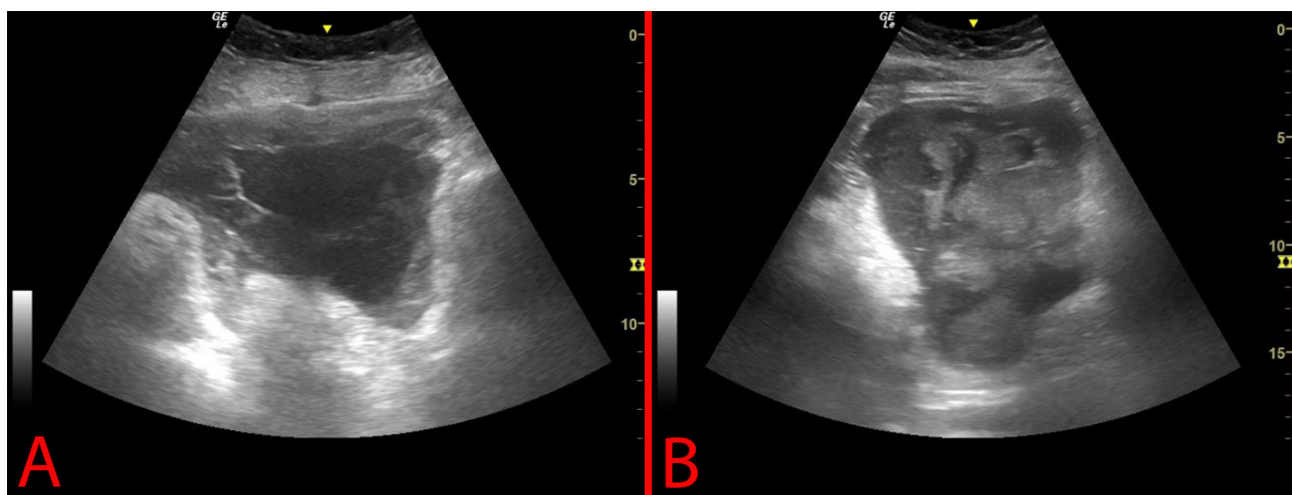
Figure 5: Catheterization of the splenic artery and embolization of the aneurysm.
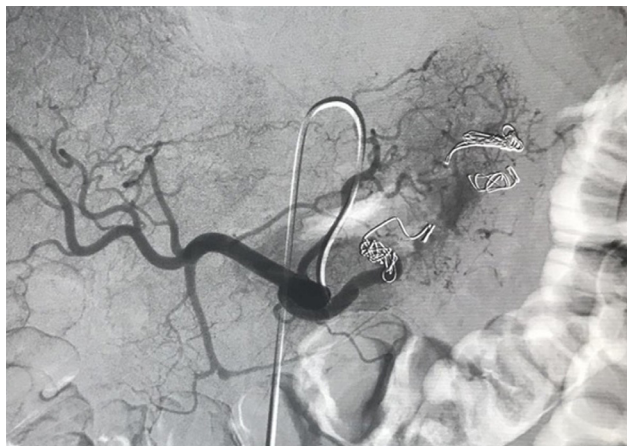
Discussion

Pseudocysts form as a result of enzyme buildup and self-digestion of the pancreas in patients with acute pancreatitis. In chronic pancreatitis, pseudocysts form as a consequence of high intraductal pressure and destruction of blocked ducts[7].

Although pseudocyst rupture is rare, it can be dangerous. Rupture usually occurs as a result of trauma, infection, or pancreatitis. The most dangerous complication of pseudocyst is bleeding, which occurs in 6-8% of cases and can be fatal[8].

Bleeding can occur immediately after an episode of pancreatitis or after some time. Initially, inflammation and lysis of the elastic component of the vessel can occur, which leads to erosion and disruption of the wall structure. Then, the pseudocyst can cause vessel damage by compression, which leads to ischemia and further injury to the vessel wall. Finally, pseudocysts can lead to compression of the surrounding vessels, thrombosis and increased intravascular pressure, which also contributes to the violation of the integrity of the vascular wall. It is important to consider that the arteries supplying the pancreas vary as well as their diameter. Therefore, damage to large branches of the splenic artery can lead to rapid and profuse bleeding[9,10]. As a result, one of the possible complications may develop: bleeding into the cyst, bleeding into the gastrointestinal tract, and bleeding into the abdominal cavity. Various locations of bleeding are shown in **Figure 6**.

