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CONCESIÓN DE BECAS Y PREMIOS 2023

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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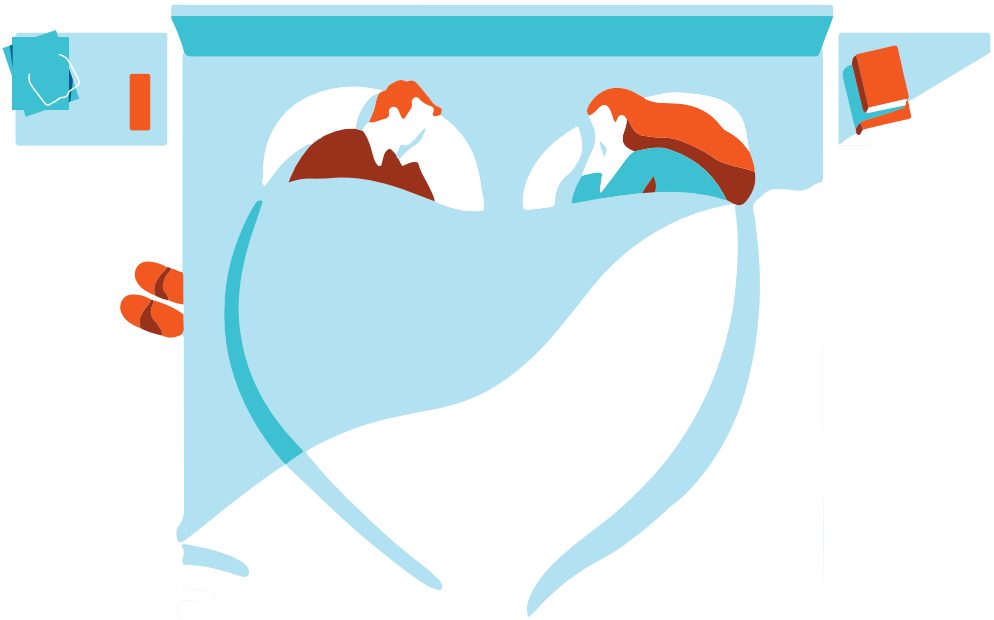

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ORIGINAL

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 la célula cancerosa 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 tumorales, quimiorresistencia, recidiva.

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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.

Evoluation 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**.

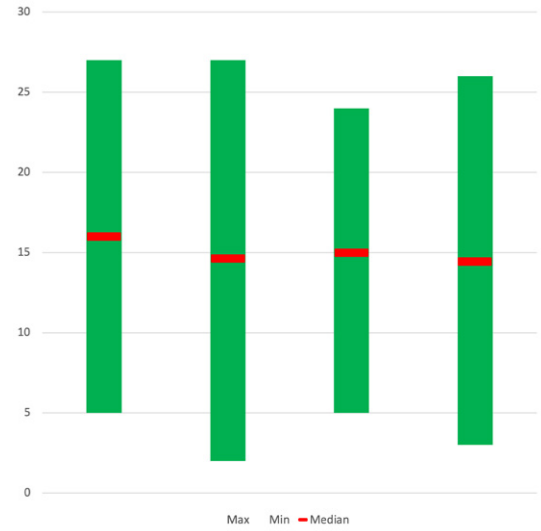
Table I: Clinical and Pathological indicators non-ABC and ABC patients.

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.

Figure 1: Evoluation 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.

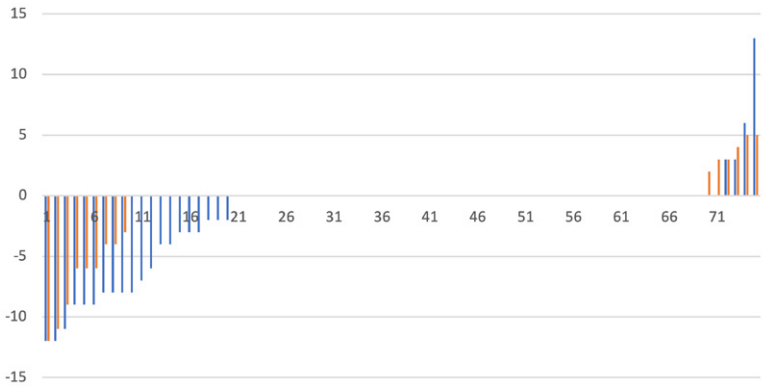


ABC patients showed a larger decline in TILs following NC (OR: 0.24, 95% CI: 0.21-0.66, p = 0.016) in a multivariate model containing all patients. A higher decline in TIL was related with a high number of TIL before to NC (OR: 0.029, 95% CI: 0.0018-0.175, p = 0.002) and a low number of TIL after NC (OR: 23.12, 95% CI: 3.57-489.76, p = 0.008) in a model including just ABC patients – **Table II**.

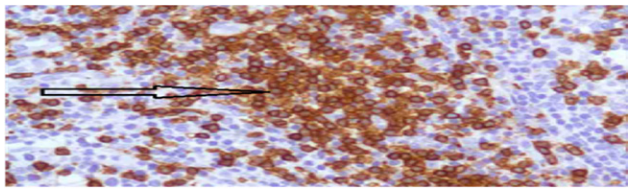
In the overall cohort (including both ABC and non-ABC patients) the number of TIL after NC seemed to largely depend on the number of TIL (OR: 2.023, 95% CI: 1.18-3.125, p = 0.04) and the remaining cancer cell count (OR: 2.05, 95% CI: 1.60-6.98, p = 0.004) -**Table II**.

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**.

Figure 1 B: ABC ;Non-ABC
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 1 a: 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 1 b: 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.

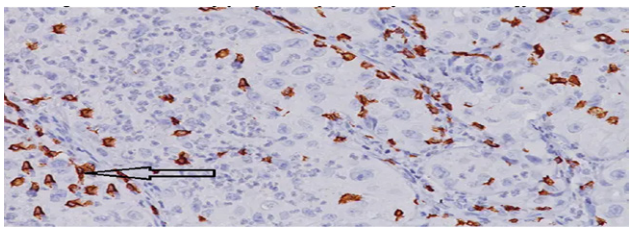
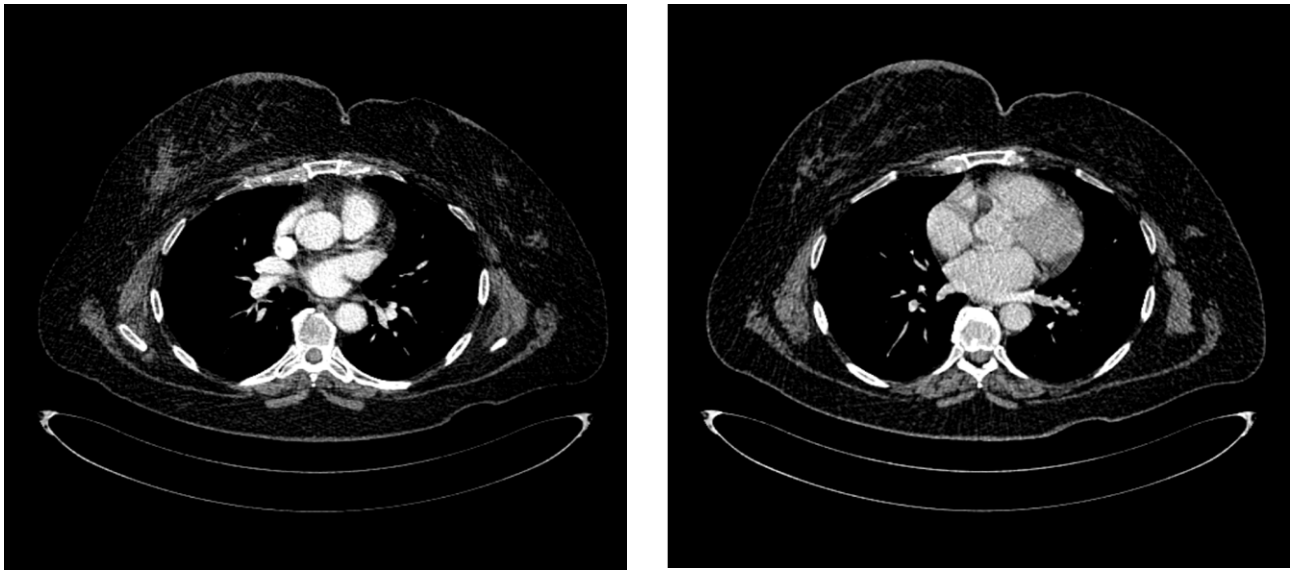


Table II: Uni- and multivariate analysis for decrease of TIL after neo-adjuvant chemotherapy.

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		

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



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 2 a; b.**

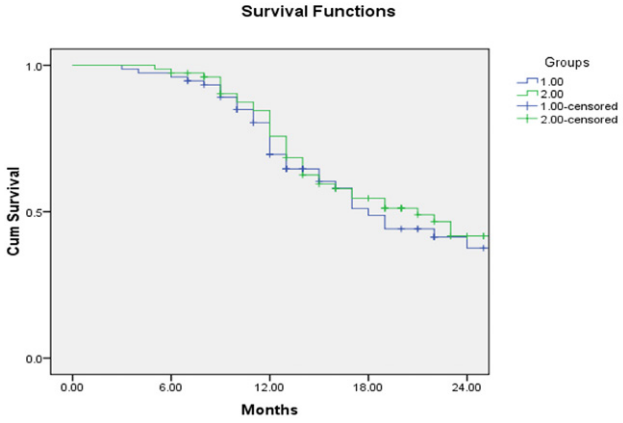
In the ABC population, HR and HER2 status had no effect on OS or RFS.

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**.

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 tumour 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), $p < 0.001$.



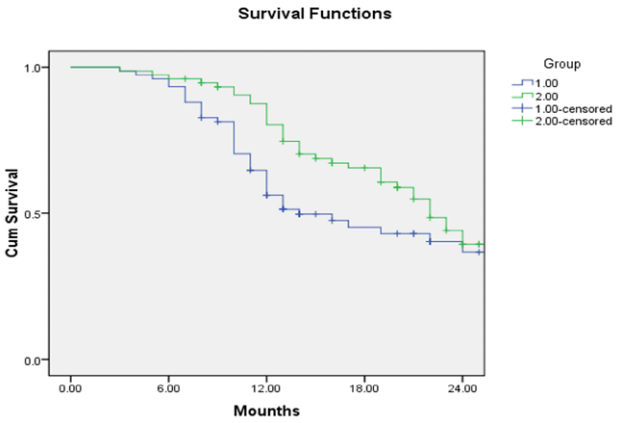


Table III: Uni- and multivariate analysis for RFS in the group of ABC patients without pCR after neo-adjuvant chemotherapy.

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

pCR – complete (partial) pathological response

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.

Acknowledgments

This work is dedicated to our friend prof. Smolanka I.I., who is courageously fighting advanced breast cancer.

Competing Interests

The authors declare that they have no competing interests.

References

1. Yang F, He Q, Dai X, Zhang X, Song D. The potential role of nanomedicine in the treatment of breast cancer to overcome the obstacles of current therapies. FrontPharmacol. 2023;14:1143102. doi:10.3389/fphar.2023.1143102.

2. Meegdes M, Geurts S, Erdkamp F, Dercksen M, Vriens B, Aaldering K et al. Real-world time trends in overall survival, treatments and patient characteristics in HR+/HER2- metastatic breast cancer: an observational study of the SONABRE Registry. Lancet Reg Health Eur. 2023;26:100573. doi:10.1016/j.lanepe.2022.100573.

3. Flood E, Krasnow A, Orbegoso C, Karantzoulis S, Bailey J, Bayet S, et al. Using qualitative interviews to identify patient-reported clinical trial endpoints and analyses that are the most meaningful to patients with advanced breast cancer. PLoS One. 2023;18(1):e0280259. doi: 10.1371/journal.pone.0280259

4. Hyder T, Bhattacharya S, Gade K, Nasrazadani A, Brufsky A. Approaching Neoadjuvant Therapy in the Management of Early-Stage Breast Cancer. Breast Cancer (Dove Med Press). 2021; 13:199-211. doi.org/10.2147/BCTT.S273058

5. Cecil K, Huppert L, Mukhtar R, Dibble EH, O'Brien SR, Ulaner GA, et al. Metabolic Positron Emission Tomography in Breast Cancer. PET Clin. 2023 Jun 25:S1556-8598(23)00036-6. doi: 10.1016/j.cpet.2023.04.004.

6. Raman D, Cimpean AM, De Miglio MR. Editorial: Drug resistance in breast cancer-mechanisms and approaches to overcome chemoresistance. Front Oncol. 2023;12:1080684.doi:10.3389.

7. Luen SJ, Salgado R, Dieci MV, Vingiani A, Curigliano G, Gould RE, et al. Prognostic implications of residual disease tumor-infiltrating lymphocytes and residual cancer burden in triple-negative breast cancer patients after neoadjuvant chemotherapy. Ann Oncol. 2019 Feb 1;30(2):236-242. doi: 10.1093/annonc/mdy547.

8. Loi S, Salgado R, Adams S, Pruneri G, Francis PA, Lacroix-Triki M, et al. Tumor infiltrating lymphocyte stratification of prognostic staging of early-stage triple negative breast cancer. NPJ Breast Cancer. 2022 Jan 11;8(1):3. doi: 10.1038/s41523-021-00362-1.

9. Du X, Zhou Z, Shao Y, Qian K, Wu Y, Zhang J, et al. Immunoarchitectural patterns as potential prognostic factors for invasive ductal breast cancer. NPJ Breast Cancer. 2022 Feb 28;8(1):26. doi: 10.1038/s41523-022-00389-y.

10. Bagmut I, Movchan O, Sheremet M, Smolanka I, Lyashenko A, Dosenko I, et al. Characteristics of certain genetical and biological properties of carcinogenesis in the development of breast cancer with type 2 diabetes mellitus and tumor relapse. Rom J Diabetes Nutr Metab Dis 2022;29 (2): 245-252. doi.org/10.46389/rjd-2022-1082

11. Song X, Ma J, Zhang H, Zhang Q. Prognostic significance of the primary tumor site and immune indexes in patients with estrogen receptor-positive, human epidermal growth factor receptor-2-negative breast cancer. Gland Surg. 2020 Oct;9(5):1450-1468. doi: 10.21037/gs-20-622.

12. Locy H, Verhulst S, Cools W, Waelput W, Brock S, Cras L, et al. Assessing Tumor-Infiltrating Lymphocytes in Breast Cancer: A Proposal for Combining Immunohistochemistry and Gene Expression Analysis to Refine Scoring. Front Immunol. 2022 Feb 11;13:794175. doi: 10.3389/fimmu.2022.794175.

13. Ochi T, Bianchini G, Ando M, Nozaki F, Kobayashi D, Criscitiello C, et al. Predictive and prognostic value of stromal tumour-infiltrating lymphocytes before and after neoadjuvant therapy in triple negative and HER2-positive breast cancer. Eur J Cancer. 2019 Sep;118:41-48. doi: 10.1016/j.ejca.2019.05.014.

14. Vagia E, Cristofanilli M. New Treatment Strategies for the Inflammatory Breast Cancer. Curr Treat Options Oncol. 2021; 22(6):50-61. doi: 10.1007/s11864-021-00843-2. PMID: 33893888

15. Van Berckelaer C, Vermeiren I, Vercauteren L, Rypens C, Oner G, Trinh XB, et al. The Evolution and Prognostic Role of Tumour-Infiltrating Lymphocytes and Peripheral Blood-Based Biomarkers in Inflammatory Breast Cancer Patients Treated with Neoadjuvant Chemotherapy. Cancers (Basel). 2021 Sep 16;13(18):4656. doi: 10.3390/cancers13184656.

16. Murthy RK, Song J, Raghavendra AS, Li Y, Hsu L, Hess KR, Barcenas CH, Valero V, Carlson RW, Tripathy D, Hortobagyi GN. Incorporation of clinical and biological factors improves prognostication and reflects contemporary clinical practice. NPJ Breast Cancer. 2020 Mar 25;6:11. doi: 10.1038/s41523-020-0152-4.

17. Zhang H, Ma G, Du S, Sun J, Zhang Q. Nomogram for predicting cancer specific survival in inflammatory breast carcinoma: a SEER population-based study. Peer J. 2019;7.

18. Ruffell B, Au A, Rugo HS, Esserman LJ, Hwang ES, Coussens LM. Leukocyte composition of human breast cancer. Proc Natl Acad Sci U S A. 2012 Feb 21;109(8):2796-801. doi: 10.1073/pnas.1104303108.

19. Garcia-Martinez E, Gil G, Benito A, Gonzalez-Billalabeitia E, Conesa M, Garcia Garcia T et al. Tumor-infiltrating immune cell profiles and their change after neoadjuvant chemotherapy predict response and prognosis of breast cancer. Breast Cancer Res. 2014;16:488. doi: 10.1186/s13058-014-0488-5.

20. Eiró N, Pidal I, Fernandez-Garcia B, Junquera S, Lamelas ML, del Casar JM, González LO, López-Muñiz A, Vizoso FJ. Impact of CD68/(CD3+CD20) ratio at the invasive front of primary tumors on distant metastasis development in breast cancer. PLoS One. 2012;7(12):e52796. doi: 10.1371/journal.pone.0052796.

21. Poddar A, Rao S, Prithviraj P, Kannourakis G, Jayachandran A. Crosstalk between Immune Checkpoint Modulators, Metabolic Reprogramming and Cellular Plasticity in Triple-Negative Breast Cancer. Current Oncology. 2022; 29(10):6847-6863. doi.org/10.3390/curroncol29100540

22. Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, André F, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)†. Ann Oncol. 2018 Aug 1;29(8):1634-1657. doi: 10.1093/annonc/mdy192.

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ORIGINAL

Prevalence of Body Dysmorphic Disorder and Its Association with Body Features and social anxiety among Female University Students

Prevalencia del trastorno dismórfico corporal y su asociación con las características corporales y la ansiedad social en mujeres universitarias

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Abstract

Body dysmorphic disorder (BDD) is characterized by significant distress or impaired thoughts. It is a common mental health disorder; however, it remains underdiagnosed in clinical settings. Therefore, this study aimed to assess the prevalence of BDD and social anxiety among female students, which is important because both conditions may adversely affect academic performance. This cross-sectional study on female students was conducted at King Abdulaziz University, Jeddah, Saudi Arabia, between January and February 2023. Data were collected using a self-administered questionnaire distributed in electronic format on university electronic platforms (blackboard). Participants were asked to fill out a questionnaire comprising three parts: 1) sociodemographic data, 2) BDD Symptomology Questionnaire, and 3) Social Interaction Anxiety Scale (SIAS). In this study, among 437 female students, most were concerned about their body parts/flaws (80.5%, n = 352). The body features of major concern included skin (32.3%, n = 141), obesity (23.6%, n = 103), teeth (21.5%, n = 94), and hair (21.3%, n = 93). In addition, our results showed a significant association between SIAS and all reported symptoms of BDD ($p < 0.001$). Notably, a significantly higher number of those with social anxiety extremely/very often experienced symptoms of BDD than those without social anxiety.

Key words: body dysmorphic disorder; social anxiety; body features.

Resumen

El trastorno dismórfico corporal (TDC) se caracteriza por una angustia significativa o pensamientos alterados. Es un trastorno de salud mental frecuente; sin embargo, sigue estando infradiagnosticado en los entornos clínicos. Por lo tanto, este estudio pretendía evaluar la prevalencia del TDC y la ansiedad social entre las estudiantes, lo cual es importante porque ambas afecciones pueden afectar negativamente al rendimiento académico. Este estudio transversal en 437 mujeres estudiantes se llevó a cabo en la Universidad Rey Abdulaziz, Jeddah, Arabia Saudita, entre enero y febrero de 2023. Los datos se recogieron mediante un cuestionario autoadministrado distribuido en formato electrónico en las plataformas electrónicas de la universidad (pizarra). Se pidió a los participantes que rellenaran un cuestionario que constaba de tres partes: 1) datos sociodemográficos, 2) Cuestionario de sintomatología del TDC y 3) Escala de ansiedad ante la interacción social (SIAS). En este estudio, entre las 437 alumnas, la mayoría estaban preocupadas por sus partes/faltas corporales (80,5%, n = 352). Las características corporales que más preocupaban eran la piel (32,3%, n = 141), la obesidad (23,6%, n = 103), los dientes (21,5%, n = 94) y el pelo (21,3%, n = 93). Además, nuestros resultados mostraron una asociación significativa entre el SIAS y todos los síntomas declarados de TDC ($p < 0,001$). En particular, un número significativamente mayor de personas con ansiedad social experimentaba síntomas de TDC con mucha/mucha frecuencia que las personas sin ansiedad social.

Palabras clave: trastorno dismórfico corporal; ansiedad social; rasgos corporals.

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Introduction

Body dysmorphic disorder (BDD) is characterized by significant distress or impaired thoughts. It is a condition in which an individual is preoccupied with perceived defects or flaws in their physical appearance that are not observable by or appear slight to others[1]. BDD is an obsessive-compulsive spectrum disorder because it has characteristics similar to those of obsessive-compulsive disorder (OCD)[2], including repetitive behaviors, such as mirror checking, excessive grooming, skin picking, and reassurance seeking. In addition, BDD is associated with mental activities in which individuals compare their appearance to that of others in response to appearance concerns. Individuals with BDD experience social, educational, and occupational challenges. Concerns regarding body image in patients with BDD are not primarily focused on body fat and weight, as observed in individuals with eating disorders[1]. BDD is often associated with mental disorders. Two studies on individuals with BDD showed that the most common comorbid psychiatric condition associated with BDD was major depressive disorder, with a lifetime prevalence of 75%, followed by substance use disorder (approximately 48.9%), social phobia (approximately 39%), and OCD (approximately 33%)[2]. Social anxiety is a significant and persistent fear of social situations or performances in which embarrassment may occur[3]. Individuals with BDD may experience social anxiety, feel embarrassment, be judged when expressing their opinions in the presence of others, or find it difficult to make or keep new friends. Individuals concerned about their appearance have higher levels of social anxiety and depressive symptoms than those who are not. It is of great importance to pay attention to BDD, especially because of the significant rates of comorbidity. One in three patients with BDD exhibit violent behaviors, which they mainly attribute to BDD symptoms (such as attacking someone or damaging property). Clinical impressions suggest that violence may be fueled by rage about looking deformed, an inability to fix the defect, and delusions of reference (such as individuals believing they are being mocked by others for the defect)[2]. Studies have shown that approximately one in three individuals with BDD are delusional, indicating a greater severity of symptoms and a higher prevalence of functional impairment[4]. Furthermore, the rates of suicidal ideation, attempts, and deaths were significantly elevated among individuals with BDD. Studies have shown that individuals with BDD are 2.6 times more likely to attempt suicide and four times more likely to experience suicidal ideation than those without BDD[2,4]. These concerns may appear trivial; however, they can significantly impair multiple areas of function, leading to social isolation, house-boundedness, and withdrawal from social activities, intimate relationships, or work and school engagements. In addition, unnecessary cosmetic surgeries pose a financial burden[4,5]. Considering the pronounced functional impairment, poor quality of life, and high suicide rates among patients with BDD, it is very important for BDD to be recognized and accurately diagnosed[6]. BDD is a common mental health disorder; however, it remains underdiagnosed in clinical settings[2]. A recent systematic review showed that a large percentage of patients with BDD visit a plastic surgery/dermatology clinic rather than seeking psychiatric help. This implies that BDD is underdiagnosed and that visiting a non-psychiatric specialty is just one factor. Notably, several studies have highlighted that the diagnosis of BDD is suboptimal, even in psychiatric settings[7]. Furthermore, only a few patients with BDD feel satisfied or show improved symptoms after cosmetic interventions. This leads to significant negative outcomes for both patients and physicians[2]. Therefore, this study aimed to assess the prevalence of BDD and social anxiety among female students, which is important because both conditions may adversely affect academic performance.

Materials and methods

This cross-sectional questionnaire-based study was conducted using convenience sampling at King Abdulaziz University, Jeddah, Saudi Arabia, between 23 January and 5 February 2023. Responses were drawn from 437 female students at King Abdulaziz University. Data were collected using a self-administered questionnaire distributed in an electronic format on university blackboard platforms. Participation in this study was voluntary, and all participants were guaranteed privacy and confidentiality. Written informed consent was obtained from each participant at the beginning of the questionnaire. Students diagnosed with anorexia nervosa or bulimia and those with missing data were excluded. The included participants were asked to fill out a questionnaire comprising three parts: 1) sociodemographic data, including age, sex, marital status, nationality, academic performance, college, weight, and height; 2) BDD Symptomology Questionnaire. BDD symptoms vary from compulsive touching of the perceived defect to compulsive mirror checking, avoiding looking into a mirror or being photographed, comparing themselves with people around them or with those in magazines and television in terms of the perceived defect, and hiding or concealing the physical defect; 3) Social Interaction Anxiety Scale (SIAS) developed by Mattick and Clarke[8]. The SIAS was used to assess the prevalence, severity, and treatment outcomes of social phobia and anxiety, and all the questions were adapted from the original SIAS without any modifications except for question 14, which was deleted for being culturally inappropriate. The possible scores range from 0 to 76. Higher scores indicate higher levels of social anxiety. The score interpretation is as follows: <36: without Social Anxiety and ≥36: with Social Anxiety. Data were analyzed using IBM SPSS version 23 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 8 (GraphPad Software Inc., San Diego, CA, USA). Simple descriptive statistics were used to define sociodemographic characteristics. Categorical variables were presented as counts and percentages, whereas continuous variables were presented as means and standard deviations. Reliability analysis was performed with a model of Alpha (Cronbach) to study the properties of measurement scales and items that compose the scales and the average inter-

item correlation. Regarding correlations, the chi-square test was used to assess the relationship between categorical variables. This test was performed under the assumption of a normal distribution. The dependent variables were defined as binary outcomes. A binary logistic regression model with backward conditional elimination, with enter criteria of 0.05 and elimination of 0.10, was used to determine the significant predictors of any given dependent variables with 95% confidence intervals (CIs). Statistical significance was set at $p < 0.05$. Ethical approval for the study was obtained from the King Abdulaziz University, the Faculty of Medicine Research Ethics Committee.

Results

This study evaluated the prevalence of BDD and its association with body features among 437 female students at King Abdulaziz University, Jeddah, Saudi Arabia. Regarding sociodemographic characteristics, the students had an average age of 22.16 ± 3.2 years (range: 18-30 years, N = 437), weight of 59.05 ± 16.7 kg (range: 30.00-157.00 kg, N = 433), height of 158.08 ± 5.9 cm (range: 11.72-69.78 cm, N = 436), and body mass index (BMI) of 23.59 ± 6.3 (range: 11.72-69.78, N = 433), as shown in **table I**. Notably, most students were single (89.5%, n = 391) or Saudi nationals (94.5%, n = 413). Approximately 50% of the students had a 4.5-5 academic grade point average (GPA) (47.4%, n = 207) and normal BMI (49.2%, n = 213). Approximately one-third were aged between 18 and 20 years (37.3%, n = 163). Regarding the current affiliated colleges, the students were mainly in the preparatory year (12.4%, n = 54), College of Arts and Humanities (13.3%, n = 58), and Faculty of Science (14.6%, n = 64).

Table I: Sociodemographic characteristics of the participants (N = 437).

Demographics		N	Min	Max	Mean	SD
Age		437	18	30	22.16	3.2
Weight		433	30.00	157.00	59.05	16.7
Height		436	140.00	175.00	158.08	5.9
BMI		433	11.72	69.78	23.59	6.3
					Count	**%**
Total					437	100.0
Age	18-20				163	37.3
	21-23				165	37.8
	24-26				55	12.6
	27-30				54	12.4
Marital status	Single				391	89.5
	Married				35	8.0
	Divorced				11	2.5
Nationality	Saudi				413	94.5
	Non-Saudi				24	5.5
Academic GPA	4.5 - 5				207	47.4
	4 - 4.5				99	22.7
	3.5 - 4				87	19.9
	<3				44	10.1
BMI	Underweight				85	19.6
	Normal				213	49.2
	Overweight				76	17.6
	Obese				59	13.6
	Missing				4	
Total					437	100.0
	Preparatory year				54	12.4
	College of Arts and Humanities				58	13.3
	Faculty of Science				64	14.6
	College of Engineering				3	0.7
	Faculty of Medicine				28	6.4
	College of Applied Medical Sciences				6	1.4
	College of Marine Sciences				2	0.5
	Applied College				14	3.2
What is your current college	Faculty of Dentistry				5	1.1
	College of Pharmacy				3	0.7
	Faculty of Tourism				10	2.3
	College of Human Sciences and Designs				18	4.1
	College of Educational Graduate Studies				11	2.5
	College of Computers and Information Technology				33	7.6
	College of Communication and Media				30	6.9
	College of Economics and Administration				41	9.4
	College of Nursing				8	1.8
	Faculty of Medical Rehabilitation Sciences				2	0.5
	Faculty of Law				32	7.3
	Faculty of Medicine in Rabigh				2	0.5
	College of Computers and Information Technology in Rabigh				2	0.5
	College of Business in Rabigh				11	2.5

Table II shows the physical characteristics of concerns among the participants (N = 437), with most worried about their body parts/flaws (80.5%, n = 352). The body features of major concern included skin (32.3%, n = 141), obesity (23.6%, n = 103), teeth (21.5%, n = 94), and hair (21.3%, n = 93).

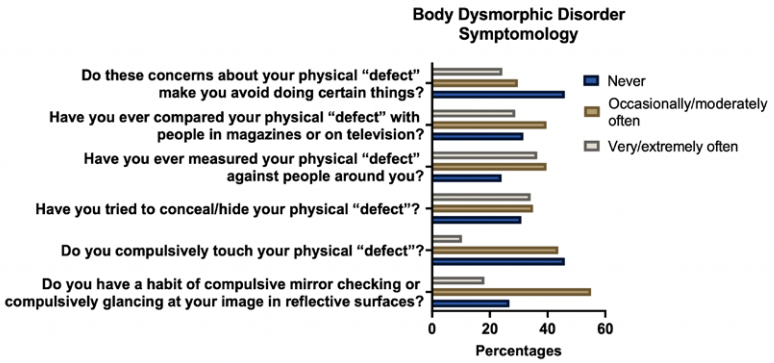
The frequency of BDD symptoms among the participants was measured. Notably, most students occasionally had the habit of compulsive mirror checking or glancing at their image on reflective surfaces (such as windows and doors) (55.1%, n = 241). Approximately 50% of the students also occasionally (a) measured their physical "defect" against the status of people around them (39.6%, n = 173) and (b) compared themselves with people in magazines or on television in terms of their physical "defect" (39.6%, n = 173). Furthermore, approximately 50% of the students reported that the concerns about their physical "defects" never made them avoid doing certain things (such as looking into a mirror, getting photographed, and avoiding social gatherings) (46.0%, n = 201). The distribution of the frequency of BDD symptoms among students is shown in **figure 1**.

Furthermore, our results revealed that most students were never diagnosed with BDD symptoms (92.0%, n = 402). The level of social interaction anxiety among the students was analyzed, and most patients slightly or did not experience many of the SIAS items, including (a) being nervous when speaking with someone in authority (52.4%, n = 229), (b) having difficulty making eye contact with others (59.5%, n = 260), (c) finding it difficult to mix comfortably with the people they work with (53.1%, n = 232), (d) being tensed up if they meet an acquaintance in the street (61.1%, n = 267), (e) not being uncomfortable when mixing socially (55.0%, n = 240), (f) feeling tensed if alone with just one other person (55.9%, n = 244), (g) feeling at ease meeting people at parties (50.1%, n = 219), (h) having difficulty talking with other people (60.0%, n = 262), (i) finding it easy to think of things to talk about (55.0%, n = 240), (j) finding it difficult to disagree with another's perspective (61.1%, n = 267), (k) feeling the urge to say something embarrassing when talking (53.5%, n = 234), (l) worrying about being ignored when mixing in a group of people (48.3%, n = 211), (m) feeling tensed mixing in a group (53.7%, n = 235), and (n) being unsure whether to greet someone they know only slightly (54.9%, n = 240). Regarding social interaction anxiety, the highest mean score of 2.46 ± 1.2 (range 0–4, N = 437) was observed for the "finding it easy to think of things to talk about (reversed)" item, whereas the lowest mean score of 1.30 ± 1.2 (range: 0-4, N = 437) was observed for the "finding it difficult to disagree

Table II: Physical features of concern among the participants (N = 437).

Variables		Count	%
Total		437	100.0
Are there any body parts/flaws that you are worried about?	Yes	352	80.5
	No	85	19.5
Which aspect/feature:	Weight	64	14.6
	Body	71	16.2
	Hair	93	21.3
	Skin	141	32.3
	Face	21	4.8
	Teeth	94	21.5
	Nose	59	13.5
	Obesity	103	23.6
	Epidermis	33	7.6
	Thin	23	5.3
	Fat	5	1.1
	Eyes	5	1.1
	Slim	3	0.7
	Height	8	1.8
	Lips	5	1.1
	None	50	11.4

Figure 1: Distribution of the frequency of body dysmorphic disorder symptoms among the participants (N = 437).



with another's perspective" item. The overall mean social interaction anxiety scores and scales are presented in **table III**. The results showed a mean value of 33.71 ± 18.5 (range: 0-73, N+ 437) for the SIAS in <50% of students. Furthermore, the results revealed that most students had no social anxiety (53.5%, n = 234).

The reliability statistics showed a favorable Cronbach's alpha value of 0.948 (N = 19) for the SIAS, as shown in **table IV**.

Notably, the association between the SIAS and participants' sociodemographic characteristics was assessed (**Table V**). A significant association was observed between the SIAS and age (p < 0.001), marital status (p = 0.046), and academic GPA (p = 0.004). Notably, the proportion of students without social anxiety was significantly higher than that of those with social anxiety, regardless of age or marital status. In addition, the number of students with academic GPA ranging from four to five (53.5-61.4%) who had no social anxiety was significantly higher than that of those with social anxiety (38.6-46.5%). Notably, the proportion of students with an academic GPA of ≤4 who had social anxiety (57.5-61.4%) was significantly higher than that of those without social anxiety (38.6-42.5%).

Table VI shows the association between the SIAS and physical flaws and diagnoses of the participants. The results revealed a significant association between the SIAS and insecurity about body features in students (P < 0.001). Notably, the proportion of students without any concern about their body parts who had no social anxiety (74.1%, n = 63) was significantly higher than that of those with social anxiety (25.9%).

Table III: Overall mean score and scale of social interaction anxiety among the participants (N = 437).

Variables	N	Min	Max	Mean	SD
Social Interaction Anxiety Scale	437	0	73	33.71	18.5
				Count	**%**
Total				437	100.0
Social Interaction Anxiety Scale		Without Social Anxiety		234	53.5
		With Social Anxiety		203	46.5

Table IV: Reliability statistics of the social interaction anxiety scale.

Reliability Statistics	Cronbach's Alpha	N of Items
Social Interaction Anxiety Scale	0.948	19

Table V: Association between the social interaction anxiety scale and sociodemographic characteristics of the participants (N = 437).

Demographics		Total	Social Interaction Anxiety Scale		p-value
			Without Social Anxiety	With Social Anxiety	
Total		437	234 (53.5%)	203 (46.5%)	-
Age	18-20	163	76 (46.6%)	87 (53.4%)	<0.001[a]
	21-23	165	86 (52.1%)	79 (47.9%)	
	24-26	55	29 (52.7%)	26 (47.3%)	
	27-30	54	43 (79.6%)	11 (20.4%)	
Marital status	Single	391	202 (51.7%)	189 (48.3%)	0.046[a]
	Married	35	23 (65.7%)	12 (34.3%)	
	Divorced	11	9 (81.8%)	2 (18.2%)	
Nationality	Saudi	413	219 (53.0%)	194 (47.0%)	0.366
	Non-Saudi	24	15 (62.5%)	9 (37.5%)	
Academic GPA	4.5 - 5	207	127 (61.4%)	80 (38.6%)	0.004[a]
	4 - 4.5	99	53 (53.5%)	46 (46.5%)	
	3.5 - 4	87	37 (42.5%)	50 (57.5%)	
	<3	44	17 (38.6%)	27 (61.4%)	
BMI	Underweight	85	42 (49.4%)	43 (50.6%)	0.098
	Normal	213	123 (57.7%)	90 (42.3%)	
	Overweight	76	43 (56.6%)	33 (43.4%)	
	Obese	59	24 (40.7%)	35 (59.3%)	

[a]-significant using Chi-Square Test at <0.05 level

Table VI: Association between the social interaction anxiety scale and physical flaws and diagnoses of the participants (N = 437).

Variables		Total	Social Interaction Anxiety Scale		p-value
			Without Social Anxiety	With Social Anxiety	
Total		437	234 (53.5%)	203 (46.5%)	-
Are there any body parts/flaws that you are worried about?	Yes	352	171 (48.6%)	181 (51.4%)	<0.001[a]
	No	85	63 (74.1%)	22 (25.9%)	
Have you been diagnosed with anorexia nervosa or bulimia?	Yes	35	15 (42.9%)	20 (57.1%)	0.186
	No	402	219 (54.5%)	183 (45.5%)	

[a]-significant using Chi-Square Test at <0.05 level

The association between the SIAS and BDD symptoms in participants was also determined (**Table VII**). The results showed a significant association between the SIAS and all reported BDD symptoms ($p < 0.001$) according to the chi-square test analysis at $p < 0.05$. Notably, a significantly higher number of those with social anxiety (61.7-80.2%) extremely/very often experienced BDD symptoms than those without social anxiety (19.8-38.3%).

Table VIII shows the association between the SIAS and physical features of concern among the students. Significant associations were observed between the SIAS and specific body features of concern, such as body ($p = 0.037$), hair ($p = 0.011$), teeth ($p = 0.016$), nose ($p < 0.001$), obesity ($p = 0.001$), and height ($p = 0.019$). Notably, a significantly higher proportion of students with social anxiety (57.4-87.5%) were concerned about these features than those without social anxiety (12.5-42.6%). Further analysis revealed the sociodemographic and academic predictors of BDD among the participants. Results showed that the age of 18-20 years was the most significant positive predictor of BDD ($p = 0.001$, B = 1.289, standard error [SE] = 0.384, Exp (B) = 3.629, 95% CI = 1.709-7.707), suggesting that students aged 18–20 years have a 1.289 chance of BDD being triggered. Other positive predictors were the age of 24-26 years ($p = 0.006$, B = 1.1191, SE = 0.436, Exp (B) = 3.289, 95% CI = 1.400-7.725) and 21–23 years ($p = 0.002$, B = 1.146, SE = 0.378, Exp (B) = 3.145, 95% CI = 1.499-6.598). In contrast, an academic GPA of 4.5-5 was a significant negative predictor of BDD ($p = 0.037$, B = -0.735, SE = 0.353, Exp (B) = 0.480, 95% CI = 0.240–0.957), suggesting that students with an academic GPA of 4.5–5 have a 0.735 chance of not exhibiting BDD.

The frequency of behavioral predictors of BDD among the participants was also examined (**Table IX**). The most significant negative predictors were BDDS6 (Never) ($p <$

Table VII: Association between the social interaction anxiety scale and symptoms of body dysmorphic disorder in the participants (N = 437).

Body dysmorphic disorder symptomology		Total	Social Interaction Anxiety Scale		p-value
			Without Social Anxiety	With Social Anxiety	
Total		437	234 (53.5%)	203 (46.5%)	-
Do you have a habit of compulsive mirror checking or glancing at your image in reflective surfaces?	Never	117	73 (62.4%)	44 (37.6%)	<0.001[a]
	Occasionally/moderately often	241	134 (55.6%)	107 (44.4%)	
	Very/Extremely often	79	27 (34.2%)	52 (65.8%)	
Do you compulsively touch your physical "defect"?	Never	201	135 (67.2%)	66 (32.8%)	<0.001[a]
	Occasionally/moderately often	191	89 (46.6%)	102 (53.4%)	
	Very/Extremely often	45	10 (22.2%)	35 (77.8%)	
Have you tried to conceal/hide your physical "defect"?	Never	135	84 (62.2%)	51 (37.8%)	<0.001[a]
	Occasionally/moderately often	153	93 (60.8%)	60 (39.2%)	
	Very/Extremely often	149	57 (38.3%)	92 (61.7%)	
Have you ever measured your physical "defect" against the status of people around you?	Never	105	69 (65.7%)	36 (34.3%)	<0.001[a]
	Occasionally/moderately often	173	111 (64.2%)	62 (35.8%)	
	Very/Extremely often	159	54 (34.0%)	105 (66.0%)	
Have you ever compared yourself with people in magazines or on television in terms of your physical "defect"?	Never	138	88 (63.8%)	50 (36.2%)	<0.001[a]
	Occasionally/moderately often	173	104 (60.1%)	69 (39.9%)	
	Very/Extremely often	126	42 (33.3%)	84 (66.7%)	
Do these concerns about your physical "defect" make you avoid doing certain things?	Never	201	144 (71.6%)	57 (28.4%)	<0.001[a]
	Occasionally/moderately often	130	69 (53.1%)	61 (46.9%)	
	Very/Extremely often	106	21 (19.8%)	85 (80.2%)	

[a]-significant using Chi-Square Test at <0.05 level

Table VIII: Association between the social interaction anxiety scale and physical features of concern among the students (N = 437).

Variables		Total	Social Interaction Anxiety Scale		p-value
			Without Social Anxiety	With Social Anxiety	
Total		437	234 (53.5%)	203 (46.5%)	-
Which aspect/feature:	Weight	64	35 (54.7%)	29 (45.3%)	0.843
	Body	71	30 (42.3%)	41 (57.7%)	0.037[a]
	Hair	93	39 (41.9%)	54 (58.1%)	0.011[a]
	Skin	141	67 (47.5%)	74 (52.5%)	0.081
	Face	21	8 (38.1%)	13 (61.9%)	0.146
	Teeth	94	40 (42.6%)	54 (57.4%)	0.016[a]
	Nose	59	16 (27.1%)	43 (72.9%)	<0.001[a]
	Obesity	103	41 (39.8%)	62 (60.2%)	0.001a
	Epidermis	33	20 (60.6%)	13 (39.4%)	0.398
	Thin	23	10 (43.5%)	13 (56.5%)	0.320
	Fat	5	3 (60.0%)	2 (40.0%)	0.771
	Eyes	5	1 (20.0%)	4 (80.0%)	0.130
	Slim	3	2 (66.7%)	1 (33.3%)	0.648
	Height	8	1 (12.5%)	7 (87.5%)	0.019[a]
	Lips	5	1 (20.0%)	4 (80.0%)	0.130

[a]-significant using Chi-Square Test at <0.05 level

0.001, B = -1.986, SE = 0.325, Exp (B) = 0.137, 95% CI = 0.073–0.260), BDDS6 (occasionally/moderately often) (p < 0.001, B = -1.322, SE = 0.311, Exp (B) = 0.267, 95% CI = 0.145–0.491), BDDS2 (Never) (p = 0.004, B = -1.254, SE = 0.430, Exp (B) = 0.285, 95% CI = 0.123–0.663), and BDDS4 (occasionally/moderately often) (p = 0.009, B = -0.673, SE = 0.259, Exp (B) = 0.510, 95% CI = 0.307–0.846).

Finally, the physical feature predictors of BDD among participants were determined (**Table X**). Results showed that the nose was the most significant positive body feature predictor of BDD (p = 0.001, B = 1.094, SE = 0.319, Exp (B) = 2.987, 95% CI = 1.597–5.586), suggesting that students insecure about their noses have a 1.094 chance of BDD being triggered. Another positive predictor was obesity (p = 0.030, B = 0.526, SE = 0.242, Exp (B) = 1.691, 95% CI = 1.052–2.718).

Table IX: Frequency of behavioral predictors of body dysmorphic disorder among the participants.

Variables in the Equation		B	SE	Exp (B)	95% CI for EXP (B)		p-value
					Lower	Upper	
First Step[a]	BDDS1						0.134
	BDDS1(Never)	-0.699	0.359	0.497	0.246	1.004	0.051
	BDDS1(Occasionally/moderately often)	-0.517	0.310	0.596	0.325	1.095	0.096
	BDDS2						0.033[b]
	BDDS2(Never)	-1.124	0.460	0.325	0.132	0.800	0.015[b]
	BDDS2(Occasionally/moderately often)	-0.696	0.440	0.499	0.210	1.181	0.114
	BDDS3						0.736
	BDDS3(Never)	0.121	0.348	1.129	0.571	2.231	0.728
	BDDS3(Occasionally/moderately often)	-0.108	0.291	0.898	0.508	1.587	0.711
	BDDS4						0.152
	BDDS4(Never)	-0.296	0.410	0.744	0.333	1.662	0.471
	BDDS4(Occasionally/moderately often)	-0.575	0.305	0.563	0.310	1.022	0.059
	BDDS5						0.221
	BDDS5(Never)	0.227	0.393	1.254	0.580	2.711	0.564
	BDDS5(Occasionally/moderately often)	-0.282	0.313	0.754	0.409	1.392	0.367
	BDDS6						<0.001[b]
	BDDS6(Never)	-2.068	0.341	0.126	0.065	0.247	<0.001[b]
	BDDS6(Occasionally/moderately often)	-1.364	0.321	0.256	0.136	0.479	<0.001[b]
	Constant	2.874	0.502	17.708			<0.001[b]
Last Step[a]	BDDS2						0.009[b]
	BDDS2(Never)	-1.254	0.430	0.285	0.123	0.663	0.004[b]
	BDDS2(Occasionally/moderately often)	-0.803	0.419	0.448	0.197	1.018	0.055
	BDDS4						0.021[b]
	BDDS4(Never)	-0.152	0.327	0.859	0.453	1.632	0.643
	BDDS4(Occasionally/moderately often)	-0.673	0.259	0.510	0.307	0.846	0.009[b]
	BDDS6						<0.001[b]
	BDDS6(Never)	-1.986	0.325	0.137	0.073	0.260	<0.001[b]
	BDDS6(Occasionally/moderately often)	-1.322	0.311	0.267	0.145	0.491	<0.001[b]
	Constant	2.421	0.442	11.259			<0.001[b]

[a]-Variable(s) entered in step 1: BDDS1 = Do you have a habit of compulsive mirror checking or glancing at your image in reflective surfaces?, BDDS2 = Do you compulsively touch your physical "defect"?, BDDS3 = Have you tried to conceal/hide your physical "defect"?, BDDS4 = Have you ever measured your physical "defect" against the status of people around you?, BDDS5 = Have you ever compared yourself with people in magazines or on television in terms of your physical "defect"?, BDDS6 = Do these concerns about your physical "defect" make you avoid doing certain things?.
[b]-Significant using Binary Logistic Regression Model with Backward Conditional Elimination, with Enter Criteria of 0.05 and Elimination of 0.10.

Table X: Physical feature predictors of body dysmorphic disorders among the participants.

Variables in the Equation		B	SE	Exp (B)	95% CI for EXP (B)		p-value
					Lower	Upper	
First Step[a]	Are there any body parts/flaws that you are worried about?(Yes)	0.654	0.288	1.923	1.093	3.382	0.023[b]
	Which aspect/feature						
	Body(Yes)	0.470	0.281	1.600	0.922	2.777	0.094
	Hair(Yes)	0.417	0.251	1.518	0.928	2.483	0.096
	Teeth(Yes)	0.247	0.255	1.281	0.777	2.111	0.332
	Nose(Yes)	1.052	0.323	2.862	1.520	5.390	0.001[b]
	Obesity(Yes)	0.576	0.246	1.780	1.099	2.883	0.019[b]
	Height(Yes)	2.083	1.091	8.026	0.946	68.056	0.056
	Constant	-1.198	0.254	0.302			<0.001[b]
Last Step[a]	Are there any body parts/flaws that you are worried about?(Yes)	0.774	0.280	2.167	1.251	3.756	0.006b
	Which aspect/feature						
	Hair(Yes)	0.437	0.249	1.549	0.951	2.521	0.078
	Nose(Yes)	1.094	0.319	2.987	1.597	5.586	0.001[b]
	Obesity(Yes)	0.526	0.242	1.691	1.052	2.718	0.030[b]
	Height(Yes)	2.089	1.086	8.077	0.961	67.862	0.054
	Constant	-1.165	0.253	0.312			<0.001[b]

[a]-Variable(s) entered in step 1: Are there any body parts/flaws that you are worried about? (Body, Hair, Teeth, Nose, Obesity, or Height).
[b]-Significant using Binary Logistic Regression Model with Backward Conditional Elimination, with Enter Criteria of 0.05 and Elimination of 0.10.

Discussion

The present study's results showed that 46.5% of the participants experienced symptoms of social anxiety, as indicated by the SIAS. This finding is inconsistent with that of a similar study conducted in Riyadh, Saudi Arabia, in which only 25% of participants exhibited symptoms of social anxiety[3]. Further analysis revealed a significant association between sociodemographic characteristics and SIAS scores in the present study. Notably, the incidence of social anxiety was associated with age ($p<0.001$), marital status ($p=0.046$), and academic GPA ($p=0.004$). Younger individuals aged 18-23 years were more likely to experience social anxiety than those aged 24-30 years, possibly due to the fact that most of our study participants were within the age range of 18-23 years old. Furthermore, regarding marital status (48.3%), single individuals exhibited symptoms of social anxiety, whereas the others (51.7%) did not. A study by Moutier and Stein (1999) suggests that individuals with social anxiety are less likely to be married than those without social anxiety[9].

In the present study, there was a significant association between social anxiety and lower academic GPA, as participants with a GPA of 4-5 (53.5-61.4%) had no social anxiety, whereas those with a GPA of ≤4 (57.5-61.4%) exhibited social anxiety. One possible reason for this could be that individuals with social anxiety struggle to perform well in academic tasks requiring public speaking, such as presentations, debates, class discussions, and other similar forms of social interaction. This finding is supported by those of a study by Fang and Hofmann, which indicates that individuals with social anxiety are less likely to be well-educated than their peers without the condition[10].

Regarding BDD symptoms, our results showed a significant association between social anxiety and all reported symptoms of BDD ($p < 0.001$). Consistent with the present study, a previous study indicated that students who were concerned about their appearance (including those who did not test positive for BDD) had higher levels of social anxiety and depressive symptoms than those who were not. In addition, students who were concerned about the appearance of parts of their body unrelated to weight had higher SIAS scores ($P<0.001$)[11]. Furthermore, in the present study, a higher proportion of the students concerned about their body, hair, teeth, nose, obesity, and height experienced social anxiety. A previous study reported a 19% rate of dissatisfaction with body image, with the most common concerns being not thin enough, not attractive enough, and feeling dissatisfied with body shape, hair, and face. This could be due to the effect of social media, as these students tended to check social media more frequently. In addition, individuals who followed celebrities and checked social media more frequently were more likely to experience depressive symptoms and social anxiety[12].

All symptoms of BDD among the participants in the present study were common. Over half of the students (55.1%) moderately often had the habit of compulsive mirror checking or glancing at their image on reflective surfaces, whereas 18.1 % of them extremely often checked out the way they looked compulsively. A study on medical students in Pakistan reported that out of the 156 participants, 57.1% were female, whereas 42.9 % were male. Notably, 78.8% of the students were dissatisfied with a few aspects of their looks and appearance, and 5.8% met the Diagnostic and Statistical Manual of Mental Disorders, fourth edition criteria for BDD. Among the patients with BDD, the male-to-female ratio was 1.7. In both the present and the Pakistani studies, over half of the students reported that these concerns made them avoid performing certain activities[13]. In the present study, the physical features of major concern were skin (32.3%) and obesity (23.6%), consistent with findings of a previous study on female medical students in Riyadh, in which the areas of major concern were skin (75%) and fat (68.8%)[3]. Notably, most were concerned about their skin, possibly due to its visibility and role in shaping their overall appearance. Furthermore, according to previous studies, this may be the reason for the remarkably greater prevalence of BDD among dermatological patients[14,15]. They were more frequently concerned about acne, skin color, and hair loss than the rest of the population. Social media can significantly impact individuals' body image and how they perceive themselves[16]. It often presents curated and idealized versions of people's lives and appearances. In addition, the availability of filters and photo-editing tools on social media distorts reality and creates unrealistic beauty standards, as individuals may start believing that the heavily edited images they see are representative of real-life beauty. People with BDD may feel pressured to meet these standards, leading to heightened distress and dissatisfaction with their own appearance by unfavorably comparing themselves to others, thus exacerbating their preoccupation with their perceived flaws[17].

This study had some limitations. First, we targeted female students from one university, and we relied on convenient sampling, which may lead to selection bias; therefore, our results may lack external validity. Second, data were collected through self-administered questionnaires; therefore, they may not be accurate because of recall bias.

Conclusions

Our results showed a significant association between social anxiety and all reported symptoms of BDD ($p < 0.001$), and a higher proportion of students concerned about their body, hair, teeth, nose, obesity, and height exhibited social anxiety. In this study, the physical features of major concern were skin (32.3%) and obesity (23.6%), which could be due to social media and its impact on body image and how individuals

perceive themselves. The availability of filters and photo-editing tools on social media creates unrealistic beauty standards, thus increasing the rate of body dissatisfaction among students.