Figure 6: Localization of bleeding depending on the area where the aneurysm is emptied.
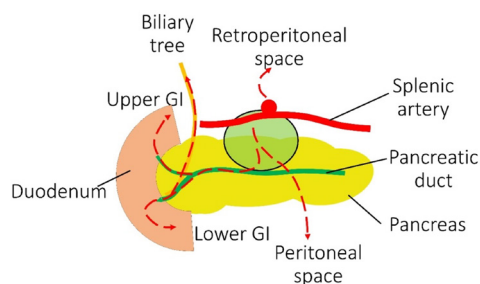
Intra-abdominal bleeding from pseudocysts is associated with high mortality (35.3-40% of cases)[11,12]. Pseudocysts are especially dangerous if they are localized near large vessels of the spleen or pancreas[12,13]. Diagnosis may require intravenous contrast-enhanced CT, ultrasound with Doppler imaging, and angiography. The optimal method of treatment is endovascular intervention with aneurysm embolization[12]. However, in hemodynamically unstable patients, the most rational method of treatment is midline laparotomy with ligation of the bleeding vessel[14]. Depending on the location of the aneurysm and the individual anatomy of the patient, splenectomy, partial resection of the cyst, ligation of the splenic artery or its branches may be required[15].

The current case demonstrates that in rare cases splenic artery can bleed into the pseudocyst and the into the ductal system of the pancreas. CT with contrast enhancement does not always allow to diagnose extravasation even in large diameter vessels when they are compressed. The presence of an aneurism in patients with acute pancreatitis and symptoms of bleeding requires reevaluation of the main source of hemorrhage with subsequent embolization or ligation of the artery.

Conclusions

Bleeding from an aneurysm of the splenic artery in the setting of acute pancreatitis is a rare but potentially life-threatening condition. Rarely, an aneurysm may empty into a pancreatic cyst and eventually into the gastrointestinal tract, giving the illusion of gastrointestinal bleeding. Depending on the hemodynamic parameters, the patient can undergo aneurysm embolization or emergency laparotomy and vessel ligation.

Informed Consent Statement
Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest
The authors declare no conflict of interest.

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CASE REPORT

3D image reconstruction & processing for retrorectal tumor

Reconstrucción y procesamiento de imágenes 3D para tumores retrorrectales

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Abstract

3D reconstruction technology (3D-IPR) could be useful in pre-surgical planning in retrorectal tumors, which pose a surgical challenge due to their location and anatomical relationships. Magnetic Resonance Imaging (MRI) is an acceptable but not always satisfactory imaging test for pre-surgical planning, since the images can be difficult to interpret.

Key words: Retrorectal tumor, 3D reconstruction.

Resumen

La tecnología de reconstrucción 3D (3D-IPR) podría ser útil en la planificación pre-quirúrgica en tumores retrorectales, que suponen un desafío quirúrgico debido a su localización y sus relaciones anatómicas. La Resonancia Magnética (MRI) es una prueba de imagen aceptable aunque no siempre satisfactoria para la planificación pre-quirúrgica, dado que las imágenes pueden ser de difícil interpretación.

Palabras clave: Tumor retrorrectal, reconstrucción 3D.

Case presentation

We present the case of a 36-year-old female patient without previous pathological history, diagnosed incidentally in November 2019 of a retrorectal tumor through complementary tests carried during pregnancy follow-up. A C-Section was performed in October 2020. 3D-IPR was done based on MRI and provided visual representation of the tumor with its pelvic relationship to other structures that must be preserved. (**Figures 1-2**).
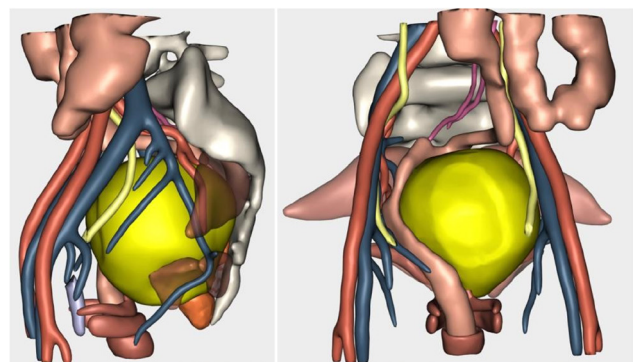
Surgery was finally performed in February 2021 by an open infraumbilical midline laparotomy exeresis with rectum suture repair and protective ileostomy. Pathology report confirmed a monodermal mature cystic teratoma. Ileostomy closure was performed after three months. (**Figure 3**).