Declarations

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Unit of Biomedical Ethics, Research Ethics Committee of King Abdulaziz University, Faculty of Medicine (Reference No 542-22) (November 24, 2022)

Informed Consent Statement

Written informed consent was obtained from all subjects at the beginning of the survey.

Author Contributions

Conceptualization, S.A.Alfakeh., and D.R.A.; methodology, A.M.B.; formal analysis, S.A.Alfakeh.; data curation, S.A.Alfakeh.; writing -original draft preparation, A.M.B., A.N.A., S.A.Albaiti., D.R.A., and S.F.B.; writing - review and editing, S.A.Alfakeh., A.M.B., A.N.A., S.A.Albaiti., D.R.A., and S.F.B.; visualization, S.A.Alfakeh.; supervision, S.A.Alfakeh.; project administration, S.A.Alfakeh. All authors have read and agreed to the published version or the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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References

1. Anderson D, Lord C, Risi S, DiLavore P, Shulman C, Thurm A, et al. American Psychiatric Association.(2013). Diagnostic and statistical manual of mental disorders . Washington, DC: Author. The Linguistic and Cognitive Effects of Bilingualism on Children with Autism Spectrum Disorders. 2017;21:175.

2. Bjornsson AS, Didie ER, Phillips KA. Body dysmorphic disorder. Dialogues Clin Neurosci. 2010.

3. Ahamed SS, Enani J, Alfaraidi L, Sannari L, Algain R, Alsawah Z, Al Hazmi, A. Prevalence of body dysmorphic disorder and its association with body features in female medical students. Iranian journal of psychiatry and behavioral sciences. 2016;10(2).

4. Nicewicz HR, Boutrouille JF. Body Dysmorphic Disorder. 2020.

5. Phillips KA. Body dysmorphic disorder: the distress of imagined ugliness. Am J Psychiatry. 1991;148(9):1138-49.

6. Alghamdi WA, Subki AH, Khatib HA, Butt NS, Alghamdi RA, Alsallum MS, et al. Body Dysmorphic Disorder Symptoms: Prevalence and Risk Factors in an Arab Middle Eastern Population. International Journal of General Medicine. 2022:2905-12.

7. Singh AR, Veale D. Understanding and treating body dysmorphic disorder. Indian journal of psychiatry. 2019;61(Suppl 1):S131.

8. Mattick RP, Clarke JC. Development and validation of measures of social phobia scrutiny fear and social interaction anxiety. Behaviour research and therapy. 1998;36(4):455-70.

9. Moutier CY, Stein MB. The history, epidemiology, and differential diagnosis of social anxiety disorder. Journal of Clinical Psychiatry. 1999;60(9):4-8.

10. Fang A, Hofmann SG. Relationship between social anxiety disorder and body dysmorphic disorder. Clinical psychology review. 2010;30(8):1040-8.

11. Liao Y, Knoesen NP, Deng Y, Tang J, Castle DJ, Bookun R, et al. Body dysmorphic disorder, social anxiety and depressive symptoms in Chinese medical students. Social Psychiatry and Psychiatric Epidemiology. 2010;45:963-71.

12. Charmaraman L, Richer AM, Liu C, Lynch AD, Moreno MA. Early adolescent social media-related body dissatisfaction: Associations with depressive symptoms, social anxiety, peers, and celebrities. Journal of developmental and behavioral pediatrics: JDBP. 2021;42(5):401.

13. Taqui AM, Shaikh M, Gowani SA, Shahid F, Khan A, Tayyeb SM, et al. Body Dysmorphic Disorder: gender differences and prevalence in a Pakistani medical student population. BMC psychiatry. 2008;8(1):1-10.

14. AlShahwan MA. Prevalence and characteristics of body dysmorphic disorder in Arab dermatology patients. Saudi medical journal. 2020;41(1):73.

15. Vulink N, Sigurdsson V, Kon M, Bruijnzeel-Koomen C, Westenberg H, Denys D. Body dysmorphic disorder in 3-8% of patients in outpatient dermatology and plastic surgery clinics. Nederlands tijdschrift voor geneeskunde. 2006;150(2):97-100.

16. Jiotsa B, Naccache B, Duval M, Rocher B, Grall-Bronnec M. Social media use and body image disorders: Association between frequency of comparing one's own physical appearance to that of people being followed on social media and body dissatisfaction and drive for thinness. International journal of environmental research and public health. 2021;18(6):2880.

17. Alsaidan MS, Altayar NS, Alshmmari SH, Alshammari MM, Alqahtani FT, Mohajer KA. The prevalence and determinants of body dysmorphic disorder among young social media users: a cross-sectional study. Dermatology reports. 2020;12(3).

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ORIGINAL

Relación entre actividad Física y Riesgo Cardiovascular: Una revisión sistemática

Relantionship between physical activity and cardiovascular risk: a systematic review

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Resumen

Introducción: La morbilidad cardiovascular representa la causa principal de mortalidad a nivel global, lo que ha generado un creciente interés en los factores de riesgo (FRCV) y los elementos protectores de la salud cardiovascular, entre los cuales se destacan el sedentarismo y la actividad física respectivamente.

Metodología: En este estudio se lleva a cabo una revisión sistemática, siguiendo las directrices PRISMA, con el principal objetivo de recopilar y contrastar la información disponible acerca del impacto que la práctica de actividad física ejerce sobre el riesgo cardiovascular (RCV).

Resultados: A través del proceso de cribado y selección, se identificaron 16 artículos científicos; los cuales indican que la práctica de actividad física, especialmente aquella de intensidades moderada y vigorosa, mejora un amplio y heterogéneo conjunto de FRCV, influyendo positivamente sobre la salud cardiovascular y global de las personas. Por otra parte, se constata una carencia de estudios que valoren la práctica de actividad física de forma objetiva.

Conclusiones: Por último, la evidencia disponible muestra que porcentajes significativos de la población no cumplen con las recomendaciones mínimas de actividad física de la OMS, lo que subraya la importancia de implementar estrategias de promoción de la salud destinadas a incentivar la realización de actividad física, especialmente entre los niños y los ancianos.

Palabras clave: riesgo cardiovascular, salud cardiovascular, ejercicio, deporte, actividad física.

Abstract

Introduction: Cardiovascular morbidity stands as the primary cause of mortality globally, eliciting a burgeoning interest in cardiovascular risk factors (CVRF) and protective elements of cardiovascular health, among which sedentarism and physical activity stand out, respectively.

Methods: This study undertakes a systematic review, adhering to PRISMA guidelines, with the primary aim of compiling and contrasting the available information regarding the impact of physical activity on cardiovascular risk.

Results: After the screening and selection process, 16 scientific articles were identified; these indicate that engaging in physical activity, particularly of moderate and vigorous intensities, enhances a broad and heterogeneous array of CVRF, positively influencing both cardiovascular and overall health. Conversely, there is a dearth of studies assessing physical activity objectively.

Discussion: Lastly, available evidence demonstrates that significant proportions of the population are failing to meet the WHO's minimum physical activity recommendations, underscoring the importance of implementing health promotion strategies aimed at encouraging physical activity, especially among children and the elderly.

Key words: heart disease risk, cardiovascular risk, cardiovascular health, exercise, sport, physical activity.

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Introducción

Riesgo cardiovascular: definición del concepto y su origen

Se entiende por "Riesgo cardiovascular", la probabilidad que una persona o población tienen de sufrir una enfermedad cardiovascular (ECV) en un plazo de tiempo determinado[30]. Habitualmente, el termino ECV incluye: la mortalidad cardiovascular, las complicaciones cardioisquémicas, cerebrovasculares y cardiovasculares (letales y no letales). En cuanto al lapso de tiempo al que se hace referencia en estas escalas de riesgo, lo más común son 10 años, aunque pueden encontrase otros, como 20 o más.

Uno de los primeros estudios relacionados con los posibles factores de riesgo cardiovascular, es el "Estudio de Framingham"[31], siendo este uno de los más conocidos en la actualidad, y que a su vez sentó un precedente en cuanto a la realización de escalas destinadas a medir y objetivar el RCV de los pacientes. En el año 1948 el Servicio de Salud Pública de los EE. UU. inició este estudio de cohortes observacional, que en un principio contó con 5209 pacientes, pero que más tarde abarcaría otras dos generaciones más, de 5124 y 4095 pacientes respectivamente[29].

Factores de riesgo cardiovascular

Se denominan FRCV a aquellas características biológicas, hábitos o estilos de vida que aumentan la probabilidad de padecer una enfermedad cardiovascular[27].

Se dividen en base a su contribución para aumentar el RCV, y en base a su alterabilidad en: modificables y no modificables. Siendo los primeros aquellos que más interés generan, ya que permiten llevar a cabo estrategias de prevención mediante la manipulación de los mismos.

Entre los más importantes se encuentran:

- FCV no modificables: edad, sexo, genética, historia familiar, etc.
- FCV modificable: tabaquismo, hipertensión arterial, hipercolesterolemia, diabetes mellitus, obesidad o sobrepeso; habitualmente relacionados con la falta de actividad física (o sedentarismo).

Siendo esta última, la inactividad física, de especial relevancia para el desarrollo del presente trabajo, por lo que más adelante se profundizará sobre ello.

Formas de evaluar el Riesgo Cardiovascular

Existen diversas escalas creadas con la intención de evaluar el RCV, cada una de las cuales considera una serie de parámetros que son los denominados "factores de riesgo cardiovascular"; estas escalas se emplean con mayor o menor frecuencia en diferentes regiones, principalmente debido a la precisión con la que evalúan a los pacientes de la población en cuestión.

En la **tabla I** que se presenta a continuación, se resumen algunos de los baremos de RCV más importantes en la actualidad[30], con sus principales características, entre las cuales encontramos: el año en el que se creó la primera versión de la misma, las variables que se tienen en cuenta, así como otros aspectos vinculados a los estudios de cohortes que fundamentaron el desarrollo de estas escalas (la cohorte de derivación y la cohorte de validación, coincidiendo esta última con el territorio principal en el que se usa cada uno de los baremos).

Tabla I: Comparación de escalas de RCV

	Framingham	SCORE	ASSIGN	Reynolds	QRISK	PROCAM
Año de inicio	1948	2003	2006	2007	2007	1990
Variables incluidas	1,2,3,4,6	1,2,3,4,6,12	1,3,4,6,10,11	1,2,3,4,6, 9,10,13	1,2,3,4,6, 10,11,14	1,2,3,5,6,7,10
Cohorte de derivación	Estados Unidos 30-62 años	Europa 45-64 años	Escocia 30-74 años	Estados Unidos (♀)45-80 años	Reino Unido 35-74 años	Alemania (♂) 35-74 años
Cohorte de validación	Diversas	Europa	Escocia	Estados Unidos	Reino Unido	Alemania

Factores de riesgo:
1. Edad y sexo
2. Tabaquismo
3. Presión arterial sistólica
4. Colesterol total
5. cLDL
6. cHDL
7. Triglicéridos
8. Diabetes Mellitus
9. Glucohemoglobina
10. Antecedentes fam. de ECV precoz
11. Precariedad social
12. Prevalencia poblacional de ECV
13. PCR
14. IMC

Tabla de elaboración propia en la que se comparan las principales características de los baremos de RCV más conocidos.

En el caso de España, cabe destacar las tablas REGICOR[28], una escala derivada de la Framingham, que fue adaptada a la población de España, calibrándola en base a la población de Cataluña; ya que, en un primer lugar, al estudiar la tabla original se pudo observar que en poblaciones con una prevalencia menor de ECV respecto a la de EE. UU. (como es el caso de España) se sobrestimaba el RCV de los pacientes.

Sin embargo, en la práctica clínica en España, las más usadas son las tablas SCORE (Systemic Coronary Risk Estimation); principalmente sus nuevas versiones SCORE2 y SCORE2-OP[21] (old people). Estas tablas sirven para estimar el riesgo de ECV mortales y no mortales en personas de entre 40 y 69 durante un periodo de 10 años, o personas mayores de 70 durante un periodo de 5 a 10 años, respectivamente.

Además, las tablas SCORE2 y SCORE2-OP han sido calibradas en función del nivel de riesgo cardiovascular nacional, tomando como referencia las tasas de mortalidad cardiovascular publicadas por la OMS, dando lugar a 4 variantes de las mismas, que permiten adaptarse aún más a las condiciones de los pacientes. España se sitúan en la primera categoría, es decir, aquella que engloba los países con bajo riesgo cardiovascular. A continuación, la clasificación[22] de los principales países:

- Países de bajo riesgo: Bélgica, Dinamarca, España, Francia, Israel, Luxemburgo, Noruega, Suiza, Países Bajos y Reino Unido.
- Países de moderado riesgo: Alemania, Austria, Chipre, Eslovenia, Finlandia, Grecia, Irlanda, Islandia, Italia, Malta, Portugal, San Marino y Suecia.
- Países de alto riesgo: Albania, Bosnia y Herzegovina, Croacia, Eslovaquia, Estonia, Hungría, Kazajistán, Polonia, República Checa y Turquía.
- Países de muy alto riesgo: Argelia, Armenia, Azerbaiyán, Bielorrusia, Bulgaria, Egipto, Federación de Rusia, Georgia, Kirguistán, Letonia, Líbano, Libia, Lituania, Marruecos, Montenegro, República de Moldavia, Rumanía, Serbia, Siria, Macedonia del Norte, Túnez, Ucrania y Uzbekistán.

Conforme se ilustra en la próxima imagen (**ilustración 1**), las tablas SCORE usan un código de siete colores que indica el riesgo cardiovascular del paciente. Para usarla, hay que ubicar al paciente en las tablas, dependiendo de su género, de si es fumador o no, del intervalo de edad al que pertenece, y finalmente en base a la PAS y el Colesterol total.

Ilustración 1: Tabla SCORE para países con bajo RCV (España).

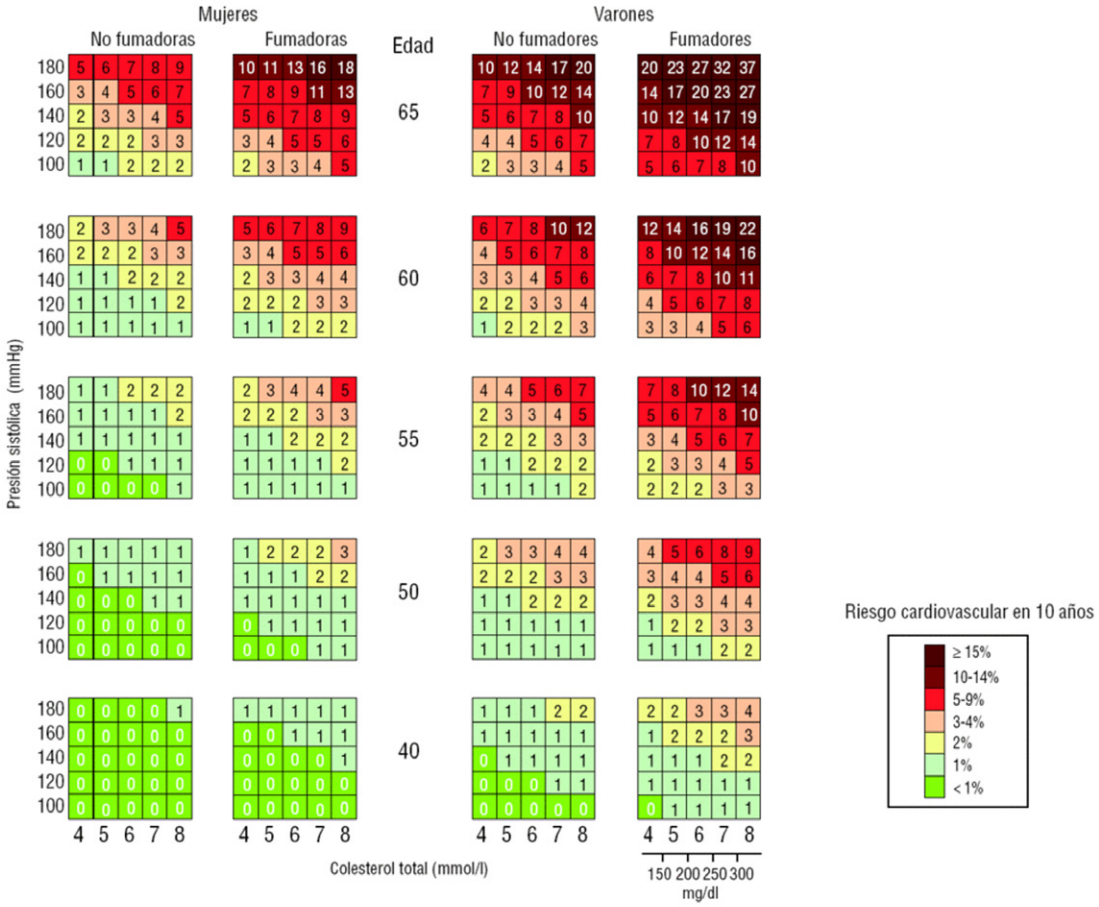


Tabla de la revista española de cardiología (https://www.revespcardiol.org/)

Actividad física: definición y diferencias con otros términos relacionados

Dependiendo de la fuente, podemos definir este concepto de distintas formas. La Organización Mundial de la Salud (OMS) define la actividad física como[25] cualquier movimiento del cuerpo, resultado de la acción de los músculos esqueléticos y que implica un consumo de energía determinado; abarcando una amplia gama de movimientos, desde aquellos que se dan en el contexto de un desplazamiento, durante tiempo de ocio, o dentro del ámbito laboral del individuo. Esta definición es respaldada por el NIH[26] (National Heart, Lung and Blood Institute de Estados Unidos), quienes además hacen referencia al valor positivo intrínseco que tiene la actividad física para la salud.

Las organizaciones previamente mencionadas, además de proporcionan sus definiciones de este concepto, frecuentemente aportan sus propias recomendaciones. Estas guías suelen estar organizadas en base al rango etario de los individuos, si bien su principal limitación radica en su carácter excesivamente general.

Para abordar la actividad física de forma adecuada, es esencial diferenciarla de otros términos parecidos como son el "ejercicio", delimitado según el NIH como aquella actividad física planificada y estructurada (como jugar a un deporte de equipo, o levantar pesas, entre otros.), y definido por la RAE como aquellos movimientos corporales repetidos que son destinados a conservar o recobrar la salud. De igual manera, es importante definir el termino de "deporte", definido según la RAE como aquella actividad física que se ejerce en forma de juego o competición sujetos a normas y que frecuentemente requieren de un entrenamiento previo.

Clasificaciones relativas a la actividad física

El INH[26] delimita los tipos de actividad física en los siguientes cinco:

- Actividades aeróbicas o de resistencia
- Actividades de fortalecimiento muscular
- Actividades de fortalecimiento óseo
- Actividades de equilibrio
- Actividades de flexibilidad

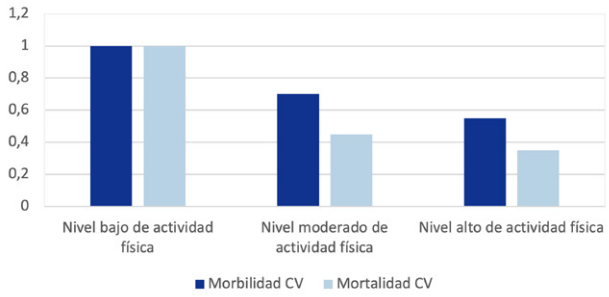
Adicionalmente, podemos clasificar la actividad física realizada por un individuo, en base a la intensidad de la misma. Según las guías de la actividad física[24] redactadas por el departamento de salud de los EE. UU. (y otras fuentes[23]), existen tres niveles de intensidad:

1. Actividades de intensidad ligera (AFL): aquellas que suponen un consumo menor de 3.0 METs. Ejemplos: caminar lentamente, cocinar o realizar tareas domésticas ligeras.
2. Actividades de intensidad moderada (AFM): aquellas que suponen un consumo situado entre 3.0 y 6.0 METs. Ejemplos: caminar rápidamente, jugar al tenis o rastrillar el jardín.
3. Actividades de intensidad vigorosa (AFV): aquellas que suponen un consumo de 6.0 METs o más. Ejemplos: trotar o correr, subir escaleras, atender a clases de deportes.

Por último, resulta de especial interés clasificar a las personas según su nivel de actividad física diaria, permitiendo objetivar si este se sitúa en el rango de lo deseable o fuera de este. En este contexto podemos identificar[24] cuatro categorías:

- Inactivo: aquellas personas que se limitan a ejecutar los movimientos básicos para las actividades diarias, es decir, que no realizan ninguna actividad física de intensidad moderada ni vigorosa.
- Insuficientemente activo: incluye a aquellos individuos que realizan cierta actividad física de intensidad moderada/vigorosa, situándose esta por debajo de los 150/75 minutos a la semana, respectivamente.
- Activo: aquel individuo que realiza el equivalente a 150-300 minutos de actividad física de intensidad moderada a la semana. Los individuos que se sitúan en este nivel cumplen con el objetivo establecidos para los adultos.
- Altamente activo: aquellos que realizan más de 300 minutos de actividad física de intensidad moderada a la semana.

Ilustración 2: Relación entre la realización de actividad física y la morbimortalidad CV.



Gráfica de elaboración propia basada en los resultados de un artículo científico[19]. El estudio se basa en una muestra de 5000 individuos de entre 65 y 74 años, que fueron clasificados en base a la cantidad de actividad física que realizaban, a los que se les hizo un seguimiento médico a lo largo de 42 años. Demostrando como la morbimortalidad por cardiovascular disminuye conforme aumenta el nivel de actividad física practicada.

El sedentarismo y sus consecuencias

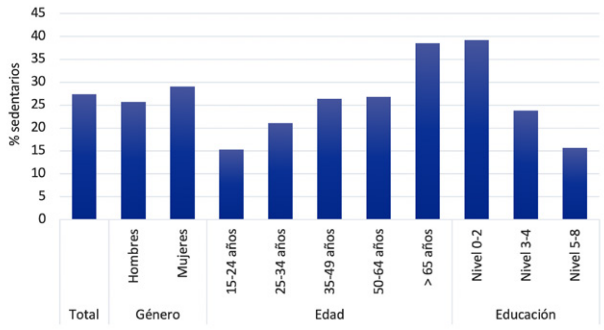
La OMS[18] define el sedentarismo como un estilo de vida carente de actividad física. Según sus estimaciones, aproximadamente un 60% de la población no realizan la cantidad de AF necesaria para obtener beneficios para la salud, clasificando a estas personas como sedentarias, siempre que realicen menos de 90 minutos de actividad física a la semana.

Además, relacionan la inactividad física con resultados de salud desfavorables, entre los cuales se encuentran:

- Incremento de grasa corporal y peso.
- Deterioro de la salud cardiometabólica, así como conductual y social.
- Reducción del tiempo y calidad del sueño.
- Aumento en la prevalencia de enfermedades cardiovasculares, cáncer y diabetes tipo 2.
- Con un consecuente incremento de la mortalidad general, y de la mortalidad por factores cardiovasculares especialmente.

Por otra parte, consultando el Instituto Nacional de Estadística[17] de España, nos podemos hacer una idea de la forma en la que se distribuye el sedentarismo a nivel geográfico, etario, por género, etc. En la última actualización disponible, del año 2022, podemos observar gráficas como las siguientes:

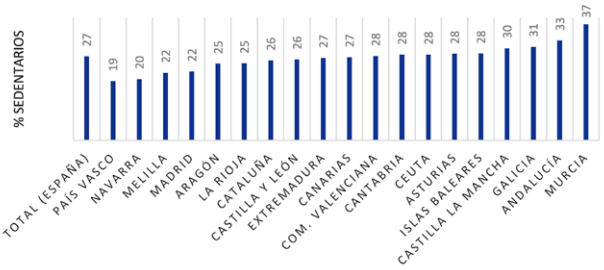
Ilustración 3: Porcentaje de personas sedentarias, clasificado por género, edad y nivel educativo.



Gráfica de elaboración propia basada en datos recabados por las encuestas del INE del año 20022, en la que se refleja el porcentaje de personas sedentarias respecto a la población general de España, clasificadas en base a su género, edad y nivel educativo. Este último se organiza de la siguiente forma:

- Nivel 0-2: preescolar, primaria y secundaria de 1ª etapa
- Nivel 3-4: secundaria de 2ª etapa y postsecundaria no superior
- Nivel 5-8: primer y segundo ciclo de educación superior y doctorado

Ilustración 4: Porcentaje de personas sedentarias, clasificado por comunidades autónomas.



Gráfica de elaboración propia basada en datos recabados por las encuestas del INE del año 20022, en la que se refleja el porcentaje de personas sedentarias respecto a la población general, en España y en las distintas comunidades autónomas.

Prescripción de actividad física

A pesar de la notoria evidencia de que la actividad física disminuye de forma significativa la morbimortalidad cardiovascular independientemente del sexo y edad del individuo (**Ilustración 2**), incluso ante el conocimiento de la correlación inversa existente entre la realización de actividad física de moderada o alta intensidad y la mortalidad por cualquier causa; hasta hace poco, no se valoraba seriamente la posibilidad de prescribir actividad física, limitándola a una mera recomendación, dándole por lo tanto un papel secundario en comparación con los tratamiento farmacológicos (entre otros).

Según la Guía ESC 2021[20], a la hora de prescribir actividad física resulta de vital importancia realizar un cribado previo, e individualizar la intensidad, duración, el tipo y la frecuencia de esta, según las condiciones del paciente en cuestión.

Adicionalmente, se expone la existencia de estrategias útiles para aumentar la motivación de los pacientes para realizar más actividad física, entre las cuales se encuentran:

1. Que el deporte o ejercicio que se prescriba encaje en la rutina diaria del paciente, y además que este disfrute haciéndolo; resulta vital conocer los gustos del paciente para poder individualizar.
2. El uso de gadgets que sirvan para controlar la actividad física realizada, como smartwatches, entre otros.
3. Poner objetivos (claros y alcanzables) en conjunto con el paciente, reevaluarlos cada cierto tiempo, asegurarse de que el paciente tiene sentimiento de autocontrol, y dar feedback.

Objetivos

El objetivo principal de este estudio consiste en analizar las publicaciones disponibles hasta la fecha, acerca del impacto que la práctica de actividad física ejerce sobre el riesgo cardiovascular.

A continuación, se detallan los objetivos secundarios que han orientado el trabajo:

- Analizar y razonar las discrepancias presentes en los artículos obtenidos durante la búsqueda sistemática, particularmente aquellas que abordan las diversas subcategorías de la población: mujeres y hombres; niños, adolescentes, adultos y ancianos.
- Exponer las limitaciones de los estudios disponibles, contribuyendo de esta forma a una evaluación crítica de la evidencia recopilada.
- Resumir las recomendaciones derivadas de la literatura revisada, respecto a la actividad física necesaria para que esta constituya un factor de protección cardiovascular.

Material y métodos

Para llevar a cabo este trabajo, se ha realizado una revisión sistemática principalmente de artículos científicos. Con el objetivo de realizar el proceso de búsqueda y selección de las fuentes, lo más preciso posible, este se ha basado en las directrices expuestas en la declaración PRISMA 2020 (Preferred Reporting Items for Systematic reviews and Meta-Analyses). Esta, es una guía pensada especialmente para revisiones sistemáticas de estudios relacionados con intervenciones sanitarias.

Planificación de la búsqueda

Con la intención de llevar a cabo una búsqueda de alta calidad en diversas bases de datos, se ha empleado el Tesauro MeSH (Medical Subject Headings) del NIH (National Library of Medicine de EE. UU.), se han seleccionado los términos "Heart Disease Risk", "Cardiovascular Risk", "Exercise", "Sport" y "Physical activity".

Adicionalmente, se han aplicado los operadores booleanos pertinentes para dar coherencia a la búsqueda en cuestión; dependiendo de la base de datos se han usado las líneas de búsqueda que se especifican a continuación:

- En Web of Science: *(((TI=(heart disease risk)) OR (TI=(cardiovascular risk))) AND ((TI=(exercise)) OR (TI=(sport)) OR (TI=(physical activity)))) AND (DOP=(2018-01-01/2022-12-31))*
- En PubMed: *((heart disease risk[Title]) OR (cardiovascular risk[Title])) AND ((exercise[Title]) OR (sport[Title]) OR (physical activity[Title])) AND (("2018/01/01"[Date - Publication] : "2022/12/31"[Date - Publication]))*

Búsqueda sistemática

La búsqueda sistemática fue realizada empleando las líneas de búsqueda mencionadas anteriormente, en dos bases de datos: PubMed y Web of Science. Además, con el objetivo de realizar una selección precisa, se definieron los siguientes criterios de inclusión y exclusión:

Se han decidido incluir aquellos resultados de la búsqueda que sean artículos científicos (ya sean revisiones, metaanálisis o estudios); excluyendo por lo tanto libros, letters, papers, etc. Además, se han incluido solo aquellos artículos escritos en inglés y en los últimos 5 años, es decir, desde 2018 hasta 2023. Se excluyen también los artículos que están duplicados o que no resultan de interés para la elaboración del trabajo, por no estar relacionados con los objetivos de este.

Ilustración 5: Flowchart PRISMA 2022.

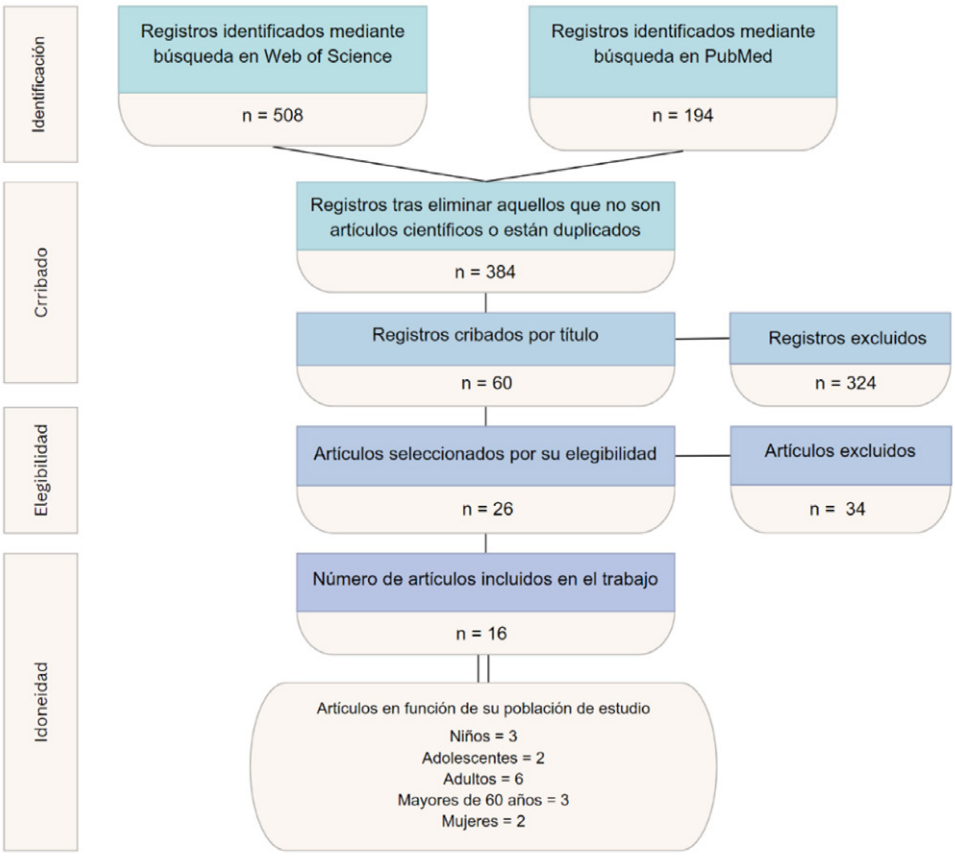


Diagrama de flujo del proceso de búsqueda sistemática siguiendo las directrices PRISMA 22 de elaboración propia.

Tal y como se indica en el diagrama de flujo (**ilustración 5**), con la primera búsqueda se obtuvieron 702 resultados (508 y 194 de "Web of Science" y "PubMed" respectivamente).

Se eliminaron aquellos resultados que no eran artículos científicos, quedando 551. Además, se quitaron aquellos que se encontraban duplicados, quedando 384 artículos.

Haciendo una revisión superficial, analizando los títulos y abstract, se hizo un cribado en base a su relación con el tema del trabajo: se excluyeron aquellos artículos que trataban otros factores (además de la actividad física) en relación con el RCV, con el objetivo de ser precisos con el tema del trabajo; además de excluir aquellos artículos que estudiaban a una población que padecía alguna patología en específico, o cuyas características pudieran distar de las presentes en la población europea general. Obteniendo 60 resultados.

Por último, se desestimaron 34 artículos por estar poco relacionados con los objetivos del trabajo, de forma que 26 artículos fueron considerados como "elegibles" ya que nos permitían obtener una imagen precisa de la evidencia disponible de la población en general y de cada uno de sus subgrupos (de edad y sexo); de los cuales, finalmente fueron usados 16.

Resultados

En la **tabla II** se exponen los resultados de la búsqueda sistemática, realizada siguiendo el procedimiento explicado en la sección anterior (materiales y métodos).

Los resultados se han organizado en base a los subgrupos poblacionales estudiados en cada artículo, ya que al realizar la selección de artículos se priorizaron aquellos que abordaban grupos poblacionales específicos. Esta elección se basa en la observación de que los artículos con enfoques generales, en múltiples ocasiones se habían realizado con una muestra única de adultos (principalmente hombres); por lo que se orientó la selección de esta forma, con el objetivo de obtener una visión más precisa sobre el tema, y al mismo tiempo, facilitar la comparación entre la información disponible para los diversos subgrupos.

Resultados enfocados en niños

***Associations between physical activity, sedentary time and cardiovascular risk factors among Dutch children:*[8]**

En este estudio transversal publicado en el 2021, durante 7 días consecutivos se midió con acelerómetros (Actigraph GT3X) el nivel de actividad física realizada por 503 niños pertenecientes a 16 escuelas primarias,

Tabla II: Resultados de la búsqueda sistemática.

Título	Autor y año	Categoría
Niños		
Associations between physical activity, sedentary time and cardiovascular risk factors among Dutch children	Ten Velde G, et all. (2021)	Estudio transversal
Changes in physical activity behavior and development of cardiovascular risk in children	Lona G, et al. (2021)	Estudio de cohortes
Preschool children's physical activity and cardiovascular disease risk: A systematic review	Bell LA, et al. (2018)	Revisión sistemática
Adolescentes		
Cardiac Autonomic Function, Cardiovascular Risk and Physical Activity in Adolescents Sports Practices and Cardiovascular Risk in Teenagers	Oliveira RS, et all. (2017) Scherr C, et all. (2017)	Estudio transversal Estudio transversal
Adultos		
Association of Habitual Physical Activity With Cardiovascular Disease Risk	Lin HH, et all. (2020)	Estudio de cohortes
Associations of specific types of physical activities with 10-year risk of cardiovascular disease among adults: Data from the national health and nutrition examination survey 1999–2006	Huang BS, et all. (2022)	Estudio transversal
Changes in leisure-time physical activity during the adult life span and relations to cardiovascular risk factors —Results from multiple Swedish studies	Lind L, et all. (2021)	Revisión bibliográfica
Physical activity and risk of cardiovascular disease by weight status among U.S adults	Zhang XC, et all. (2020)	Estudio transversal
Physical activity without weight loss reduces the development of cardiovascular disease risk factors –a prospective cohort study of more than one hundred thousand adults	Martinez Gomez D, et all. (2020)	Estudio de cohortes
The effects of physical activity during childhood, adolescence, and adulthood on cardiovascular risk factors among adults	Werneck AO, et all. (2019)	Estudio transversal
> 60 años		
Cardiovascular disease risk and all-cause mortality associated with accelerometer-measured physical activity and sedentary time –a prospective population-based study in older adults	Länsitie M, et all. (2022)	Estudio de cohortes
Cardiovascular Risk Factors and Physical Activity for the Prevention of Cardiovascular Diseases in the Elderly	Ciumarnean L, et all. (2022)	Revisión bibliográfica
Effect of 5 years of exercise training on the cardiovascular risk profile of older adults: the Generation 100 randomized trial	Letnes JM, et all. (2022)	Ensayo aletorizado
Mujeres		
Physical Activity and Incident Cardiovascular Disease in Women: Is the Relation Modified by Level of Global Cardiovascular Risk?	Chomistek AK, et all. (2018)	Estudio de cohortes
The effect of lifestyle physical activity in reducing cardiovascular disease risk factors (blood pressure and cholesterol) in women: A systematic review	Akgöz AD, et all. (2021)	Revisión sistemática

Tabla de elaboración propia, en la que se exponen las principales características de los artículos científicos resultados de la búsqueda sistemática realizada para la elaboración del presente "trabajo de fin de grado".

cuya edad media era de 10 años; además, estos niños completaron un cuestionario que recogía información relativa a las características de la actividad física realizada. Por otra parte, se midió el perímetro abdominal, peso, altura e IMC de los participantes; así como su presión arterial, y la capacidad aeróbica (CRF) medida mediante la prueba de Léger.

El estudio encontró una relación inversa entre la AF medida de forma objetiva y el IMC o el perímetro abdominal de los participantes; así como, una relación directa entre la AF y el CRF. Estas asociaciones no fueron significativas para la actividad física de intensidad ligera; mientras que si lo fueron para aquellos niveles moderados o vigorosos de actividad física. Además, se observó que la mayoría de los participantes realizaban un nivel insuficiente de AF, el 58% de ellos no cumplían con las recomendaciones de 60 min al día de AFMV. Por último, cabe destacar que no se observó ninguna asociación entre la AF y la PA.

Changes in physical activity behavior and development of cardiovascular risk in children[7]

Este estudio de cohortes evaluó a 391 niños de entre 6 y 8 años pertenecientes a 26 escuelas de Basel (Suiza), los participantes respondieron unos cuestionarios para aportar la información relativa a la actividad física que realizaban, y al tiempo de pantalla. Además, se midió la presión arterial, IMC, CRF (prueba de Léger) y diámetros arteriolares y venulares retinianos, usando estos últimos como indicador del estado de los pequeños vasos. Tras cuatro años, 262 de los participantes fueron reevaluados.

En la reevaluación realizada tras los 4 años, se encontró que a pesar de la existencia de una reducción en la AF realizada en los niños de 10 a 12 años, hasta un 65% de los niños cumplían con las recomendaciones de la OMS.

Además, se demostró una relación significativa entre la mejora del CRF durante los 4 años de seguimiento con la reducción del peso corporal y del IMC de los participantes; causando de forma indirecta un aumento en el diámetro de los vasos retinianos.

Preschool children's physical activity and cardiovascular disease risk: Systematic review[5]

Esta revisión sistemática publicada en el 2018 abarca un total de 12 artículos que investigan la asociación entre la actividad física y distintos factores de riesgo cardiovascular, en niños en edad preescolar (3 – 5,5 años).

Los artículos pertenecen a 11 estudios diferentes realizados en Europa, EE. UU., Canadá y la India; de los cuales, uno es un estudio transversal, mientras que el resto se consideran estudios de cohortes. Entre los factores analizados en los artículos, seis estudiaban el perfil lipídico, otros seis la presión arterial, cuatro la resistencia a la insulina, dos usaron un score combinado de ECV, uno incluye el grosor arterial, y otro la rigidez arterial.

A pesar de que exista evidencia que sostiene la relación entre el RCV y la AF realizada por niños mayores, esta asociación no parece ser tan clara en el caso de los niños en edad preescolar. Es más, los autores recalcan la escasez de estudios y la inconsistencia entre las evidencias que relacionan la actividad física realizada en los primeros años de vida con los diferentes factores de riesgo cardiovascular. No obstante, destacan que es razonable sospechar que exista una relación entre ambos; y enfatizan la necesidad de promover la realización de actividad física entre los niños, debido a los beneficios ya demostrados que esta conlleva.

Resultados enfocados en adolescentes

Cardiac Autonomic Function, Cardiovascular Risk and Physical Activity in Adolescents[16]

Este estudio transversal cuenta con una muestra de 54 alumnos pertenecientes a dos escuelas secundarias de Inglaterra. Los participantes del estudio, durante una semana realizaron tres visitas (desarrollado en la **tabla III**) a un laboratorio localizado en la propia escuela.

Los resultados del estudio demostraron una relación inversa significativa entre la AFM y el IMC, el porcentaje de grasa corporal, perímetro abdominal y la PA; y una relación similar entre la AFV y el porcentaje de grasa corporal de los participantes. De igual forma, se observó una correlación inversa entre la capacidad cardiorrespiratoria de los alumnos y su IMC, porcentaje de grasa corporal y perímetro abdominal.

Respecto a los FRCV "no tradicionales" se observó una relación entre la AFMV y la RMSSD ("Desviación estándar de las diferencias absolutas sucesivas de los intervalos R-R"), que sirve como indicador del estado de salud cardiovascular; la tasa de recuperación del corazón (HRRτ), que mide la velocidad con la que la FR disminuye al cesar una actividad física; y el índice T30, que indica la recuperación de la FR tras un periodo de descanso de 30 segundos.

Tabla III: Desarrollo de visitas al laboratorio realizadas por los participantes.

Visita	Mediciones y otras acciones realizadas
Primera	Estatura (bipedestación y sedestación), peso, perímetro abdominal, pliegues cutáneos (tricipital y subescapular), % grasa corporal, y pico de velocidad de crecimiento.
Segunda	FC en reposo, perfil lipídico y glucemia.
Tercera	Capacidad cardiorrespiratoria (prueba en bicicleta hasta el agotamiento), y recuperación de FC en 10 min. Proporcionan acelerómetro (llevar 7 días).

Tabla de elaboración propia, en la que se exponen las mediciones y otras acciones llevadas a cabo en las tres visitas que los adolescentes realizaron al laboratorio, para la ejecución del estudio.

Por último, se analizó como variaba el RCV siguiendo una escala que incluía los FRCV tradicionales, otra para los no tradicionales y una combinada. Se demostró una disminución del riesgo cardiovascular de todos los tipos en aquellos que realizaban AFM. Además, en aquellos que tenían una mayor capacidad cardiorrespiratoria (ajustada al IMC), se observó una mejora significativa del RCV tradicional. Sin embargo, en los participantes que realizaban AFV, se demostró una asociación significativa solo para el RCV no tradicional y el combinado.

Sports Practices and Cardiovascular Risk in Teenagers[15]

Este estudio transversal incluye a 422 estudiantes, cuya edad media era de 12.5 años, pertenecientes a dos escuelas de Rio de Janeiro: 148 estudiantes de la escuela "Figueiredo Pimentel" (EFP), y 274 de la "Experimental Olympic Gymnasium" (EOG) que destaca por su programa de entrenamiento y las prácticas deportivas que se llevan a cabo con los estudiantes. Los estudiantes de la primera escuela hacían 1 hora de actividad física semanal durante el periodo lectivo, y recibían una comida al día en el colegio; mientras que los estudiantes del EOG practicaban 10 horas de actividad física semanal durante el periodo lectivo, y recibían 5 comidas al día en la propia escuela.

Se entrevistó a cada participante, anotando el deporte realizado por cada uno de los estudiantes; y se les clasificó en base a los METs consumidos durante la práctica deportiva realizada (por encima o por debajo de 5). Además, se midió su PA y perímetro abdominal; igualmente, se tomaron muestras de sangre para cuantificar la glucosa, colesterol, y triglicéridos en sangre. Por último, se le realizó un ecocardiograma a cada uno de los participantes.

Aunque los resultados del estudio expusieron la existencia de diferencias entre ambas escuelas en múltiples de las variantes medidas (expuestas en la **tabla IV**), solo se demostró una relación significativa entre la mejoría del perfil metabólico, y en consecuencia de múltiples factores de riesgo cardiovascular, en aquellos estudiantes que más actividad física realizaban (los inscritos en la EOG). Por otra parte, se observó una diferencia significativa en la cantidad de actividad física realizada por los padres de los estudiantes, siendo esta significativamente mayor en los padres de los alumnos inscritos en la EOG.

Resultados enfocados en adultos

Association of Habitual Physical Activity With Cardiovascular Disease Risk[14]

Este estudio de cohortes clasificó a 903 adultos con una edad media de 53 años que eran participantes del eFHS (electronic Framingham Heart Study) en base a la intensidad de AF que realizaban, infiriendo esto último gracias al recuento de pasos registrado en un smartwatch de Apple que se les proporcionó al inicio del estudio. Además, calcularon el RCV de los participantes, usando la escala Framingham, con la intención de analizar la relación entre ambos.

Entre los hallazgos del estudio, se observó que mayores cantidades de AF estaban asociadas a menores índices de RCV. Además, se pudo determinar una mejoría del 0,18% en el índice de RCV por cada mil pasos adicionales que los participantes caminaban; y esta relación seguía siendo significativa tras ajustarlo al IMC de los participantes.

Associations of specific types of physical activities with 10-year risk of cardiovascular disease among adults: Data from the NHANES 1999-2006[13]

Este estudio transversal que extrae sus datos de la Encuesta Nacional de Examen de Salud y Nutrición de EE. UU. incluye a 10829 participantes mayores de 30 años, con una edad media de 53,46 años. En primer lugar, se les hizo una encuesta relativa a la actividad física que habían realizado en el último mes, y posteriormente se cuantificó su RCV con la escala de Framingham.

Entre los resultados del estudio, se encontraron diferencias significativas entre hombre y mujeres en multiples aspectos: destacando un mayor RCV entre los hombres, y una preferencia por los deportes de raqueta, el ciclismo, correr, futbol americano o baloncesto; mientras que se observó una preferencia por el aerobic entre las mujeres.

En cuanto a los distintos tipos de AF y su asociación con el RCV, se observó una relación inversamente significativa con el futbol americano, sobre todo, aunque también con el ciclismo, running y aerobic. Respecto a la intensidad de los deportes practicados por los participantes, se demostró una relación más fuerte entre la AF vigorosa, que la misma, pero de intensidad moderada, en el ciclismo, running, natación, futbol americano y aerobic. En lo que respecta a la duración del deporte realizado por los participantes, en el caso del fútbol americano, running, baloncesto o aerobic, al aumentar la duración de la práctica de estos deportes, disminuía el RCV de forma significativa. Por último, se observó mejoras en el RCV al aumentar el volumen de participación en todos los deportes, menos en aquellos de raqueta y en el baloncesto.

Tabla IV: Diferencias entre participantes de ambas escuelas.

Variante	EOG	EFP
Peso	52.4 kg	52.3
IMC	20.7	21.2
Colesterol total	158.3 mg/dl	164.3 mg/dl
PA	101 / 65 mmHg	110 / 66 mmHg

Tabla de elaboración propia, en la que se exponen las principales diferencias que se encontraron entre los alumnos de la EOG (donde se realizaba más AF), y la EFP.

Changes in leisure-time physical activity during the adult life span and relations to cardiovascular risk factors—Results from multiple Swedish studies[11]
Este artículo es una revisión bibliográfica, la cual recoge la información de 6 estudios diferentes (expuestos en la **tabla V**) realizados en Suecia, que analizan la asociación entre la AF realizada en el tiempo libre y el RCV.

En los resultados se observó un aumento en la práctica de AF en adultos hasta los 70 años hombres, y desde los 70 años un decremento en la AF realizada. Además, se determinó una relación significativa entre la AF realizada y los niveles de triglicéridos o HDL en sangre; así como, con las concentraciones de glucosa en sangre, los niveles de tensión arterial o el IMC. Estas relaciones perdían fortaleza con el incremento de la edad de los participantes.

Physical activity and risk of cardiovascular disease by weight status among U.S adults[12]
Para este estudio transversal publicado en el año 2020 se extrajo información del NHANES desde el 2007 hasta 2016. Se incluyeron 22476 participantes de entre 30 y 64 años, con una edad media de 45,9 años. Por una parte, se les interrogó sobre las características de la AF que realizaban y se les clasificó en 3 categorías en base a la cantidad de AFMV practicada (sedentarios, inactivos y activos). Por otra parte, se calculó el RCV de cada uno de los participantes usando la escala de Framingham.

Entre los resultados del estudio, destaca que un 33,6% de los participantes tenían sobrepeso y un 35,7% tenían obesidad; y estos dos grupos tenían característicamente un mayor RCV, en comparación con aquellos con un IMC sano. Además, entre aquellos participantes con un IMC alto (obesos o con sobrepeso) se encontró una asociación significativa entre la realización de cualquier cantidad de AF y la mejora del RCV. Mientras que, entre los individuos con un IMC saludable, se apreció esta asociación tan solo entre aquellos que fueron clasificados como "activos" (realizaban más de 150 minutos de AFMV a la semana).

En cuanto a la relación existente entre la práctica de AF, el peso de los participantes y su RCV; se demostró que la AF estaba más fuertemente relacionada con la mejora del RCV, que el peso.

Physical activity without weight loss reduces the development of cardiovascular disease risk factors – a prospective cohort study of more than one hundred thousand adults[2]
Este estudio de cohortes se llevó a cabo usando los datos de la cohorte de "Taiwan MJ", e incluye a 116mil personas mayores de 18 años, cuya edad media era de 37,8 años. Se llevaron a cabo tres evaluaciones, entre la primera y la segunda pasaron una media de 1,9 años; y de la segunda a la tercera reevaluación pasaron 5,7 años de media.

Los participantes completaron el cuestionario "MJ PA", aportando la información necesaria, relativa a la AF practicada durante el último mes: intensidad, frecuencia, duración y ejemplos. Posteriormente, estandarizando los METs consumidos en las distintas actividades físicas, calcularon objetivamente el volumen de AF que cada uno den los participantes había realizado en el último mes (unidad de medida: MET-h/semana).

En cada una de las reevaluaciones, los participantes respondieron este cuestionario, permitiendo hacer un seguimiento de sus hábitos, de esta forma fueron clasificados en base a si la cantidad de AF que realizaban había aumentado, disminuido o se mantenía estable. Además, durante las reevaluaciones se llevó a cabo un seguimiento del IMC, porcentaje de grasa corporal y TA; así como del peso de los participantes, en función de este último, los clasificaron en base a si habían ganado peso, perdido peso, o se habían mantenido estables. Adicionalmente, se incluyeron otros datos del historial médico de los pacientes, como si sufrían HTA, hipercolesterolemia, dislipemia aterogénica, síndrome metabólico, o su estado de inflamación sistémica.

Tabla V: Artículos incluidos en la revisión bibliográfica "Changes in leisure-time physical activity during the adult …".

Estudio o artículo	Participantes	Localidad y años	Reevaluaciones
ULSAM (Uppsala Longitudinal Study of Adult Men)	82% Hombres >50 años	Uppsala 1970 - 1974	60, 70, 77, 82, 88, 93 (edad)
PIVUS (Prospective Investigation of Vasculature in Uppsala Seniors)	50% Mixto >70 años	Uppsala 2001 - 2004	75, 80 (edad)
EpiHealth (Epidemiology for Health)	20% Mixto 45-75 años	Uppsala y Malmo 2011 - 2018	-
LifeGene	Mixto < 50 años	Stockholm, Umeå, y Alingsås 2009 - 2018	-
SHE (Sleep and Health in Women)	71.6% Mujeres >20 años	Uppsala 2000	2010
SHM (Sleep and Health in Men)	79,6% Hombres 30-69 años	Uppsala 1994	1994, 2007

Tabla de elaboración propia, en la que se exponen los artículos incluidos en la revisión bibliográfica nombrada anteriormente, y las principales características de estas. La información relativa a los participantes describe la tasa de participación, género y edad de estos.

Entre los resultados de este estudio destacan, la relación significativa entre el aumento de peso, del IMC y del porcentaje de grasa corporal de los participantes, con el empeoramiento de los distintos FRCV. Mientras que, se objetivó una asociación inversa entre la cantidad de AF realizada y la incidencia de HTA, dislipemia aterogénica, síndrome metabólico o DM2. En cuanto a los resultados observados al combinar los cambios en AF y el peso de los participantes, destacan:

1. Un mayor RCV en aquellos que habían aumentado de peso y disminuido la AF realizada, respecto a aquellos que practicaban más AF y habían disminuido su peso.
2. Aumentar o mantener el nivel de AF realizada, reducía o conseguía mantener constantes ciertos FRCV, cuando los participantes aumentaban de peso o se mantenían estables.
3. Entre los participantes que perdieron peso, el descenso de la AF realizada no se asoció con un empeoramiento de los FRCV.

***The effects of physical activity during childhood, adolescence, and adulthood on cardiovascular risk factors among adults*[10]**

El objetivo de este estudio transversal, que incluye a 101 personas de entre 30 y 50 años, es relacionar el RCV de los adultos con las características de la actividad física que practican en el momento de la investigación (medida mediante un podómetro usado por una semana) o han practicado en etapas anteriores de la vida (referida mediante cuestionarios).