After 30 months of follow-up there was no evidence of recurrence. (**Figure 4**).

Figure 1: MRI showing a large retrorectal tumor with rectum displacement.
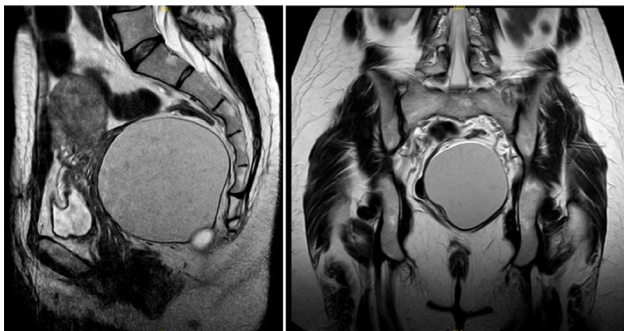

Figure 2: 3D-IPR showing retrorectal tumor (yellow) with rectum right lateral displacement as well as its relationship with iliac vessels and urethers (light yellow) and levator ani muscles (faded brown).

Figure 3: Surgical specimen compared to 3D-IPR specimen. 3D-IPR measured 11.45 cm as longitudinal length which is similar to complete extracted surgical specimen. Surgery performed was an open infraumbilical midline laparotomy exeresis with rectum suture repair and protective ileostomy. Pathology report confirmed a monodermal mature cystic teratoma. Ileostomy closure was performed after three months.
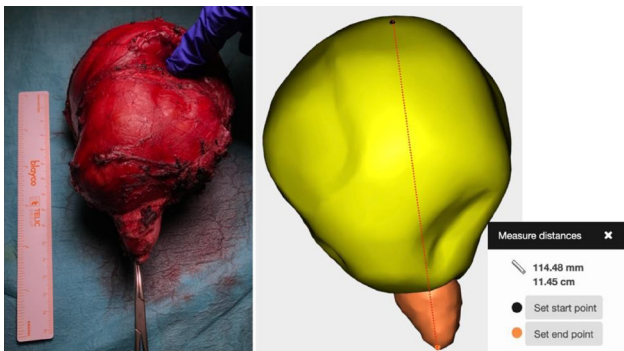
Figure 4: Post-operative MRI after three months of surgical intervention confirmed complete retrorectal tumor excision without any relapse.
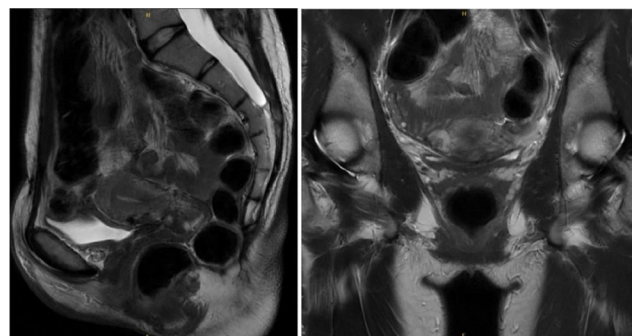
Discussion

Retrorectal tumors are a rare heterogeneous group of lesions arising within retrorectal space, and though they are often benign lesions, they require resection to prevent potential malignant transformation, to control symptoms and to establish a definitive diagnosis.

It is important to avoid intraoperative opening of the mass and this requires surgical planning. For this reason imaging plays a crucial role in this kind of tumors. Conventional MRI is not always satisfactory for surgical planning due to difficulty interpreting structures, specially in case of inflammatory changes.

3D image reconstruction & processing (3D-IPR) and artificial intelligence (AI) can evaluate, using mathematical algorithms, if tumors infiltrate surrounding structures as it could change surgical attitude, improving surgical planning and reducing risk of intraoperative complications.

In this case, 3D-IPR identified a retrorectal tumor with right lateral rectal displacement as well as its relationship with iliac vessels, urethra and levator ani muscles. All of which provided the surgical team an enhaced visual representation to improve resection and post operative outcomes.

Conclusion

3D-IPR is an ideal strategy for surgical planning of these rare tumors, as they are surgically challenging due to their location and given the lack of standarized protocols of image acquisition.

Conflicts of Interest

The authors declare no conflict of interest.

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