Además, se midió el porcentaje de grasa corporal de los participantes; y otros FRCV, entre los que se encuentran: la TAS y TAD, marcadores de inflamación (PCR), la insulinorresistencia (HOMA, calculada con la glucemia e insulinemia), colesterol total, HDL y triglicéridos en sangre.

Entre los resultados destaca una asociación significativa entre la práctica de AF durante la infancia y adolescencia o durante estas mismas etapas y la adultez, con menores valores de porcentaje de grasa corporal, trigliceridemia, resistencia a la insulina, PCR, y un aumento del colesterol HDL.

Al ajustarlo en base algunas covariables (IMC y consumo de tabaco y alcohol) solo se mantenía significativa esta asociación en el caso del porcentaje de grasa corporal, triglicéridos en sangre y la resistencia la insulina; y la PCR en aquellos que también realizaban AF en la adultez.

Adicionalmente, se introdujeron estos mismos indicadores como covariables; al ajustarlo de esta forma, solo se mantuvieron significativas la asociación con la PCR en aquellos que habían realizado AF durante todas las etapas, y con el porcentaje de grasa corporal en aquellos que habían realizado AF durante todas las etapas, o durante la infancia y adolescencia.

Resultados enfocados en mayores de 60 años

***Cardiovascular disease risk and all-cause mortality associated with accelerometer- measured physical activity and sedentary time –a prospective population-based study in older adults*[6]**

Este estudio de cohortes publicado en el año 2022 se incluyeron a 660 personas cuya edad media era de 68.9 años, realizó un seguimiento de los participantes durante 6 años; con la intención de estudiar la asociación entre la AF medida objetivamente al inicio del estudio mediante un acelerómetro de muñeca, y el RCV estimado mediante las tablas de Framingham, así como la mortalidad por cualquier causa.

Entre los resultados del estudio, destaca un mayor tiempo dedicado a realizar AF en el caso de las mujeres, respecto de los hombres. Específicamente, el tiempo de AF ligera era de 13 minutos más en el caso de las mujeres; sin diferencias significativas en el caso de la AF moderada o vigorosa.

Por otra parte, se aprecia también una diferencia significativa entre ambos sexos, en lo que respecta al RCV estimado en los participantes, siendo este alto en el 83,3% de los hombres y en el 23,8% de las mujeres solamente.

Además, este estudio permite observar una asociación inversa entre el tiempo empleado en practicar AF de cualquier tipo y el RCV estimado de los participantes.

***Cardiovascular Risk Factors and Physical Activity for the Prevention of Cardiovascular Diseases in the Elderly*[3]**

Esta revisión bibliográfica aborda el rol preventivo de la AF para las enfermedades cardiovasculares. El artículo describe como la realización de AF conlleva numerosas repercusiones positivas para la salud cardiovascular de los ancianos, expuestos a continuación:

- Mejorar los parámetros fisiológicos cardiacos y los síntomas cardiovasculares.
- Reducir la obesidad, y aumentar la distancia que son capaces de caminar
- Mejorar la TA y la FC.
- Reducir el riesgo de coronariopatía y de enfermedad vascular periférica.
- Mejorar el perfil lipídico y la sensibilidad a la insulina.

Respecto al tipo de AF recomendada en los ancianos (de forma general), el artículo menciona que lo ideal es practicar AF aeróbica acompañada de ejercicios de fuerza, flexibilidad y equilibrio. La recomendación según el Servicio Nacional de Salud del Reino Unido (NHS), respaldado por el Centro para el Control y la Prevención de Enfermedades de EE. UU. (CDC), consiste en 150 minutos de AFM a la semana; pudiendo sustituirse por 75 minutos de AFV a la semana si se tratara de ancianos activos. Además, se menciona que el tipo de AF más

frecuentemente recomendada en este ámbito es caminar, que contaría como AF de intensidad moderada.

Adicionalmente, el artículo desarrolla la relación entre la AF y la sensibilidad a la glucosa: se ha demostrado que la activación de las células musculares disminuye la glucemia, aportando un mejor control en los ancianos diabéticos, reduciendo el RCV de los mismos. Igualmente analiza la relación de entre la AF y la mejora de la PA: se ha demostrado que la práctica de AF mantenida en el tiempo, disminuye la PAS 5 mmHg y la PAD 3,5 mmHg de media, reduciendo consecuentemente el RCV.

***Effect of 5 years of exercise training on the cardiovascular risk profile of older adults: the Generation 100 randomized trial*[4]**
Este ensayo aletorizado, que incluye a 1567 personas de entre 70 y 77 años, analiza el resultado obtenido tras la realización de HIIT (entrenamiento de intervalos de alta intensidad) o MICT (entrenamiento continuo de intensidad moderada) durante 5 años, comparando la variación en el RCV entre ambos grupos y respecto con otro grupo control (el cual únicamente recibió recomendaciones generales respecto a la AF aconsejada). Para el análisis de los datos, solo se tuvieron en cuenta aquellos participantes que asistieron a más de la mitad de las sesiones de HIIT o MICT.

Entre los resultados destaca un aumento significativo en el grupo de individuos que hacían HIIT de la capacidad aeróbica máxima ($VO_{2\ Max}$), que hace referencia a la cantidad máxima de oxígeno que el individuo es capaz de procesar y consumir, respecto al grupo control. Además, se observaron diferencias significativas en algunos FRCV aislados (glucemia, FC basal…) entre estos mismos dos grupos. Por lo demás, no se apreció un índice menor de ACV, ni una mejora evidente del RCV global de los individuos.

Resultados enfocados en mujeres

***Physical Activity and Incident Cardiovascular Disease in Women: Is the Relation Modified by Level of Global Cardiovascular Risk?*[9]**
Este estudio de cohortes publicado en el 2018 por la AHA (asociación americana del corazón) usa los datos recabados por el estudio WHS (Women's Health Study) que cuenta con una muestra de 27536 mujeres. Se registró mediante cuestionarios la AF que las participantes practicaban en su tiempo libre al empezar el estudio entre los años 1992 y 1995; y se realizó seguimiento de la misma, hasta el año 2013.

Entre los resultados, destaca la asociación inversa entre la realización de AF y los IAM, ACV y ECV en general. Aunque, este estudio también intentó analizar cómo el RCV de las mujeres influía sobre la repercusión que la práctica de AF tenía en el riesgo de enfermedad cardiovascular incidente, y no se apreciaron diferencias significativas. A pesar de esto, los autores mantienen la recomendación de realizar AF en mujeres de todas las edades, debido a sus multiples beneficios, que han sido demostrados en otros estudios.

***The effect of lifestyle physical activity in reducing cardiovascular disease risk factors (blood pressure and cholesterol) in women: A systematic review*[1]**
Esta revisión sistemática incluye 8 artículos que estudian la relación entre la AF y el RCV en las mujeres. Se destaca como el tipo de AF más comúnmente realizado por las mujeres es ejercicio aeróbico de moderada intensidad, con una frecuencia media de 2 o 3 veces a la semana.

En todos los estudios incluidos, excepto uno, se relacionaba inversamente la AF con la TAS y el colesterol total. Además, en los distintos estudios se destacan los beneficios de los ejercicios de suelo pélvico, de fuerza muscular y de meditación (adicionalmente al ejercicio aeróbico moderado) para el control lipídico y de la TA, el manejo del peso corporal y la reducción del riesgo de desarrollar diabetes tipo 2, entre otros.

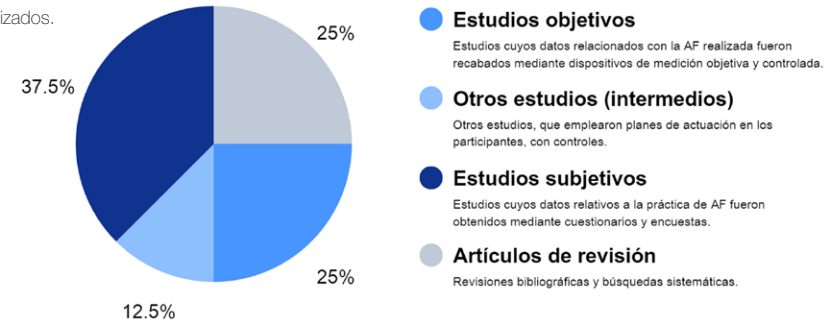
Discusión

Existe escasez de artículos o investigaciones que emplean métodos objetivos para cuantificar la cantidad de actividad física realizada por las personas a lo largo del tiempo. Tal y como se expone en la **ilustración 6**, de los 16 resultados obtenidos en la búsqueda, 4 son revisiones bibliográficas o búsquedas sistemáticas, y 12 son estudios de distintos tipos; dentro de estos últimos, tan solo 3 medían objetivamente la AF que los individuos realizaban (mediante acelerómetros o cuentapasos), 6 lo hacían mediante encuestas o formularios subjetivos, en 1 se empleaba una combinación de los dos métodos comentados anteriormente, y otros 2 estudios ejecutaban planes de actuación con registros de asistencia que permitían mantener un control más o menos objetivo.

En cuanto a la metodología empleada para medir el RCV, ciertos estudios utilizan variables objetivas (colesterolemia, TA, IMC, etc.) que cuando se encuentran alteradas resultan por sí mismas factores de riesgo cardiovascular; mientras que otros, realizan cálculos del RCV global mediante el empleo de escalas, siendo la de Framingham las más utilizada.

Al analizar la AF en base a su intensidad, gran parte de los estudios coincidían en que la realización de AF de intensidad ligera está relacionada de forma cuestionable con la mejoría del RCV de las personas, resultando no significativo en la mayoría de los casos; no siendo así, al estudiar la AF de intensidades moderada o vigorosa.
Respecto a los estudios realizados sobre poblaciones pediátricas, la mayoría evalúan a niños mayores de 6 años, resultando en una insuficiente evidencia que relacione la AF con el RCV de los niños que se encuentran en edad preescolar[5].

Ilustración 6:
Gráfica clasificatoria de los artículos utilizados.



Gráfica de elaboración propia, en la que se expone la proporción de artículos obtenidos en la revisión sistemática, clasificándolos en base al método de obtención de los datos relativos a la cantidad y características de la AF practicada por los participantes.

Además, estos mismos estudios permiten esclarecer como, entre un 45%[7] y un 58%[8] de los niños no realizaban la AF necesaria para cumplir con las recomendaciones de la OMS, lo que pone de manifiesto la necesidad de ejecutar estrategias de promoción de la salud que incluyan el fomento de la AF en la población pediátrica. La aplicación de estas medidas sería idónea en los centros educativos, tal y como demuestra el estudio "Sports Practices and Cardiovascular Risk in Teenagers"[15], que objetivó una mejora de multiples FRCV relacionados con el perfil metabólico de los estudiantes que acudían a escuelas con programas deportivos más extensos y completos. Por otra parte, al revisar aquellos estudios que abordan poblaciones en edad adulta, se destaca[10] la repercusión mantenida en el tiempo que tiene la AF realizada durante la niñez y adolescencia sobre determinados FRCV, como el porcentaje de grasa corporal, o el estado inflamatorio (medido mediante la PCR); reafirmando la necesidad de promover la práctica de AF en edades tempranas.

Resulta relevante señalar como multiples estudios analizan la relación entre la AF y el peso (con la consiguiente variación del IMC), con el RCV. Evidenciando[12] que, en personas con un IMC alto, realizar cualquier nivel de AF es beneficioso para el RCV; mientras que en aquellas personas que tienen un IMC saludable, solo se observa un beneficio significativo al realizar AF de intensidad moderada o vigorosa. Adicionalmente, al estudiar[2] esta relación desde una perspectiva dinámica, otro estudio constata el valor "amortiguador" que tienen la AF y el peso recíprocamente. Demostrando como, a pesar de haber aumentado su peso a lo largo del tiempo, aquellos que habían aumentado la AF realizada, lograban mantener constantes o incluso mejorar ciertos FRCV; y de igual forma, aquellos que habían disminuido la AF realizada, pero habían disminuido de peso durante el mismo periodo de tiempo, mantenían los FRCV sin empeoramientos significativos.

Tal como se preveía, multiples estudios sostienen la presencia de peores indicadores de RCV en el género masculino en comparación con el femenino. Esta disparidad se manifiesta de forma especialmente notable, al tratarse de personas mayores de 60 años, un estudio[6] constató como el 83% de los hombres estudiados tenían un RCV alto, significativamente mayor en comparación con un 24% de las mujeres.

Adicionalmente, otros estudios realizados en poblaciones geriátricas[3] destacaron como la práctica de AF influía positivamente sobre indicadores menos estudiados hasta la fecha: estos incluyen la sensibilidad a la glucosa, demostrando un mejor control de la DM, el aumento de la distancia que los ancianos son capaces de caminar, la mejora de la TA (la práctica de AF mantenida en el tiempo, disminuye la PAS 5 mmHg y la PAD 3,5 mmHg en promedio), así como reduciendo el riesgo de coronariopatía y de enfermedad vascular periférica, entre otros. Esto subraya la necesidad de que los ancianos incorporen la actividad física en su rutina diaria. A pesar de esto, se ha demostrado[11] que la realización de AF tiende a aumentar hasta los 70 años, para posteriormente descender.

En relación con las disparidades observadas entre hombres y mujeres, aparte del mayor RCV en hombres que ya he mencionado anteriormente en este apartado, diversos estudios sostienen que las mujeres suelen optar más la práctica de ejercicio aeróbico (aerobic) de moderada intensidad (con una frecuencia media de 2 o 3 veces a la semana)[1]; mientras que, por lo general los hombres muestran preferencia los deportes de raqueta, el ciclismo, correr, futbol americano o baloncesto[13]. Por el contrario, un estudio realizado en personas mayores de 60 años determinó que no se apreciaban diferencias significativas respecto al tiempo invertido en la práctica de AF de intensidades moderada o vigorosa, pero si en la AF ligera, siendo mayor por 13 minutos de media en el caso de las mujeres[6].

Por último, considero necesario destacar que todos los estudios seleccionados coincidían en la mejoría de diversos FRCV, como resultado de la práctica de AF. Aunque en algunos casos esto se tradujera en una mejora significativa de los indicadores de RCV globales, y en otros casos no se observara tal efecto.

Conclusiones

1. A pesar de la abundante literatura que aborda la influencia de la actividad física en el riesgo cardiovascular, que refleja la importancia de este argumento en la actualidad, existe una carencia de estudios que midan la práctica de actividad física de forma objetiva, mediante acelerómetros, podómetros o relojes inteligentes, entre otros.

2. La práctica de actividad física se consolida de forma prácticamente irrefutable como beneficiosa para la salud de las personas.

3. La actividad física desencadena cambios beneficiosos en múltiples factores de riesgo cardiovascular, lo que implica una mejoría, ya sea en mayor o en menor media, del riesgo cardiovascular global de las personas.

4. Una parte significativa de la población no sigue las recomendaciones mínimas de actividad física, subrayando la importancia de implementar estrategias de promoción de la salud destinadas a incentivar la realización de actividad física, especialmente entre los niños y personas mayores.

Siglas usadas

- ECV: Enfermedad/Evento Cardiovascular
- RCV: Riesgo Cardiovascular
- FRCV: Factores de Riesgo Cardiovascular
- DM: Diabetes Mellitus
- PAS/D: Presión Arterial Sistólica/Diastólica
- RAE: Real Academia de la lengua española
- AF: Actividad Física
- AFMV: Actividad Física Moderada o Vigorosa
- AFL: Actividad Física Ligera
- PA: Presión Arterial
- IMC: Índice de Masa Corporal
- CRF: Cardiorespiratory Fitness (capacidad aeróbica, en español)
- FC: Frecuencia Cardiaca

Conflicto de intereses

Los autores declaran no tener conflicto de intereses.

Bibliografía

1. Dağıstan Akgöz A, Ozer Z, Gözüm S. The effect of lifestyle physical activity in reducing cardiovascular disease risk factors (blood pressure and cholesterol) in women: A systematic review. Vol. 42, Health Care for Women International. Bellwether Publishing, Ltd.; 2021. p. 4-27.

2. Martinez-Gomez D, Lavie CJ, Hamer M, Cabanas-Sanchez V, Garcia-Esquinas E, Pareja-Galeano H, et al. Physical activity without weight loss reduces the development of cardiovascular disease risk factors – a prospective cohort study of more than one hundred thousand adults. Vol. 62, Progress in Cardiovascular Diseases. W.B. Saunders; 2019. p. 522-30.

3. Ciumărnean L, Milaciu MV, Negrean V, Orăşan OH, Vesa SC, Sălăgean O, et al. Cardiovascular risk factors and physical activity for the prevention of cardiovascular diseases in the elderly. Vol. 19, International Journal of Environmental Research and Public Health. MDPI; 2022.

4. Letnes JM, Berglund I, Johnson KE, Dalen H, Nes BM, Lydersen S, et al. Effect of 5 years of exercise training on the cardiovascular risk profile of older adults: The Generation 100 randomized trial. Eur Heart J. 2022 Jun 1;43(21):2065-75.

5. Bell LA, Fletcher EA, Timperio A, Vuillermin P, Hesketh K. Preschool children's physical activity and cardiovascular disease risk: A systematic review. Vol. 22, Journal of Science and Medicine in Sport. Elsevier Ltd; 2019. p. 568-73.

6. Länsitie M, Kangas M, Jokelainen J, Venojärvi M, Timonen M, Keinänen-Kiukaanniemi S, et al. Cardiovascular disease risk and all-cause mortality associated with accelerometer-measured physical activity and sedentary time –a prospective population-based study in older adults. BMC Geriatr. 2022 Dec 1;22(1).

7. Lona G, Hauser C, Köchli S, Infanger D, Endes K, Faude O, et al. Changes in physical activity behavior and development of cardiovascular risk in children. Scand J Med Sci Sports. 2021 Jun 1;31(6):1313-23.

8. ten Velde G, Plasqui G, Willeboordse M, Winkens B, Vreugdenhil A. Associations between physical activity, sedentary time and cardiovascular risk factors among Dutch children. PLoS One. 2021 Aug 1;16(8 August).

9. Chomistek AK, Cook NR, Rimm EB, Ridker PM, Buring JE, Lee IM. Physical activity and incident cardiovascular disease in women: Is

the relation modified by level of global cardiovascular risk? J Am Heart Assoc. 2018 Jun 1;7(12).

10. Werneck AO, Agostinete RR, Lima MCS de, Turi-Lynch BC, Fernandes RA. The effects of physical activity during childhood, adolescence, and adulthood on cardiovascular risk factors among adults. Rev Assoc Med Bras (1992). 2019 Nov 1;65(11):1337-42.

11. Lind L, Zethelius B, Lindberg E, Pedersen NL, Byberg L. Changes in leisure-time physical activity during the adult life span and relations to cardiovascular risk factors-Results from multiple Swedish studies. PLoS One. 2021 Aug 1;16(8 August).

12. Zhang X, Cash RE, Bower JK, Focht BC, Paskett ED. Physical activity and risk of cardiovascular disease by weight status among U.S adults. PLoS One. 2020 May 1;15(5).

13. Mary Alessio H, Cousins J, Slattery E, Du C. Associations of specific types of physical activities with 10-year risk of cardiovascular disease among adults: Data from the national health and nutrition examination survey 1999–2006 [Internet]. Available from: https://www.cdc.gov/

14. Lin H, Sardana M, Zhang Y, Liu C, Trinquart L, Benjamin EJ, et al. Association of Habitual Physical Activity with Cardiovascular Disease Risk. Circ Res. 2020 Oct 23;127(10):1253-60.

15. Scherr C, Fabiano LCC, Guerra RL, Belém LHJ, Câmara ACG, Campos A. Sports practices and cardiovascular risk in teenagers. Arq Bras Cardiol. 2018 Mar 1;110(3):248-55.

16. Oliveira RS, Barker AR, Williams CA. Cardiac Autonomic Function, Cardiovascular Risk and Physical Activity in Adolescents. Int J Sports Med. 2018 Feb 1;39(2):89-96.

17. Productos y Servicios/Publicaciones/Publicaciones de descarga gratuita [Internet]. [cited 2023 Dec 29]. Available from: https://www.ine.es/ss/Satellite?param1=PYSDetalleFichaIndicador&c=INESeccion_C&param3=1259947308577&p=1254735110672&pagename=ProductosYServicios%2FPYSLayout&cid=1259944495973&L=0

18. Actividad física [Internet]. [cited 2023 Dec 29]. Available from: https://www.who.int/es/news-room/fact-sheets/detail/physical-activity

19. Barengo NC, Antikainen R, Borodulin K, Harald K, Jousilahti P. Leisure-Time Physical Activity Reduces Total and Cardiovascular Mortality and Cardiovascular Disease Incidence in Older Adults. J Am Geriatr Soc. 2017 Mar 1;65(3):504-10.

20. Pelliccia A, Sharma S, Gati S, Bäck M, Börjesson M, Caselli S, et al. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease: The Task Force on sports cardiology and exercise in patients with cardiovascular disease of the European Society of Cardiology (ESC). Eur Heart J [Internet]. 2021 Jan 1 [cited 2023 Oct 5];42(1):17-96. Available from: https://dx.doi.org/10.1093/eurheartj/ehaa605

21. Sans S, Fitzgerald AP, Royo D, Conroy R, Graham I. Calibración de la tabla SCORE de riesgo cardiovascular para España. Rev Esp Cardiol [Internet]. 2007 May 1 [cited 2023 Oct 5];60(5):476-85. Available from: http://www.revespcardiol.org/es-calibracion-tabla-score-riesgo-cardiovascular-articulo-13106180

22. L.J. Visseren F, Mach F, M. Smulders Y, Carballo D, C. Koskinas K, Bäck M, et al. Guía ESC 2021 sobre la prevención de la enfermedad cardiovascular en la práctica clínica. Rev Esp Cardiol [Internet]. 2022 May 1 [cited 2023 Oct 5];75(5):429.e1-429.e104. Available from: http://www.revespcardiol.org/es-guia-esc-2021-sobre-prevencion-articulo-S0300893221004620

23. Tipos de actividad física por intensidad | ElNASalut - Ciudadanía activa - ElNAsalut [Internet]. [cited 2023 Oct 2]. Available from: https://einasalut.caib.es/web/ciudadania-activa/tipos-de-actividad-fisica-por-intensidad

24. Piercy KL, Troiano RP, Ballard RM, Carlson SA, Fulton JE, Galuska DA, et al. The Physical Activity Guidelines for Americans. JAMA [Internet]. 2018 Nov 20 [cited 2024 Feb 17];320(19):2020-8. Available from: https://pubmed.ncbi.nlm.nih.gov/30418471/

25. Actividad física [Internet]. [cited 2023 Oct 2]. Available from: https://www.who.int/es/news-room/fact-sheets/detail/physical-activity

26. La actividad física y el corazón - ¿Qué es la actividad física? | NHLBI, NIH [Internet]. [cited 2023 Oct 2]. Available from: https://www.nhlbi.nih.gov/es/salud/corazon/actividad-fisica

27. Lobos Bejarano JM, Brotons Cuixart C. Factores de riesgo cardiovascular y atención primaria: evaluación e intervención. Aten Primaria [Internet]. 2011 Dec 1 [cited 2023 Sep 24];43(12):668-77. Available from: https://www.elsevier.es/es-revista-atencion-primaria-27-articulo-factores-riesgo-cardiovascular-atencion-primaria-S0212656711004689

28. Marrugat J, Solanas P, D'Agostino R, Sullivan L, Ordovas J, Cordón F, et al. Estimación del riesgo coronario en España mediante la ecuación de Framingham calibrada. Rev Esp Cardiol [Internet]. 2003 Mar 1 [cited 2023 Sep 24];56(3):253-61. Available from: http://www.revespcardiol.org/es-estimacion-del-riesgo-coronario-espana-articulo-13043951

29. Andersson C, Nayor M, Tsao CW, Levy D, Vasan RS. Framingham Heart Study: JACC Focus Seminar, 1/8. Vol. 77, Journal of the American College of Cardiology. Elsevier Inc.; 2021. p. 2680-92.

30. Alegría Ezquerra E, Alegría Barrero A, Alegría Barrero E. Estratificación del riesgo cardiovascular: importancia y aplicaciones. Rev Esp Cardiol [Internet]. 2012 Jun 1 [cited 2023 Sep 24];12(SUPPL.3):8-11. Available from: http://www.revespcardiol.org/es-estratificacion-del-riesgo-cardiovascular-importancia-articulo-S1131358712700390

31. Estudio de Framingham | Boston Medical Center [Internet]. [cited 2023 Sep 24]. Available from: https://www.bmc.org/es/stroke-and-cerebrovascular-center/research/framingham-study

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ORIGINAL

Assessing Fracture Strength in Root Canals: A Comparative In-Vitro Analysis of Single-File Instrumentation Systems

Evaluación de la resistencia a la fractura en conductos radiculares: Análisis comparativo in vitro de sistemas de instrumentación de una sola lima

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Abstract

Introduction: Root canal obturation is a procedure used in endodontic therapy to seal up the root canal space and make the tooth more resistant to breaking. After endodontic treatment, teeth are more likely to break, according to certain reports. The pulp and crown must be cared for and protected, thus a proper restoration is essential. The drying out of the coronal and radicular dentin caused by the excessive loss of tooth structure during endodontic treatment, is the most often stated cause of dental weakness. The study's goal is to compare the results of five distinct single-file rotational preparation techniques for strengthening the mesial roots of mandibular first molars in the event of a fracture.

Methods: Ultrasonic scaler tips were used in conjunction with normal saline irrigation to debride and clean the pulp chambers of the removed teeth. After preparing the mesio-buccal canal to the working length using a 6# K file, a digital radiograph was taken in the bucco-lingual direction. Cavity-filled teeth were taken out of the mouth. The root canal curvature was then calculated after the teeth were evaluated using the Schneiders method for canal curvature.

Results: Following the manufacturers' guidelines, we used the single-file approach to measure the lengths of both canals in the mesial root to set up the experimental groups. The samples were reopened after 72 hours and obturated again. After that, a base forming was used to attach them to resin bases. The load at fracture was measured by applying a vertical load with a 3mm stainless steel tip in a universal testing machine. Following the fracturing process, the fracture type was evaluated. Tabulated and statistically examined findings.

Conclusion: Roots created using single-file systems had a comparable resistance to fracture to those generated using the control group, within the scope and standardization methods of this investigation. Clinical examination and further parameter testing of these single-file systems is strongly encouraged.

Key words: Root canal obturation, buccolingual fractures, single file system.

Resumen

Introducción: La obturación del conducto radicular es un procedimiento utilizado en la terapia endodóntica para sellar el espacio del conducto radicular y hacer que el diente sea más resistente a la rotura. Según algunos informes, después de un tratamiento endodóntico, los dientes son más propensos a romperse. La pulpa y la corona deben cuidarse y protegerse, por lo que es esencial una restauración adecuada. La desecación de la dentina coronal y radicular, causada por la pérdida excesiva de estructura dental durante el tratamiento endodóntico, es la causa más frecuente de debilidad dental. El objetivo del estudio es comparar los resultados de cinco técnicas distintas de preparación rotacional de una sola lima para reforzar las raíces mesiales de los primeros molares mandibulares en caso de fractura.

Métodos: Se utilizaron puntas de escarificador ultrasónico junto con irrigación salina normal para desbridar y limpiar las cámaras pulpares de los dientes extraídos. Tras preparar el conducto mesio-bucal hasta la longitud de trabajo utilizando una lima K de 6#, se tomó una radiografía digital en dirección bucolingual. Los dientes llenos de caries se extrajeron de la boca. A continuación se calculó la curvatura del conducto radicular tras evaluar los dientes con el método de Schneiders para la curvatura del conducto.

Resultados: Siguiendo las directrices de los fabricantes, utilizamos el método de una sola lima para medir las longitudes de ambos conductos en la raíz mesial para establecer los grupos experimentales. Las muestras se volvieron a abrir al cabo de 72 horas y se obturaron de nuevo. A continuación, se utilizó un conformador de bases para fijarlas a las bases de resina. La carga a la fractura se midió aplicando una carga vertical con una punta de acero inoxidable de 3 mm en una máquina universal de pruebas. Tras el proceso de fractura, se evaluó el tipo de fractura. Se tabularon y examinaron estadísticamente los resultados.

Conclusiones: Las raíces creadas con sistemas de lima única presentaron una resistencia a la fractura comparable a las generadas con el grupo de control, dentro del ámbito y los métodos de estandarización de esta investigación. Se recomienda encarecidamente realizar un examen clínico y más pruebas de parámetros de estos sistemas de lima única.

Palabras clave: Obturación del conducto radicular, fracturas bucolinguales, sistema de lima única.

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Introduction

The canal used to be enlarged by a factor of three from the first initial file to bind at the apical third of the root when it was still usual practise to use manual instrumentation. Thanks to the expansion, the canal system was able to be thoroughly cleaned, and the irrigators and medicines could be distributed throughout its whole length. NiTi hand tools were first used in endodontics approximately twenty years ago, and their flexibility greatly aided in the improvement of preparations. The greatest benefit was the assurance of consistent management over the cooking process. The alloy was super-elastic, shape-memory, and corrosion-resistant. Thanks to the development of nickel titanium rotary instrumentation, negotiating even very curved canals is now a straightforward, thorough, and time-efficient process.

When preparing a canal, these rotational devices may cause localised stress that can lead to microscopic fractures or craze lines, which can eventually make the tooth more prone to a vertical root fracture. There is a lot of pressure on the root canal wall, especially right in the centre. Because of the high stress concentrations in the coronal one-third of the root's radicular dentin, teeth are more susceptible to shatter at the cemento-enamel junction. The root thickness of a tooth directly correlates to its resistance to lateral stresses. Scientists have shown that the probability of a tooth cracking is proportional to the quantity of healthy dentin still present in the tooth[1].

There may be a connection between the make-up of nickel titanium rotary tools and the occurrence of vertical root fractures, according to research[2]. To some extent, the mechanical behaviour and geometry of the spinning instruments, as well as the operator's training and skill, define the nature of the issues encountered in usage.

Root fractures in teeth that have been treated with endodontics might show up in a few different ways. It is possible to classify root fractures as either horizontal or vertical. After endodontic treatment, 11-13% of removed teeth were found to have vertical root fractures, according to a number of clinical investigations[3]. One of the most serious side effects of root canal procedures is vertical root fracture, which may happen before, during, or after obturation. The standard treatment for this is to remove the tooth[4]. Tooth extraction is the most common treatment for vertical root fractue, which may occur before, during, or after root canal obturation and is one of the most significant consequences of root canal treatments[5].

As a result, several studies have focused on finding ways to strengthen the link between the crown and the root. Root canals are often filled with gutta-percha and sealed, however because to gutta-percha's low elastic modulus, the treated roots get little to no reinforcement[6].

As a result, new materials and techniques must be developed to address the limitations of conventional endodontic fillings and effectively strengthen root structure. Reducing coronal leakage in endodontically treated teeth is possible with the use of an intra-orifice barrier[7]. In order to boost the root's resistance to fracture, this method is used to fortify the canal orifices soon after the coronal section of gutta-percha and sealer has been removed[8] Materials including resin modified GIC, flowable composite, and bonded amalgam are ideal for use as intra-orifice barriers. Inadequate post endodontic restoration was shown to almost increase the failure rate for endodontically treated teeth, according to a study of 9. Newer generations of materials often have enhanced bonding between radicular dentin and the sealer and the sealer-core contact, both of which work to increase fracture resistance and restrict invasion paths. If the root filling material is to provide enough support for the roots, its modulus of elasticity should be near to that of the dentin[10]. Here we see the monoblock notion put forward, It aims to create mechanically stable homologous units of radicular dentin. The complexity, inaccessibility, and cleanliness issues of the canal system make consistently achieving the ideal monoblock unit difficult. Using a sealer and core material to prime the radicular dentinal surface and form a bond may be necessary to achieve this. In order to do this, several types of sealer and core materials have been created. Load pressures must be distributed uniformly throughout the monoblock, therefore the post, filling material, and sealer must all have a modulus of elasticity comparable to radicular dentin[11].

Typically, rotary NiTi file systems included a number of separate rotary instruments meant to be used together. Newer file systems with a single rotary file have been introduced due to advancements in metallurgy and have proven to be efficient and effective. Rotating files that may be used in a sawing action have also been developed. An revolutionary endodontic file, the self-adjusting file system, uses vibration and continuous irrigation to conform to the unique dimensions of each canal[12]. These single-file systems have been favored because to their convenience, ease of use, shortening of clinical work time, and lowered stress levels on canal walls. They've been suggested and made for one-time usage to avoid the risks of contamination and contamination during sterilization.

Methodology

Collection of teeth

Up to 72 hours following extraction, around 160 human primary molars were stored in isotonic saline solution. Collection, storage, sterilisation, and handling procedures complied with all applicable OSHA and CDC guidelines for infection prevention.

Selection of samples

Teeth that had not had extensive decay, repair, or endodontic therapy were set aside. The teeth were examined under a microscope to rule out those with visible fissures. The teeth used in the research had to have fully developed root apices. The chosen teeth were placed in a standard saline solution and chilled to 4 degrees Celsius for later use. In all, 120 teeth were chosen for this analysis.

Standardization of samples

Ultrasonic scaler tips were used to debride and clean the pulp chambers of the removed teeth, which were then irrigated with normal saline. After advancing a 60 K file through the mesiobuccal canal to its working length, a bucco-lingual digital radiograph was obtained. Calcified canal teeth were thrown away. The root canal curvature was then calculated after the teeth were evaluated using the Schneiders method.

Teeth were chosen for the research based on their mesial root curvature, which had to be more than 25 degrees but less than 35 degrees. At the furcation, the mesial roots were cut in two. Each root was given a unique code and logged for future reference. Normal saline was used to keep the roots of the included plants moist so that they wouldn't dry up throughout the experiment.

Using digital Vernier callipers, the mesio-distal and bucco-lingual diameters of the teeth were measured. After that, a precision weighing equipment was used to determine the exact weight of each sample. Each of the six test and control groups received an equal number of samples. After washing in distilled water, the roots were placed in normal saline at 4 degrees Celsius in individual glass bottles.

Preparation of the Sample

A size 6K file (Dentsply Maillefer, Ballaigues, Switzerland) was passively moved into the canal under a loupe until its tip was visible at the apical foramen, at which time the working length was determined. After recording the length of each sample's canal, we subtracted 0.5 mm from that number to get the working length. The experimetal groups' canal systems were constructed using the single file system that had been allotted to them in accordance with the manufacturer's guidelines.

Root Canal Preparation Technique

Ballaigues, Switzerland; Dentsply; Maillefer; Switzerland The manufacturer-recommended single-file rotary system was employed when K files up to size 10 were used as the principal instrument. The NEOLIX, ONESHAPE, WAVEONE GOLD, RECIPROC, and SELF-ADJUSTING FILES single-file systems were employed in this research. A 28-gauge side vent needle (Prime dent) was used to inject the irrigant at the needle's working length. Before moving on to the next tool, 1 cc of the irrigant was used to flush the canals and eliminate any remaining debris. Manufacturer instructions were followed for installation and operation of the Self-adjusting file system. Other organisations' instrumentation strategies recommended using 5 ml of 5% sodium hypochlorite as an irrigant. Extracted from human permanent mandibular first molars, all roots in this study had their mesial root canals instrumented and processed in accordance with the protocols outlined by the associated single file system.

Final Rinse of Samples

The samples were given one last rinsing with 5 cc of the irrigant solution after the canal was cleaned. The first and last washes were administered to each group in accordance with the instructions provided by the manufacturer. Finally, a 28-gauge side vent needle (Prime dent) was used to inject 5 millilitres of 17% EDTA into the gums as an irrigant. The final rinsing solution was left exposed for three minutes. At the end of three minutes, the canal system was irrigated with 10 cc of distilled water to remove any lingering final rinse irrigant.

Obturation of the samples

After the canals were cleaned and dried using a lentulospiral, a sealant was applied to them. All of the groups utilised AH plus as their sealer. After that, gutta-percha cones were used in a cold lateral condensation procedure for obturation; any surplus was scraped away and the cones were left to set for 72 hours in a humid environment. Radio-visiography was used to verify the effectiveness of root canal fillings. Luxacore, a core building material, was used to prep, bind, and seal the access cavities. The samples were kept for 72 hours at 37 degrees Celsius and 100% relative humidity. Separate systems were used for processing and storing each group for further examination.

Preparation for fracture testing

All of the specimens were dismounted from their bases and remounted on resin blocks (40 mm in height and 30 mm in diameter) using a base block maker. The adhesive, which reached just to the very tip of the root, ran vertically along the long axis of the block. After the adhesive had dried on the sample blocks, they were given codes. Prior to undergoing fracture testing, the samples were stored under damp cotton and a wet towel to keep them from drying out.

Fracture testing procedure:

The samples were examined with the use of a standardised testing apparatus. Both the tooth specimen block and the 3 mm metal indenter were attached to the upper and lower jig arms, respectively. The load was delivered to the tooth's surface in a direction perpendicular to the tooth's long axis from above at a cross head speed of 1mm/min. The number of Newtons of force needed to crack the tooth sample was also recorded.

Tabulation of result

The results of the test were based on the highest breaking force that was measured. The fracture type and fracture strength values were evaluated. Each sample was

examined under a microscope to determine the different kinds of fractures that had occurred. Two independent evaluators reviewed the data and compared their findings.

Statistical analysis

Each group was assigned a certain number of samples depending on their weight and level of similarity. The continuous variables were tested statistically to see whether they followed a normal distribution. One-way analysis of variance (ANOVA) and Tukey's post hoc test for multiple comparisons (P.05) were used to assess the fracture test findings statistically.

Results

Table I presents the distribution of types of fracture. Buccolingual fracture was seen in 53.33% of the samples; mesiodistal fracture was seen in 30.83% of the samples; communited fracture was seen in 11.67% of the samples; and transverse fracture was seen in 4.17% of the samples.

Table II and **figure 1** presents the distribution of the type of fracture. In group I, buccolingual fracture was seen in 50% of the samples; mesiodistal fracture was seen in 35% of the samples; and communited fracture was seen in 15% of the samples. In group II, buccolingual fracture was seen in 60% of the samples; mesiodistal fracture was seen in 30% of the samples; and communited fracture was seen in 10% of the samples. In group III, buccolingual fracture was seen in 50% of the samples; mesiodistal fracture was seen in 35% of the samples; and communited fracture was seen in 15% of the samples. In group IV, buccolingual fracture was seen in 55% of the samples; mesiodistal fracture was seen in 25% of the samples; communited fracture was seen in 10% of the samples; and transverse fracture was seen in 10% of the samples. In group V, buccolingual fracture was seen in 55% of the samples; mesiodistal fracture was seen in 30% of the samples; communited fracture was seen in 10% of the samples; and transverse fracture was seen in 5% of the samples. In group VI, buccolingual fracture was seen in 50% of the samples; mesiodistal fracture was seen in 30% of the samples; communited fracture was seen in 10% of the samples; and transverse fracture was seen in 10% of the samples.

Table III presents the sample distribution data for the groups. Mean buccolingual width in Gr I, Gr II, Gr III, Gr IV, Gr V, and Gr VI was 9.050mm, 8.942mm, 9.052mm, 9.149mm, 9.089mm, and 8.973mm respectively. Mean mesiodistal width in Gr I, Gr II, Gr III, Gr IV, Gr V, and Gr VI was 4.359mm, 3.955mm, 4.085mm, 3.883mm, 4.167mm, and 4.034mm respectively. The mean weight of the root in Gr I, Gr II, Gr III, Gr IV, Gr V, and Gr VI was 0.511g, 0.551g, 0.510g, 0.501g, 0.570g, and 0.542g.

Figure 1: Distribution of the type of fracture n (%).

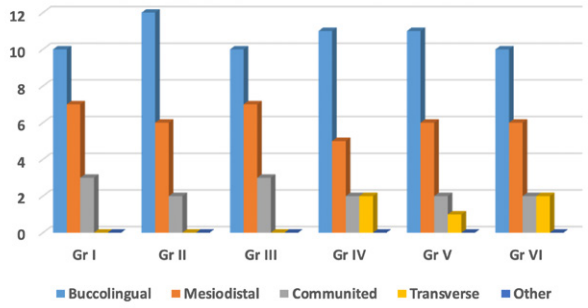

Table I: Type of fracture (in %).

Group (n=120)	Buccolingual	Mesiodistal	Communited	Transverse	Other
120	53.33%	30.83%	11.67%	4.17%	0

Table II: Distribution of type of fracture n (%).

Group (n=20)	Buccolingual	Mesiodistal	Communited	Transverse	Other
Gr I	10 (50%)	7 (35%)	3 (15%)	0	0
Gr II	12 (60%)	6 (30%)	2 (10%)	0	0
Gr III	10 (50%)	7 (35%)	3 (15%)	0	0
Gr IV	11 (55%)	5 (25%)	2 (10%)	2 (10%)	0
Gr V	11 (55%)	6 (30%)	2 (10%)	1 (5%)	0
Gr VI	10 (50%)	6 (30%)	2 (10%)	2 (10%)	0
Overall	**53.33%**	**30.83%**	**11.67%**	**4.17%**	**0**

Table III: Sample distribution data for the groups.

Groups (n=20)	Buccolingual Width (A)		Mesiodistal Width (B)		A*B		A+B		Weight (g)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Gr I	9.050	0.30	4.359	0.94	39.608	9.47	13.409	1.15	0.511	0.06
Gr II	8.942	0.38	3.955	1.03	35.468	9.76	12.897	1.19	0.551	0.06
Gr III	9.052	0.32	4.085	0.65	37.018	6.37	13.137	0.78	0.510	0.06
Gr IV	9.149	0.52	3.883	0.64	35.686	7.22	13.032	1.01	0.501	0.06
Gr V	9.089	0.52	4.167	0.47	38.015	5.72	13.256	0.88	0.570	0.07
Gr VI	8.973	0.40	4.034	0.56	36.273	5.89	13.007	0.80	0.542	0.08

Table IV and **figure 2** presents the maximum load values for root fracture. Mean load for root fracture (in Newton) in Gr I, Gr II, Gr III, Gr IV, Gr V, and Gr VI was 961.35, 1068.75, 1256.20, 1043.60, 1152.50 and 1143.05 respectively.

Table V shows Comparison of mean fracture strength (mean load in Newton) among six experimental groups showed a non-significant difference among six groups (F=1.057; p=0.388).

All of the root's physical qualities are positively correlated with load, as seen in **table VI**, which displays the association between the two variables.

Discussion

The root canal system is quite intricate, with many different components such as auxiliary canals, fins, Cul de sacs, and transverse anastomoses. Halfway through the radicular dentin of diseased teeth, dentinal tubules get colonized by the bacteria that have been shown to live there. Therefore, biomechanical preparation of the canal (the process of shaping and cleaning the channel) is regarded as an essential step in endodontic therapy for disinfecting the infected root canal space. The therapy would fail and the results of the treatment would be subpar if the cleaning procedure was insufficient[13].

Cleaning, preparing the canal area, delivering the irrigant, and replacing the canal filling might be difficult due to the root canal's unique structure and the curved roots, This may be seen most clearly in the back teeth (mandibular and maxillary). It is possible to visualize the root canal system as a triangle, with the coronal canal being the most easily accessible and the apical canal being the most difficult to reach. Significant quantities of radicular dentin in the coronal and middle third must be removed in the case of bent roots to reach the apical third of the canals and conduct adequate debridement and cleaning, which may endanger the structural integrity of the root. After endodontic treatment, the tooth becomes more susceptible to damage because of this [4]. The thickness of a tooth's root determines how effectively it can bear lateral strains. How much of the tooth's natural dentin remains predicts how resistant it is to fracture, according to studies[15].

Studies have shown that nickel titanium rotary instruments may contribute to the development of vertical root fractures[16]. It is the mechanical characteristic and geometry of the rotary instruments, as well as the operator's training and experience, that determine the nature of the issues faced during use. Flexibility is improved over that of traditional NiTi alloys by the introduction of the M-wire NiTi alloy with regulated memory[17].

Figure 2: Mean Load values for root fracture.

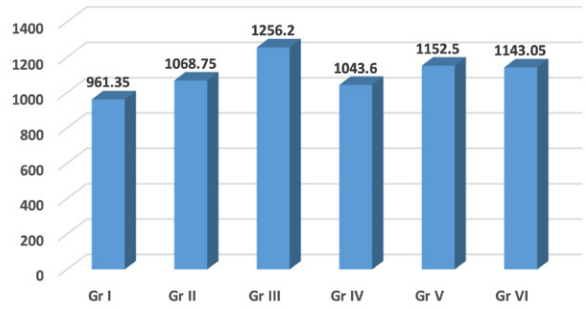

Table IV: Maximum Load Values for Root Fracture.

Group (n=20)	Minimum	Maximum	Mean	SD	Median	95% Confidence interval	
						Lower	Upper
Gr I	412	1751	961.35	412.04	919.5	768.51	1154.19
Gr II	372	1849	1068.75	417.29	1017.5	873.45	1264.05
Gr III	535	2336	1256.20	542.24	1150.5	1002.42	1509.98
Gr IV	376	1882	1043.60	391.46	990.5	860.39	1226.81
Gr V	403	1862	1152.50	458.85	1146	937.75	1367.25
Gr VI	501	1802	1143.05	430.67	1229.5	941.49	1344.61

Table V: Comparison of mean fracture strength values.

	Sum of Squares	df	Mean Square	F	p-value
Between Groups	1045627.74	5	209125.5	1.057	0.388
Within Groups	22556608.25	114	197865		
Total	23602235.99	119			

Table VI: Correlation of physical properties of roots with load.

Physical properties of root	r value	p-value
Buccolingual Width (A)	0.217	0.017*
Mesiodistal width (B)	0.272	0.003*
A*B	0.287	0.001*
A+B	0.300	0.001*
Weight (g)	0.281	0.002*

There is evidence that retreatment increases the quantity of dentin removed from the canal space, making the tooth more brittle. It has been shown that using rotary files to remove gutta percha during re-treatment removes surface dentin and enlarges the apical thirds for better washing, both of which lead to a decreased fracture resistance of the root. Dentin removal during retreatment operations has been shown to correlate with decreased fracture resistance[18].

Upon removal, 160 mandibular first molars were collected, cleaned, and kept at 30 degrees Celsius in 1% thymol in normal saline. Root morphology and the existence of a patent canal devoid of abnormalities, extensive damage, and restorations were among the criteria examined. Selected samples had a curvature of 20-35 degrees at the mesial root, based on an analysis of the data. After that, we cut out the mesial roots, labelled them, and put them in a different location. Each sample was weighed, Before being randomly allocated to the test or control groups, Measurements were taken of the buccolingual and mesiodistal areas, and the teeth were cleaned in distilled water before being placed in normal saline and refrigerated at 4 degrees Celsius in individual glass containers. Subjects' mesial root canals were measured to determine their working lengths, and then each group used their assigned single-file system to perform the necessary preparations in accordance with the manufacturer's guidelines. After 72 hours, the samples were unsealed and allowed to set without obturation. They were then placed on base formers and attached to resin bases for display.

Fracture testing was conducted using a universal testing equipment, with a 3mm stainless steel point applied in a vertical direction to determine the load at fracture. The analysis of fracture kind came after the testing procedure. A statistical breakdown and tabulation of the findings.

Conclusion

Conclusions on the fracture strength of roots instrumented with single file systems are drawn due to the prevalence of buccolingual fractures across all experimental groups. The mesiodistal type of fracture was the next commonest. The incidence of communited and transverse This form of fracture occurred seldom. Among both the test and control groups, buccolingual fractures were the most prevalent. Roots created using single-file systems had a comparable resistance to fracture to those generated using the control group, within the bounds of the research and the standardised techniques used to evaluate them. It is suggested that these single file systems be further assessed in a clinical context and evaluated using additional factors.

Consent for publication
The author reviewed and approved the final version and has agreed to be accountable for all aspects of the work, including any accuracy or integrity issues.

Disclosure
The author declares that they do not have any financial involvement or affiliations with any organization, association, or entity directly or indirectly with the subject matter or materials presented in this editorial. This includes honoraria, expert testimony, employment, ownership of stocks or options, patents, or grants received or pending royalties.

Ethical approval
The IRB approval was obtained from The Deanship of Scientific Research, Majmaah University, Majmaah, Saudi Arabia.

Data availability
The data is exclusively available from the principal author for research purposes only.

Authorship contribution
Conception, design, utilization, collection, analysis, and interpretation of data, drafting, revision, or critical review was done by.

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Conflict of interest
The author declares that he has no conflict of interest.

References

1. Khoroushi M, Feiz A, Khodamoradi R. Fracture resistance of endodontically- treated teeth: effect of combination bleaching and an antioxidant. Oper Dent 2010; 35 (5): 530-7.

2. Vicente-Herrero MT, Iniguez de la Torre MV, Capdevila Garcia L. Dental erosion and occupational Risk factors. Bibliographic review. Medicina Balear 2019; 34 (1): 20-4.

3. Fuss Z, Lustig J, Tamse A. Prevalence of vertical root fractures in extracted endodontically treated teeth. Int Endod J 1999; 32 (4): 283-86.

4. Cantor ML, Acosta JM. Direct instruction and inquiry-based method in teaching endodontics among preclinical dentistry students. Medicina Balear 2021; 36 (3): 113-6

5. Meister Jr F, Lommel TJ, Gerstein H. Oral Surgery Oral Medicine and Oral Pathology 1980: 49 (3): 243-53.

6. Mohammadian F, Hazinehei SS, Hashemikamangar SS, Dibaji F, Kharrazifard MJ. Fracture resistance of teeth with simulated cervical rootresorptions restored by various materials. Medicina Balear 2021; 36 (2): 136-41

7. Yavari HR, Samiei M, Shahi S, Aghazadeh M, Jafari M, Abdolrahimi M, et al. Microleakage comparison of four dental materials as intra-orifice barriers in endodontically treated teeth. Iran Endod J 2012; 7 (1): 25-30.

8. Roghanizad N, Jones JJ. Evaluation of coronal microleakage after endodontic treatment. J Endod 1996; 22 (9): 471-3.

9. Williams C, Loushine RJ, Weller RN, Pashley DH, Tay FR. A comparison of cohesive strength and stiffness of Resilon and gutta-percha. J Endod 2006; 32: 553-5.

10. Tay FR, Pashley DH. Monoblocks in root canals: A hypothetical or a tangible goal. J Endod 2007; 33: 391-8.

11. Metzger Z, Teperovich E, Zary R, Cohen R. The self-adjusting file(SAF) Part 1: Respecting the root canal anatomy- A new concept of endodontic files and its implementation. J Endod 2010; 36 (4): 679-90.

12. Klevant FJH, Eggink CO, The effect of canal preparation on periapical disease. Int Endod J 1983; 16: 68-75.

13. Sornkul E, Stannard JG. Strength of roots before and after endodontic treatment and restoration. J Endod 1992; 18: 440-3.

14. Lertchirakarn V, Timyam A, Messer HH. Effects of root canal sealers on vertical root fracture resistance of endodontically treated teeth. J Endod 2002; 28: 217-9.

15. Lam PP, Palamara JE, Messer HH. Fracture strength of tooth roots following canal preparation by hand and rotary instrumentation. J Endod 2005; 31 (7): 529-32.

16. Capar ID, Saygili G, Ergun H, Gok T, Arslan H, Ertas H. Effects of root canal preparation, various filling techniques and retreatment after filling on vertical root fracture and crack formation. Dent Traumatol 2015 Aug; 31 (4): 302-7.

17. Ganesh A, Venkatesh Babu N, John A, Deenadhayalan G, Kandaswamy D. A comparative assessment of fracture resistance of endodontically treated and re- treated teeth: An in-vitro study. Jour of Cons Dent 2014; 17 (1): 61-5.

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ORIGINAL

Cardiometabolic risk level in 43.074 Spanish office workers: associated variables

Nivel de riesgo cardiometabólico en 43.074 oficinistas españoles: variables asociadas

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Abstract

Introduction: It is well known that cardiometabolic diseases are the main cause of morbidity and mortality in most countries around the world. These diseases are multifactorial, with one of the most important factors being a sedentary lifestyle. Office workers typically have sedentary jobs, so the aim of this study is to assess the level of cardiometabolic risk among office workers.
Methodology: This was a descriptive and cross-sectional study conducted on 43,074 office workers from different regions of Spain during the years 2021-2023. The level of cardiometabolic risk was determined by applying various scales, including insulin resistance, nonalcoholic fatty liver disease, atherogenic risk, and metabolic syndrome.
Results: Most of the risk scales analyzed showed moderate values, and in some cases, high values were observed, despite the average age of the participants being 40 years old. The profile of the most at-risk worker is a male over 50 years of age who is sedentary and a smoker.
Conclusions: Sedentary office work appears to increase the risk of presenting moderate to high cardiometabolic risk values.

Key words: Cardiometabolic risk, office workers, obesity, metabolic syndrome, insulin resistance.

Resumen

Introducción: De todos es conocido que las enfermedades cardiometabólicas constituyen la principal causa de morbimortalidad en la mayoría de países del mundo. Estas enfermedades son multifactoriales y uno de los factores más importantes es el sedentarismo. Los trabajadores de oficina tienen un trabajo sedentario, por ello el objetivo de este trabajo es valora el nivel de riesgo cardiometabólico en trabajadores de oficina.
Metodología: Estudio descriptivo y transversal en 43.074 oficinistas de diferentes regiones españolas durante los años 2021-2023 en los que se determina el nivel de riesgo cardiometabólico aplicando diferentes escalas entre las que podemos destacar resistencia a la insulina, hígado graso no alcohólico, riesgo aterogénico, síndrome metabólico y síndrome metabólico.
Resultados: La mayoría de escalas de riesgo analizadas presentan valores moderados e incluso en algún caso altos pese a que la edad media de los participante es de 40 años. El perfil de trabajador de mayor riesgo es un varón mayor de 50 años, sedentario y fumador.
Conclusiones: El trabajo sedentario de oficina parece incrementar el riesgo de presentar valores moderados-altos de riesgo cardiometabólico.

Palabras clave: riesgo cardiometabolico, trabajadores de oficina, obesidad, síndrome metabólico, resistencia a la insulina.

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Introduction

Cardiometabolic diseases are currently believed to be the leading cause of morbidity and mortality worldwide[1]. The World Health Organization (WHO) has reported that this disease causes more deaths per year than any other disease[2]. Consequently, this organization created an action plan to reduce premature deaths related to this cause, focusing on improving public services and policies, particularly those affecting non-communicable diseases, among which cardiovascular diseases are a significant factor[3].

Various scales are available to assess cardiometabolic risk (CMR), some of which measure it directly by calculating the risk of suffering a cardiovascular event over a period, generally 10 years. Examples include the Registre Gironí del Cor (REGICOR)[4] and the Spanish Cardiovascular Risk Equation (ERICE) in Spain[5]. The Systematic Coronary Risk Evaluation (SCORE) scale measures the risk of suffering a fatal cardiovascular event over time[6]. Other direct risk scales developed in recent years include vascular and cardiac age scales[7,8].

Indirect assessments of CMR are conducted using scales for overweight and obesity, atherogenic indices[9], metabolic syndrome[10], insulin resistance[11], and fatty liver disease[12], among others. The methodology section will discuss all these scales.

While many studies have determined CMR in both the general population and the working population, few have assessed it in office workers, a sedentary profession. This situation should lead to a worsening of cardiometabolic risk in this group.

The aim of this study was to determine the level of CMR in Spanish office workers and the influence of age, sex, and tobacco consumption on this risk.

Methods

A descriptive, cross-sectional study was conducted on 43,074 Spanish office workers between January 2021 and December 2023. Of these, 2,219 workers were excluded: 1,851 did not have the necessary parameters to calculate different CMR scales, 103 did not agree to participate, and 265 had a history of previous cardiovascular events. The remaining 43,074 workers included 27,458 women (63%), with a mean age of 40 years, and 15,616 men (36%), with a mean age of 41.7 years.

Participants were selected from employees who attended regular occupational medical check-ups in various companies across Spain.

Inclusion criteria

- Consent for participation in the investigation and use of data for epidemiological purposes.
- Absence of cardiovascular history.
- Office employment.
- Employment in a participating company.

Health professionals from different occupational health units standardized the measurement techniques and conducted anthropometric, clinical, and analytical assessments.

The evaluation included the following parameters:

- Weight (in kg) and height (in cm) measured using a SECA 700 scale and a SECA 220 measuring rod, respectively.
- Abdominal waist circumference (in cm) measured using a SECA 200 tape measure, with the cutoff point set at 0.50 for the waist-to-height ratio[13].

- Blood pressure measured in the supine position using a calibrated OMRON M3 automatic sphygmomanometer after a 10-minute rest period. Hypertension was considered if systolic blood pressure was 140 mm Hg or diastolic blood pressure was 90 mm Hg or if the worker was receiving antihypertensive treatment[14].

- Blood glucose, total cholesterol, and triglycerides measured after a fast of at least 12 hours using peripheral venipuncture. Automated enzymatic methods were used to measure blood glucose, total cholesterol, and triglycerides. HDL was measured using dextran sulfate precipitation, and LDL was calculated using Friedewald's formula[15].

LDL-c = Total cholesterol-HDL-c + Triglycerides/5

- Abnormal values were considered at 200 mg/dL for cholesterol, 130 mg/dL for LDL, and 150 mg/dL for triglycerides, or if the worker was receiving treatment for any of these factors[16].

The American Diabetes Association (ADA) criteria classified blood glucose levels as indicative of diabetes if they measured 126 mg/dL or higher, or if individuals were receiving hypoglycemic treatment [17].

Weight was divided by height in meters squared to obtain the body mass index (BMI), with obesity defined as a BMI of 30 kg/m^2 [18].

Various scales were utilized to measure overweight and obesity, including the Clínica Universitaria de Navarra body adiposity estimator (CUN BAE)[19], Cordoba equation body adiposity estimator (ECORE-BF)[20], relative fat mass (RFM)[21], Palafolls formula[22], Deurenberg formula[23], visceral adiposity index (VAI)[24], body roundness index[25],

body shape index (ABSI)[26], conicity index (CI)[27], body surface index (BSI)[28], and metabolic score for visceral fat (METS-VF)[29].

Additionally, the following indexes were employed: triglyceride-glucose index[30], triglyceride-glucose-IMC index[31], triglyceride-glucose-waist index[32], and metabolic score to measure insulin resistance (METS-IR)[33]. The waist triglyceride index[34] served as an indicator of cardiometabolic risk. For assessing nonalcoholic fatty liver disease, the Fatty liver index (FLI)[35], hepatic steatosis index (HSI)[36], Zhejian University (ZJU) index[37], fatty liver disease (FLD) index[38], Framingham steatosis index (FSI)[39], and lipid accumulation product (LAP)[40] were utilized.

The atherogenic indexes determined were:

• Total cholesterol/HDL (considered as high > 5 in men and > 4.5 in women), LDL/HDL and triglycerides/HDL (high > 3);Triglycerides/HDL (high >3)[41].

Cardiometabolic indicators:

• Hypertriglyceridemic Waist Phenotype[42]: Waist > 102 cm (men) > 88cm (women); and Triglycerides > 150 mg/dL or treatment of hypertriglyceridemia.

Three models were employed to identify the metabolic syndrome[43]:

1. The Adult Cholesterol Education Panel III (NCEP ATP III) defines metabolic syndrome when three or more of the following factors are present: a waist circumference greater than 88 cm in women and 102 cm in men; blood pressure exceeding 130/85 mmHg; HDL levels below 40 mg/dL in women or 50 mg/dL in men, or receiving specific treatment for this lipid disorder; and fasting blood glucose levels higher than 100 mg/dL or undergoing treatment.

2. The International Diabetes Federation (IDF) characterizes central obesity as a waist circumference surpassing 80 cm in women and 94 cm in men, along with two of the aforementioned factors from ATP III (triglycerides, HDL, blood pressure, and blood glucose).

3. The JIS model aligns with the criteria of NCEP ATPIII, but adjusts the waist circumference cutoff points to 80 cm for women and 94 cm for men.

Atherogenic dyslipidemia is marked by elevated triglyceride levels (> 150 mg/dL), low HDL levels (< 40 mg/dL in men and < 50 mg/dL in women), and normal or slightly elevated LDL. LDL readings exceeding 160 mg/dL indicate the lipid triad[44].

The Framingham scale, tailored for the Spanish population and known as REGICOR[45], assesses an individual's 10-year risk of a cardiovascular event, applicable to those aged 35 to 74. A risk of 5% or higher is considered moderate, while 10% or higher is deemed high.

Spain utilizes the SCORE scale 46 to assess the likelihood of a catastrophic cerebrovascular event over ten years, applicable to individuals aged 40 to 65. A risk exceeding 5% is classified as high, while 4% is considered moderate.

ERICE, based on seven population-based cohort studies across Spain, estimates the ten-year risk of experiencing a fatal or non-fatal cerebrovascular event for individuals aged 30 to 80. Age, sex, smoking status, diabetes, systolic blood pressure, antihypertensive medication use, and total cholesterol levels are considered in risk calculation. ERICE categorizes risk as

Table I: Different scales used in the study.

Determination	Scale	Parameters
Overweight-obesity	CUN BAE	Age, gender, BMI
	ECORE-BF	Age, gender, BMI
	Palafolls's formula	Gender, BMI, waist
	Deurenberg's formula	Age, gender, BMI
	Relative fat mass	Gender, height, waist
	VAI	Gender, BMI, waist, HDL, triglycerides
	Body roundness index	Waist, height
	BSI	Weight, height
	Conicity index	Weight, height, waist
	ABSI	Waist, height, BMI
	NWAI	Weight, height
	METS-VF	Weight, height, age, gender, glucose, HDL, triglycerides
Insulin resistance	Triglyceride glucose index	Glucose, triglycerides
	METS-IR	Weight, height, glucose, HDL, triglycerides
Cardiometabolic risk	Waist triglyceride index	Waist, triglycerides
	Cardiometabolic index	Height, waist, HDL, triglycerides
Fat liver	Fatty liver index	Triglycerides, BMI, GGT, waist
	Hepatic steatosis index	AST, ALT, BMI, diabetes, gender
	Zhejiang University index	Triglycerides, BMI, glucose, ALT, AST, gender
	Fatty liver disease index	Triglycerides, BMI, glucose, ALT, AST
	Framingham steatosis index	Age, gender, BMI, triglycerides, hypertension, diabetes, AST, ALT
	Lipid accumulation product	Waist, triglycerides, gender

ABSI = body shape index; BMI = body mass index; BSI = body surface index; CUN BAE = Clínica Universitaria de Navarra Body Adiposity Estimator; ECORE-BF = Equation Córdoba Estimator Body Fat; NWAI = normalized weight-adjusted index; VAI = visceral adiposity index. METS-VF Metabolic score for visceral fat. METS-IR Metabolic score for insulin resistance.

Table II: Characteristics of the office workers.

	Women n=27458	Men n=15616	Total n=43074	
	mean ± SD	mean ± SD	mean ± SD	p-value
Age	40.0 ± 9.6	41.7 ± 10.5	40.6 ± 10.0	<0.0001
Height	162.9 ± 6.3	175.8 ± 6.8	167.6 ± 9.0	<0.0001
Weight	65.2 ± 13.2	82.3 ± 13.7	71.4 ± 15.7	<0.0001
Waist circumference	73.8 ± 10.0	86.9 ± 10.3	78.6 ± 11.9	<0.0001
SBP	116.4 ± 15.0	127.6 ± 15.0	120.5 ± 15.9	<0.0001
DBP	72.0 ± 10.2	78.0 ± 10.0	74.2 ± 10.8	<0.0001
Total cholesterol	191.0 ± 34.4	195.3 ± 36.5	192.6 ± 35.2	<0.0001
HDL-c	57.4 ± 9.2	50.5 ± 8.4	54.9 ± 9.5	<0.0001
LDL-c	116.3 ± 33.4	121.0 ± 34.8	118.0 ± 34.0	<0.0001
Triglycerides	87.3 ± 43.3	120.6 ± 75.7	99.4 ± 59.4	<0.0001
Glucose	86.7 ± 12.7	91.4 ± 16.3	88.4 ± 14.3	<0.0001
	%	%	%	p-value
< 30 years	15.3	14.5	15.0	<0.0001
30-39 years	16.9	24.5	19.7	
40-49 years	35.1	33.1	34.3	
≥ 50 years	32.7	27.9	31.0	
Smokers	31.5	31.3	31.4	0.625
Non-smokers	68.5	68.7	68.6	
Sedentarism	61.6	66.4	63.4	<0.0001
Non sedentarism	38.4	33.6	36.6	

SBP Systolic blood pressure. DBP Diastolic blood pressure. HDL-c High density lipoprotein cholesterol. LDL Low density lipoprotein cholesterol. SD Standar deviation

Table III: Mean values of the different cardiovascular risk scales in office workers according to sex.

	Women n=27458	Men n=15616	
	mean ± SD	mean ± SD	p-value
BMI	24,6 ± 4,8	26,6 ± 4,1	<0.0001
Waist to height ratio	0,45 ± 0,1	0,49 ± 0,1	<0.0001
CUN BAE	34,3 ± 6,6	25,6 ± 6,0	<0.0001
ECORE-BF	34,2 ± 6,7	25,6 ± 5,8	<0.0001
Relative fat mass	31,2 ± 5,4	23,0 ± 4,6	<0.0001
Palafolls formula	37,9 ± 5,0	29,7 ± 4,3	<0.0001
Deuremberg formula	33,3 ± 6,4	25,3 ± 6,0	<0.0001
Body fat index	26,0 ± 7,4	22,5 ± 7,5	<0.0001
Body surface index	49,8 ± 7,6	58,2 ± 7,3	<0.0001
Normalized weight adjusted index	0,2 ± 1,3	0,6 ± 1,3	<0.0001
Body roundness index	2,6 ± 1,1	3,3 ± 1,1	<0.0001
Body shape index	0,069 ± 0,01	0,073 ± 0,01	<0.0001
Visceral adiposity index	2,6 ± 1,6	7,3 ± 6,3	<0.0001
Conicity index	1,1 ± 0,1	1,2 ± 0,1	<0.0001
METS-VF	5,3 ± 0,8	6,2 ± 0,7	<0.0001
Triglyceride glucose index	8,1 ± 0,5	8,5 ± 0,5	<0.0001
Triglyceride glucose index-BMI	200,5 ± 45,1	226,1 ± 43,1	<0.0001
Triglyceride glucose index-waist	601,8 ± 97,9	737,4 ± 112,6	<0.0001
METS-IR	31,4 ± 7,4	36,4 ± 7,7	<0.0001
Waist triglyceride index	74,0 ± 42,5	120,7 ± 84,9	<0.0001
Waist weight index	9,2 ± 0,7	9,6 ± 0,7	<0.0001
ALLY vascular age*	3,4 ± 5,0	7,1 ± 6,7	<0.0001
SCORE *	0,3 ± 0,8	1,6 ± 2,1	<0.0001
REGICOR **	1,9 ± 1,6	3,3 ± 2,2	<0.0001
ERICE ***	2,2 ± 2,8	4,5 ± 5,2	<0.0001
Nº factors metabolic syndrome NCEP ATPIII	0,8 ± 1,0	1,2 ± 1,2	<0.0001
Nº factors metabolic syndrome JIS	0,8 ± 1,1	1,7 ± 1,3	<0.0001
Cholesterol/HDL-c	3,4 ± 0,9	4,0 ± 1,1	<0.0001
Triglycerides /HDL-c	1,6 ± 0,9	2,5 ± 2,0	<0.0001
LDL-c/HDL-c	2,1 ± 0,8	2,5 ± 0,9	<0.0001
Cardiometabolic index	0,7 ± 0,5	1,3 ± 1,1	<0.0001
Lipid accumulation product	16,8 ± 17,4	32,1 ± 32,9	<0.0001
Fatty liver index	16,2 ± 20,5	37,1 ± 26,1	<0.0001
Hepatic steatosis index	35,9 ± 6,6	37,2 ± 5,0	<0.0001
Zhejian University index	36,4 ± 5,7	37,2 ± 5,0	<0.0001
Fatty liver disease index	29,5 ± 5,5	32,1 ± 4,8	<0.0001

(*) women n= 14263 men n=8929 total n=23192) (**) women n= 19192 men n=11389 total n=30581).
(***) women n= 23264 men n=13351 total n=36615) BMI Body mass index. CUN BAE Clínica Universitaria de Navarra Body Adiposity Estimator ECORE-BF Ecuación Córdoba-Body Fat. ECORE-BF Equation Cordoba estimator body fat. METS-VF Metabolic score for visceral fat. METS-IR Metabolic score for insulin resistance. SCORE Systematic coronary risk evaluation. REGICOR Registre Gironi del Cor. ERICE Spanish cardiovascular risk Equation. NCEP ATP III National cholesterol education program Adult treatment panel III. JIS Joint Interim Statement. HDL-c High density lipoprotein cholesterol. LDL Low density lipoprotein cholesterol. VLDL Very low density lipoprotein cholesterol. SD Standard deviation.

moderate (> 5%), moderate-high (15-19%), high (20-39%), or very high (> 39%).

Vascular age determination requires age, sex, total cholesterol, HDL-c, systolic blood pressure, antihypertensive medication use, smoking status, and diabetes status. It can be calculated from age thirty onwards.

Avoidable lost life years (ALLY) represent the disparity between biological age and vascular age, applicable to both vascular ages[47].

Individuals who have smoked at least one cigarette per day (or equivalent) within the past month, or who quit smoking less than a year ago, are classified as smokers.

Statistical analysis

Descriptive analysis determined the frequency and distribution of answers for each category variable. The percentage was computed for qualitative factors, and the mean and standard deviation were calculated for quantitative data. The Student's t-test for independent samples and the chi-square test were used for bivariate association analysis. Multivariate analysis employed binary logistic regression with the Wald method, including the Hosmer-Lemeshow goodness-of-fit test and the computation of odds ratios. SPSS version 29.0 was used for statistical analysis, with a significance level set at 0.05.

Ethical aspects

The Illes Balears Ethics Committee approved this study.

Results

All clinical indicators showed statistically higher values in men. There was a notable prevalence of smoking and sedentarism among both men and women.

Men exhibited higher mean values for all scales except those measuring body fat percentage, which are typically higher in women. The mean values for the remaining scales analyzed, including overweight and obesity, metabolic syndrome, nonalcoholic fatty liver disease, insulin resistance, atherogenic risk, and cardiovascular risk, were higher in men. **Table III** presents the data.

Our analysis of the prevalence of elevated scores on various scales related to cardiometabolic risk showed that in all cases (insulin resistance, non-alcoholic fatty

Table IV: Prevalence of high values of cardiometabolic risk scales in office workers.

	women n=27458	men n=15616	
	%	%	p-value
Waist to height ratio >0,5	10,7	16,6	<0.0001
Obesity BMI	17,3	12,1	<0.0001
Obesity CUN BAE	40,9	51,5	<0.0001
Obesity ECORE-BF	39,9	51,6	<0.0001
Obesity relative fat mass	28,2	52,5	<0.0001
METS-VF high	0,7	6,7	<0.0001
Hypertension	11,3	29,2	<0.0001
Cholesterol ≥200 mg/dl	36,8	43,0	<0.0001
LDL-c ≥130 mg/dl	31,5	38,8	<0.0001
Triglyceride ≥ 150 mg/dl	7,5	22,4	<0.0001
Glucose ≥ 100 mg/dl	10,1	20,6	<0.0001
SCORE moderate-high*	2,3	23,6	<0.0001
REGICOR moderate-high**	7,4	20,8	<0.0001
ERICE moderate-high***	1,6	13,0	<0.0001
Non metabolically healthy	18,6	33,2	<0.0001
Metabolic syndrome NCEP ATPIII	7,2	15,0	<0.0001
Metabolic syndrome IDF	7,1	12,3	<0.0001
Metabolic syndrome JIS	8,5	25,0	<0.0001
Atherogenic dyslipidemia	3,8	7,5	<0.0001
Lipid triad	0,9	2,2	<0.0001
Hypertriglyceridemic waist	1,4	8,2	<0.0001
Cholesterol/HDL-c moderate-high	11,0	16,7	<0.0001
Triglyceride/HDL-c high	6,6	25,2	<0.0001
LDL-c/HDL-c high	12,3	26,1	<0.0001
Lipid accumulation product high	14,5	40,6	<0.0001
Fatty liver index high	6,3	21,9	<0.0001
Hepatic steatosis index high	42,2	51,2	<0.0001
Zhejian University index high	31,4	37,6	<0.0001
Fatty liver disease index high	36,8	43,8	<0.0001
TyG index high	8,2	25,0	<0.0001
METS-IR high	2,8	5,9	<0.0001

(*) women n= 14263 men n=8929 total n=23192) (**) women n= 19192 men n=11389 total n=30581). (***) women n= 23264 men n=13351 total n=36615) BMI Body mass index. CUN BAE Clínica Universitaria de Navarra Body Adiposity Estimator ECORE-BF Ecuación Córdoba-Body Fat. ECORE-BF Equation Cordoba estimator body fat. METS-VF Metabolic score for visceral fat. METS-IR Metabolic score for insulin resistance. SCORE Systematic coronary risk 1reatment1. REGICOR Registre Gironi del Cor. ERICE Spanish. Cardiovascular risk Equation. NCEP ATP III National cholesterol education program Adult 1reatment panel III. JIS Joint Interim Statement. HDL-c High density lipoprotein cholesterol. LDL Low density lipoprotein cholesterol.

liver disease, excess weight, atherogenic risk, metabolic syndrome, and cardiovascular risk), males had higher values. **Table IV** contains the complete data.

In the multivariate analysis, male gender increased the risk of presenting high values for all the cardiometabolic risk scales analyzed except the Deurenberg formula. Advanced age is a factor, as is a sedentary lifestyle, which increases the risk of presenting high values for all the cardiometabolic risk scales analyzed. Smoking does not always increase this risk but only in the scales of cardiovascular risk, metabolic syndrome, hypertriglyceridemic waist circumference, nonalcoholic fatty liver disease, and insulin resistance. Of all these variables, the one with the highest overall odds ratio is a sedentary lifestyle (see **table V**). The profile of the office worker with the highest cardiometabolic risk would be a male over 50 years of age, sedentary, and a smoker.

Discussion

Our findings indicate that the prevalence of altered values in various scales assessing cardiometabolic risk, both directly and indirectly, among office workers is generally moderate and even high in some cases, particularly among men.

A study conducted by So R et al. in 1749 office workers in Japan assessed the impact of sedentary work on this group and concluded that the prevalence of cardiometabolic disorders was high[48].

Similarly, a study by Nketiah GB et al. in Ghana, involving 219 bank office workers of similar age to our sample, found a much higher level of sedentary work (over 81%) and a correspondingly higher cardiometabolic risk[49].

Phaswana M et al.'s study in 62 South African office workers demonstrated high levels of sedentary lifestyle and cardiometabolic risk, which decreased with the implementation of physical activity promotion programs[50].

In another study in Nigeria involving 235 office workers, a high prevalence of arterial hypertension was observed, ranging from 25.9% to 53.9% depending on the criteria used, with 5.5% classified as having high cardiovascular risk using the Framingham scale[51].

Table V: Binomial logistic regression.

	Men			≥ 50 years			Tobacco			Sedentarism		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Waist to height ratio >0,5	3.4	3.2-3.5	<0.0001	1.4	1.3-1.5	<0.0001			ns	2.7	2.5-2.9	<0.0001
Obesity IMC	1.4	1.3-1.5	<0.0001	1.6	1.5-1.7	<0.0001			ns	3.7	3.5-3.9	<0.0001
Obesity CUN BAE	1.4	1.3-1.5	<0.0001	4.3	4.1-4.5	<0.0001			ns	3.3	3.2-3.4	<0.0001
Obesity ECORE-BF	1.5	1.4-1.5	<0.0001	3.9	3.7-4.1	<0.0001			ns	3.3	3.2-3.4	<0.0001
Obesity relative fat mass	2.7	2.6-2.9	<0.0001	1.4	1.3-1.5	<0.0001			ns	2.8	2.6-3.0	<0.0001
Obesity Deuremberg	0.5	0.4-0.5	<0.0001	2.7	1.7-3.8	<0.0001			ns	2.7	2.5-2.9	<0.0001
METS-VF high	4.8	4.4-5.2	<0.0001	3.2	3.0-3.4	<0.0001			ns	6.9	6.4-7.4	<0.0001
Hypertension	3.0	2.9-3.2	<0.0001	3.4	3.2-3.6	<0.0001			ns	1.8	1.6-1.9	<0.0001
Cholesterol ≥200 mg/dl	1.2	1.1-1.2	<0.0001	3.0	2.9-3.2	<0.0001			ns	2.3	2.1-2.5	<0.0001
LDL-c ≥130 mg/dl	1.3	1.2-1.3	<0.0001	2.8	2.7-3.0	<0.0001			ns	1.9	1.7-2.1	<0.0001
Triglyceride ≥ 150 mg/dl	2.0	1.8-2.1	<0.0001	3.4	3.2-3.6	<0.0001	1,3	1.2-1.4	0.023	2.3	2.0-2.6	<0.0001
Glucose ≥ 100 mg/dl	2.1	2.0-2.2	<0.0001	3.4	3.2-3.6	<0.0001			ns	1.5	1.3-1.7	<0.0001
SCORE moderate-high*	1.8	1.7-2.0	<0.0001	6.5	5.9-7.11	<0.0001	1.2	1.1-1.3	<0.0001	3.6	3.2-4.0	<0.0001
REGICOR moderate-high**	1.3	1.2-1.4	<0.0001	6.4	5.8-7.0	<0.0001	1.2	1.1-1.3	<0.0001	6.1	5.5-6.8	<0.0001
ERICE moderate-high***	1.8	1.6-2.0	<0.0001	8.2	7.2-9.2	<0.0001	1.2	1.1-1.4	0.001	3.0	2.6-3.4	<0.0001
Non metabolically healthy	1.9	1.8-2.0	<0.0001	2.1	1.9-2.3	<0.0001	4.1	3.9-4.4	<0.0001	1.1	1.0-1.1	0.045
Metabolic syndrome NCEP ATPIII	2.0	1.9-2.2	<0.0001	3.5	3.3-3.8	<0.0001	2.8	2.6-3.0	<0.0001	3.7	3.5-3.9	<0.0001
Metabolic syndrome IDF	1.6	1.5-1.8	<0.0001	2.2	2.1-2.4	<0.0001	1.9	1.7-2.1	<0.0001	3.5	3.3-3.7	<0.0001
Metabolic syndrome JIS	3.5	3.3-3.7	<0.0001	3.5	3.2-3.7	<0.0001	1.8	1.7-1.9	<0.0001	3.1	3.0-3.2	<0.0001
Atherogenic dyslipidemia	1.8	1.7-2.0	<0.0001	2.3	2.1-2.5	<0.0001	1.3	1.2-1.4	<0.0001	2.8	2.6-3.0	<0.0001
Lipid triad	2.0	1.7-2.4	<0.0001	2.9	2.5-3.4	<0.0001	1.4	1.3-1.5	<0.0001	2.9	2.7-3.1	<0.0001
Hypertriglyceridemic waist	5.9	5.3-6.7	<0.0001	1.7	1.5-1.9	<0.0001	1.6	1.4-1.8	<0.0001	2.3	2.1-2.5	<0.0001
Cholesterol/HDL-c moderate-high	1.4	1.4-1.5	<0.0001	2.8	2.6-3.0	<0.0001			ns	5.3	4.9-5.7	<0.0001
Triglyceride/HDL-c high	4.7	4.4-5.0	<0.0001	2.3	2.1-2.4	<0.0001			ns	4.9	4.6-5.3	<0.0001
LDL-c/HDL-c high	2.4	2.3-2.6	<0.0001	2.7	2.6-2.9	<0.0001			ns	1.1	1.0-1.2	0.010
Lipid accumulation product high	2.6	2.4-2.8	<0.0001	2.4	2.2-2.6	<0.0001	1.3	1.2-1.3	<0.0001	4.8	4.0-5.2	<0.0001
Fatty liver index high	2.9	2.6-3.2	<0.0001	2.6	2.4-2.8	<0.0001	1.4	1.3-1.5	<0.0001	5.2	4.7-5.8	<0.0001
Hepatic steatosis index high	3.1	2.8-3.4	<0.0001	2.8	2.5-3.0	<0.0001	1.5	1.4-1.6	<0.0001	5.3	4.8-5.8	<0.0001
Zhejian University index high	3.5	3.2-3.8	<0.0001	1.9	1.7-2.1	<0.0001	1.2	1.2-1.3	<0.0001	4.8	4.4-5.2	<0.0001
Fatty liver disease index high	3.0	2.8-3.3	<0.0001	3.0	2.6-3.4	<0.0001	1.3	1.2-1.4	<0.0001	6.1	5.5-6.7	<0.0001
TyG index high	2.9	2.6-3.2	<0.0001	2.5	2.1-2.9	<0.0001	1.1	1.0-1.2	<0.0001	5.6	5.0-6.1	<0.0001
METS-IR high	3.4	3.1-3.7	<0.0001	2.3	2.0-2.6	<0.0001	1.4	1.3-1.5	<0.0001	5.3	4.8-5.8	<0.0001

(*) women n= 14263 men n=8929 total n=23192) (**) women n= 19192 men n=11389 total n=30581).(***) women n= 23264 men n=13351 total n=36615) BMI Body mass index. CUN BAE Clínica Universitaria de Navarra Body Adiposity Estimator ECORE-BF Ecuación Córdoba-Body Fat. ECORE-BF Equation Cordoba estimator body fat. METS-VF Metabolic score for visceral fat. METS-IR Metabolic score for insulin resistance. SCORE Systematic coronary risk evaluation. REGICOR Registre Gironi del Cor. ERICE Spanish. cardiovascular risk Equation. NCEP ATP III National cholesterol education program Adult treatment panel III. JIS Joint Interim Statement. HDL-c High density lipoprotein cholesterol. LDL Low density lipoprotein cholesterol.

Studies conducted in Germany, such as the one involving 46 office workers in the North Rhine-Westphalia region and another involving 30 office workers, highlighted a high prevalence of pre-obesity, elevated waist circumference, and increased risk of cardiometabolic diseases among sedentary office workers, particularly in men[52,53].

The study conducted by the MAZ[54,55] occupational accident mutual insurance company in 2012, involving nearly 7000 workers in the tertiary sector, reported figures that were generally less favorable compared to ours, with higher rates of overweight, hypercholesterolemia, hypertension, and smoking, as well as sedentary lifestyle.

Strengths of our study include the large sample size of over 43,000 office workers and the wide variety of scales used to assess cardiometabolic risk. However, it is noteworthy that some risk scales were applied instead of objective diagnostic tests, such as ultrasound for assessing nonalcoholic fatty liver disease or HOMA for insulin resistance.

Conclusion

The prevalence of scales related to cardiometabolic risk among office workers is moderate to high, particularly considering their relatively young average age.

Competing Interests

The authors declare that they have no competing interests.

References

1. Lavie CJ, German CA, Sanchis-Gomar F. Reducing Mortality and Cardiovascular Disease: Stepping Up Our Game. J Am Coll Cardiol. 2023 Oct 10;82(15):1495-1498. doi: 10.1016/j.jacc.2023.08.007.

2. Townsend N, Kazakiewicz D, Lucy Wright F, Timmis A, Huculeci R, Torbica A, et al. Epidemiology of cardiovascular disease in Europe. Nat Rev Cardiol. 2022 Feb;19(2):133-143. doi: 10.1038/s41569-021-00607-3.

3. Joseph P, Leong D, McKee M, Anand SS, Schwalm JD, Teo K, et al. Reducing the Global Burden of Cardiovascular Disease, Part 1: The Epidemiology and Risk Factors. Circ Res. 2017 Sep 1;121(6):677-694. doi: 10.1161/CIRCRESAHA.117.308903.

4. Manzanero RZ, López-González AA, Tomás-Gil P, Paublini H, Martínez-Jover A, Ramírez-Manent JI. Estimation of cardiometabolic risk in 25.030 Spanish kitchen workers. Academic Journal of Health Sciences 2023; 38 (6):101-110 doi: 10.3306/AJHS.2023.38.06.101

5. Gabriel R, Brotons C, Tormo MJ, Segura A, Rigo F, Elosua R, et al. The ERICE-score: the new native cardiovascular score for the low-risk and aged Mediterrane-an population of Spain. Rev Esp Cardiol (Engl Ed). 2015 Mar;68(3):205-15. doi: 10.1016/j.rec.2014.03.019.

6. Wohlfahrt P, Bruthans J, Krajčoviechová A, Šulc P, Linhart A, Filipovský J, et al. Sys-tematic COronary Risk Evaluation (SCORE) and 20-year risk of cardiovascular mortality and cancer. Eur J Intern Med. 2020 Sep;79:63-69. doi: 10.1016/j.ejim.2020.05.034.

7. Montero-Muñoz N, López-González AA, Tomás-Gil P, Martínez-Jover A, Paublini H, Ramírez-Manent JI. Relationship between sociodemographic variables and to-bacco consumption with vascular age values using the Framinghan model in 336,450 spanish workers. Academic Journal of Health Sciences 2023;38 (5): 61-66 doi: 10.3306/AJHS.2023.38.05.61

8. Sastre Alzamora T, Tomás-Gil P, Martí-Lliteras P, Pallarés-Ferreres L, Ramírez-Manent JI, López-González AA. Estimation of heart age in 139.634 spanish work-ers: influence of sociodemographic variables and healthy habits and determina-tion of cut-off points. Academic Journal of Health Sciences 2023;38 (2):24-30 doi: 10.3306/AJHS.2023.38.02.24

9. López-González ÁA, Riutord Sbert P, Arroyo Bote S, González San Miguel H, Vidal Real C, Ramirez-Manent JI. Determination of Cardiovascular Risk in 56,262 Span-ish Construction Workers: Cardiovascular Risk in Construction Workers. J Occup Environ Med. 2021 Dec 1;63(12):e911-e917. doi: 10.1097/JOM.0000000000002402.

10. Manzanero RZ, López-González AA, Tomás-Gil P, Paublini H, Martínez-Jover A, Ramírez-Manent JI. Determination of cardiometabolic risk scales in 7.962 hotel re-ceptionists. Academic Journal of Health Sciences 2024; 39 (1):113-122 doi: 10.3306/AJHS.2024.39.01.113

11. Tao LC, Xu JN, Wang TT, Hua F, Li JJ. Triglyceride-glucose index as a marker in cardiovascular diseases: landscape and limitations. Cardiovasc Diabetol. 2022 May 6;21(1):68. doi: 10.1186/s12933-022-01511-x.

12. Kaneva AM, Bojko ER. Fatty liver index (FLI): more than a marker of hepatic stea-tosis. J Physiol Biochem. 2024 Feb;80(1):11-26. doi: 10.1007/s13105-023-00991-z.

13. Yoo EG. Waist-to-height ratio as a screening tool for obesity and cardiometabolic risk. Korean J Pediatr. 2016 Nov;59(11):425-431. doi: 10.3345/kjp.2016.59.11.425.

14. Bakris G, Ali W, Parati G. ACC/AHA Versus ESC/ESH on Hypertension Guidelines: JACC Guideline Comparison. J Am Coll Cardiol. 2019 Jun 18;73(23):3018-3026. doi: 10.1016/j.jacc.2019.03.507.

15. Tseng YW, Jiang JF, Er TK. Evaluation of Friedewald's Formula for Plasma LDL-Cholesterol Estimation. Clin Lab. 2023 Apr 1;69(4). doi: 10.7754/Clin.Lab.2022.220801.

16. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020 Jan 1;41(1):111-188. doi: 10.1093/eurheartj/ehz455.

17. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 2. Classification and Diagnosis of Diabetes: Standards of Care in Diabetes-2023. Diabetes Care. 2023 Jan 1;46(Suppl 1):S19-S40. doi: 10.2337/dc23-S002. Erra-tum in: Diabetes Care. 2023 Feb 01;: Erratum in: Diabetes Care. 2023 Sep 1;46(9):1715.

18. Vilallonga R, Pereira-Cunill JL, Morales-Conde S, Alarcón I, Breton I, Domínguez-Adame E, et al. A Spanish Society joint SECO and SEEDO approach to the Post-operative management of the patients undergoing surgery for obesity. Obes Surg. 2019 Dec;29(12):3842-3853. doi: 10.1007/s11695-019-04043-8.

19. Gómez-Ambrosi J, Silva C, Catalán V, Rodríguez A, Galofré JC, Escalada J, et al. Clinical usefulness of a new equation for estimating body fat. Diabetes Care. 2012 Feb;35(2):383-8. doi: 10.2337/dc11-1334. Epub 2011 Dec 16.

20. Molina-Luque R, Romero-Saldaña M, Álvarez-Fernández C, Bennasar-Veny M, Álvarez-López Á, Molina-Recio G. Equation Córdoba: A Simplified Method for Es-timation of Body Fat (ECORE-BF). Int J Environ Res Public Health. 2019 Nov 15;16(22):4529. doi: 10.3390/ijerph16224529.

21. Senkus KE, Crowe-White KM, Locher JL, Ard JD. Relative fat mass assessment estimates changes in adiposity among female older adults with obesity after a 12-month exercise and diet intervention. Ann Med. 2022 Dec;54(1):1160-1166. doi: 10.1080/07853890.2022.2067352.

22. Mill-Ferreyra E, Cameno-Carrillo V, Saúl-Gordo H, Camí-Lavado MC. Estimación del porcentaje de grasa corporal en función del índice de masa corporal y períme-tro abdominal: fórmula Palafolls. Semergen. 2019 Mar;45(2):101-108. Spanish. doi: 10.1016/j.semerg.2018.04.007.

23. López-González AA, Jover AM, Martínez CS, Artal PM, Bote SA, Jané BA, Ramírez-Manent JI. The CUN-BAE, Deurenberg Fat Mass, and visceral adiposity index as confident anthropometric indices for early detection of metabolic syndrome com-ponents in adults. Sci Rep. 2022 Sep 15;12(1):15486. doi: 10.1038/s41598-022-19343-w.

24. Vicente-Herrero MT, Egea-Sancho M, Ramírez Iñiguez de la Torre MV, López-González AA. Relación de los índices de adiposidad visceral (VAI) y adiposidad disfuncional (DAI) con las escalas de riesgo de resistencia a la insulina y predia-betes. Academic Journal of Health Sciences 2024;39 (2): 25-31 doi: 10.3306/AJHS.2024.39.02.25

25. Cai X, Song S, Hu J, Zhu Q, Yang W, Hong J, et al. Body roundness index im-proves the predictive value of cardiovascular disease risk in hypertensive patients with obstructive sleep apnea: a cohort study. Clin Exp Hypertens. 2023 Dec 31;45(1):2259132. doi: 10.1080/10641963.2023.2259132.

26. Krakauer NY, Krakauer JC. A new body shape index predicts mortality hazard in-dependently of body mass index. PLoS One. 2012;7(7):e39504. doi: 10.1371/journal.pone.0039504.

27. Zhang A, Li Y, Ma S, Bao Q, Sun J, Cai S, et al. Conicity-index predicts all-cause mortality in Chinese older people: a 10-year community follow-up. BMC Geriatr. 2022 Dec 16;22(1):971. doi: 10.1186/s12877-022-03664-6.

28. Sirisena A, Okeahialam B. Association of obesity anthropometric indices with hy-pertension, diabetes mellitus and hypertriglyceridemia in apparently healthy adult Nigerian population. World J Cardiol. 2022 Jun 26;14(6):363-371. doi: 10.4330/wjc.v14.i6.363.

29. Feng L, Chen T, Wang X, Xiong C, Chen J, Wu S, et al. Metabolism Score for Vis-ceral Fat (METS-VF): A New Predictive Surrogate for CKD Risk. Diabetes Metab Syndr Obes. 2022 Jul 29;15:2249-2258. doi: 10.2147/DMSO.S370222.

30. Ramdas Nayak VK, Satheesh P, Shenoy MT, Kalra S. Triglyceride Glucose (TyG) Index: A surrogate biomarker of insulin resistance. J Pak Med Assoc. 2022 May;72(5):986-988. doi: 10.47391/JPMA.22-63.

31. Peng H, Pan L, Ran S, Wang M, Huang S, Zhao M, et al. Prediction of MAFLD and NAFLD using different screening indexes: A cross-sectional study in U.S. adults. Front Endocrinol (Lausanne). 2023 Jan 19;14:1083032. doi: 10.3389/fendo.2023.1083032.

32. Mirr M, Braszak-Cymerman A, Ludziejewska A, Kręgielska-Narożna M, Bogdański P, Bryl W, et al. Serum Asprosin Correlates with Indirect Insulin Resistance Indices. Biomedicines. 2023 May 28;11(6):1568. doi: 10.3390/biomedicines11061568.

33. Widjaja NA, Irawan R, Hanindita MH, Ugrasena I, Handajani R. METS-IR vs. HOMA-AD and Metabolic Syndrome in Obese Adolescents. J Med Invest. 2023;70(1.2):7-16. doi: 10.2152/jmi.70.7.

34. Sun Q, Ren Q, Du L, Chen S, Wu S, Zhang B, et al. Cardiometabolic Index (CMI), Lipid Accumulation Products (LAP), Waist Triglyceride Index (WTI) and the risk of acute pancreatitis: a prospective study in adults of North China. Lipids Health Dis. 2023 Nov 9;22(1):190. doi: 10.1186/s12944-023-01948-3.

35. Zou B, Yeo YH, Cheung R, Ingelsson E, Nguyen MH. Fatty Liver Index and Devel-opment of Cardiovascular Disease: Findings from the UK Biobank. Dig Dis Sci. 2021 Jun;66(6):2092-2100. doi: 10.1007/s10620-021-06954-y.

36. Chang JW, Lee HW, Kim BK, Park JY, Kim DY, Ahn SH, et al. Hepatic Steatosis In-dex in the Detection of Fatty Liver in Patients with Chronic Hepatitis B Receiving Antiviral Therapy. Gut Liver. 2021 Jan 15;15(1):117-127. doi: 10.5009/gnl19301.

37. Wang L, Nie G, Yan F, Zhou N, Zhang M, Peng W. The ZJU index is associated with the risk of obstructive sleep apnea syndrome in Chinese middle-aged and older people: a cross-sectional study. Lipids Health Dis. 2023 Nov 29;22(1):207. doi: 10.1186/s12944-023-01974-1.

38. Zhang L, Zhang M, Wang M, Wang M, Zhang R, Wang H, et al. External validation and comparison of simple tools to screen for nonalcoholic fatty liver disease in Chinese community population. Eur J Gastroenterol Hepatol. 2022 Aug 1;34(8):865-872. doi: 10.1097/MEG.0000000000002399

39. Motamed N, Nikkhah M, Karbalaie Niya MH, Khoonsari M, Perumal D, Ashrafi GH, et al. The Ability of the Framingham Steatosis Index (FSI) to Predict Non-alcoholic Fatty Liver Disease (NAFLD): A Cohort Study. Clin Res Hepatol Gastroenterol. 2021 Nov;45(6):101567. doi: 10.1016/j.clinre.2020.10.011.

40. Ebrahimi M, Seyedi SA, Nabipoorashrafi SA, Rabizadeh S, Sarzaeim M, Yadegar A, et al Lipid accumulation product (LAP) index for the diagnosis of nonalcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis. Lipids Health Dis. 2023 Mar 15;22(1):41. doi: 10.1186/s12944-023-01802-6.

41. López González ÁA, Rivero Ledo YI, Vicente Herrero MT, Gil Llinás M, Tomás Sal-vá M, Riutord Fe B. Índices aterogénicos en trabajadores de diferentes sectores laborales del área Mediterránea Española. Clin Investig Arterioscler. 2015 May-Jun;27(3):118-28. Spanish. doi: 10.1016/j.arteri.2014.10.004.

42. Lu N, Cheng G, Ma CM, Liu XL. Hypertriglyceridemic waist phenotype, hypertri-glyceridemic waist-to-height ratio phenotype and abnormal glucose metabolism in adolescents. Diabetes Res Clin Pract. 2023 Apr;198:110622. doi: 10.1016/j.diabres.2023.110622.

43. Ramírez-Manent JI, Jover AM, Martinez CS, Tomás-Gil P, Martí-Lliteras P, López-González ÁA. Waist Circumference Is an Essential Factor in Predicting Insulin Re-sistance and Early Detection of Metabolic Syndrome in Adults. Nutrients. 2023 Jan 4;15(2):257. doi: 10.3390/nu15020257.

44. Ramírez-Manent JI, Tomás-Gil P , Coll-Villalonga JL , Marti-Lliteras P, López-González AA, Paublini H. Relationship between atherogenic dyslipidemia and li-pid triad with scales that assess non alcoholic liver

disease in 418,343 spanish workers. Academic Journal of Health Sciences 2023; 38 (6):66-73 doi: 10.3306/AJHS.2023.38.06.66

45. Amor AJ, Serra-Mir M, Martínez-González MA, Corella D, Salas-Salvadó J, Fitó M, et al. Prediction of Cardiovascular Disease by the Framingham-REGICOR Equa-tion in the High-Risk PREDIMED Cohort: Impact of the Mediterranean Diet Across Different Risk Strata. J Am Heart Assoc. 2017 Mar 13;6(3):e004803. doi: 10.1161/JAHA.116.004803.

46. Cebrian A, Escobar C, Aranda U, Palacios B, Capel M, Sicras A, et al. Including KDIGO cardiovascular risk stratification into SCORE scale could improve the accu-racy to better stratify cardiovascular risk. Nefrologia (Engl Ed). 2022 Dec 6:S2013-2514(22)00151-1. doi: 10.1016/j.nefroe.2021.11.016.

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

48. So R, Murai F, Fujii M, Watanabe S, Matsuo T. Association of sitting time and cardi-orespiratory fitness with cardiovascular disease risk and healthcare costs among office workers. Ind Health. 2023 Sep 22;61(5):368-378. doi: 10.2486/indhealth.2022-0010.

49. Nketiah GB, Odoi-Agyarko K, Ndanu TA, Hayford FEA, Amoh G, Lawson H. Physi-cal inactivity among corporate bank workers in Accra, Ghana: Implications for health promotion. PLoS One. 2023 May 11;18(5):e0277994. doi: 10.1371/journal.pone.0277994.

50. Phaswana M, Jean-Luc Gradidge P. Ukumela impilo randomised trial: preliminary findings of height-adjustable sit-to-stand workstations on health outcomes of South African office workers. BMC Res Notes. 2023 Dec 7;16(1):361. doi: 10.1186/s13104-023-06642-2.

51. Ofori SN, Obosi J. Prevalence of hypertension among office workers in a multi-national company in the Niger-Delta with the 2017 American College of Cardiolo-gy/American Heart Association Blood Pressure Guidelines. Prev Med Rep. 2019 May 18;15:100899. doi: 10.1016/j.pmedr.2019.100899.

52. Strauss M, Foshag P, Leischik R. Prospective Evaluation of Cardiovascular, Cardi-orespiratory, and Metabolic Risk of German Office Workers in Comparison to Inter-national Data. Int J Environ Res Public Health. 2020 Mar 1;17(5):1590. doi: 10.3390/ijerph17051590.

53. Tatzber F, Zelzer S, Obermayer-Pietsch B, Rinnerhofer S, Kundi M, Cvirn G, et al. Occupational Health Aspects with Special Focus on Physiological Differences be-tween Office and Metalworkers. Antioxidants (Basel). 2022 Mar 25;11(4):633. doi: 10.3390/antiox11040633.

54. Martínez Abadía B, Arbués ER. Prevalencia de los factores de riesgo cardiovascu-lar en trabajadores de los sectores laborales secundario y terciario. Enferm. Glob 2012; 11(28): 31-40

55. Fernández Rodríguez AM, Rueda Garrido JC, Serrano RL, López González Ángel A, Vicente-Herrero MT. Ageing in the working population associated with obesity and cardiovascular risk parameters. J Clin Trials Exp Investig. 2023;2(3):111-120.

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ORIGINAL

Evaluation of the Anti-hyperglycemic Activity of Ononis natrix aqueous extract against alloxan-induced experimental model of insulinopenic diabetes in albino Swiss mice

Evaluación de la actividad antihiperglucémica del extracto acuoso de Ononis natrix contra el modelo experimental de diabetes insulinopénica inducida por alloxan en ratones albinos suizos

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Abstract

Objective: To continue research on the biological properties of Moroccan medicinal plants, this study was carried out to assess the antidiabetic activity of the aqueous extract of *Ononis natrix* (ONAE) traditionally used in herbal medicine in the region of Ouarzazate, Morocco.
Methods: The acute toxicity of the extract was assessed by oral administration to Swiss albino mice at single doses of 50, 150, 250 and 5000 mg/kg body weight. Diabetes was induced by a single dose injection (300 mg/kg BW) of alloxan monohydrate intraperitoneally and the animals were treated with aqueous extracts of *Ononis natrix* at a dose of 500 mg/kg BW. To evaluate alloxan-induced tissue damage, blood glucose levels were assessed and a pancreatic histopathology study was done.
Results:The acute toxicity study shows that the aqueous extract of *Ononis natrix* does not present acute toxicity with doses lower than 5000mg/kg of body weight and that the approximate LD50 is higher than 5000 mg/kg. Furthermore, hypoglycemic activity tests revealed that the aqueous extract effectively lowered blood glucose levels in mice given a 500 mg/kg dosage. According to the pancreas histopathology study, the aqueous extract of *Ononis natrix* significantly repaired the islets of Langerhans against alloxan-induced tissue damage.
Conclusions: The histopathological study of the pancreas demonstrated that the aqueous extract of *Ononis natrix* significantly restored the islets of Langerhans against alloxan-induced tissue damage.

Key words: Ononis natrix, Aqueous extract, Alloxan monohydrate, Antidiabetic, β cells, Hypoglycemic activity.

Resumen

Objetivo: Para continuar la investigación sobre las propiedades biológicas de las plantas medicinales marroquíes, este estudio se llevó a cabo para evaluar la actividad antidiabética del extracto acuoso de *Ononis natrix* (ONAE) tradicionalmente utilizado en la medicina herbal en la región de Ouarzazate, Marruecos.
Métodos: La toxicidad aguda del extracto se evaluó mediante administración oral a ratones albinos suizos a dosis únicas de 50, 150, 250 y 5000 mg/kg de peso corporal. La diabetes fue inducida por una inyección de dosis única (300 mg/kg de peso corporal) de monohidrato de aloxano intraperitonealmente y los animales fueron tratados con extractos acuosos de *Ononis natrix* a una dosis de 500 mg/kg de peso corporal. Para evaluar el daño tisular inducido por aloxano, se evaluaron los niveles de glucosa en sangre y se realizó un estudio de histopatología pancreática.
Resultados: El estudio de toxicidad aguda muestra que el extracto acuoso de *Ononis natrix* no presenta toxicidad aguda con dosis inferiores a 5000 mg/kg de peso corporal y que la DL50 aproximada es superior a 5000 mg/kg. Además, las pruebas de actividad hipoglucémica revelaron que el extracto acuoso redujo eficazmente los niveles de glucosa en sangre en ratones a los que se les administró una dosis de 500 mg/kg. Según el estudio de histopatología pancreática, el extracto acuoso de *Ononis natrix* reparó significativamente los islotes de Langerhans contra el daño tisular inducido por aloxano.
Conclusiones: El estudio histopatológico del páncreas demostró que el extracto acuoso de *Ononis natrix* restauró significativamente los islotes de Langerhans contra el daño tisular inducido por aloxano. Palabras clave *Ononis natrix*, Extracto acuoso, Aloxano monohidrato, Antidiabético, Células β, Actividad hipoglucémica.

Palabras clave: Ononis natrix, Extracto acuoso, Monohidrato de aloxano, Antidiabético, Células β, Actividad hipoglucemiante.

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Introduction

Diabetes is considered as one of the oldest diseases that humanity has ever known., the prevalence and incidence of which are steadily increasing and have reached epidemic levels in several countries[1]. Diabetes is experiencing a very significant expansion according to the latest estimates (2016) from the World Health Organization (WHO) and the International Diabetes Federation (IDF), with around 422 million people diagnosed with diabetes worldwide and this figure is expected to reach 552 million by the year 2030. According to the Ministry of Health, in Morocco (2016), there are more than 2 million people aged 25 and over who are diabetic and unfortunately, 50% of all diabetics do not know their disease. Type 1 diabetes is caused by an insulin shortage, whereas type 2 diabetes is caused by insulin resistance[2]. Type 1 diabetes (T1D) constitutes about 5-10% of diabetes cases[3]. It is a chronic condition that is associated with an inability to produce insulin. The selective and progressive autoimmune destruction of the islets of Langerhans' insulin-secreting cells results from genetic susceptibility and is likely a response to an unidentified environmental factor. The mechanisms of triggering the autoimmune disease are not known but seem to be able to intervene very early in life[3]. The common trait of T1D is a lack of insulin production. It requires the use of exogenous insulin treatment, in order to manage the symptoms associated with hyperglycaemia, polyuropolydipsic syndrome, weight loss and muscle wasting, to which are added the metabolic complications associated with lipolysis and ketoacidosis which, if left untreated, can lead to coma and death[4].

Chronic hyperglycemia is associated with serious complications over time. Indeed, it is the first cause of end-stage kidney failure, blindness and amputation of the lower limbs, cardiovascular diseases, also affecting the nerves and vessels; it is also the sixth cause of death (WHO and IDF., 2016;[5-7] .All these harmful effects of diabetes justify the need to balance blood sugar as perfectly as possible[8].

For good glycemic control in people with diabetes, a balanced and low-calorie diet, exercise and medication are necessary. For type 1 diabetics, treatment is only insulin. While it consists of oral antidiabetics (ADO), and insulin in type 2 diabetics. However, during chronic use, most of this classic antidiabetic medication causes several serious side effects such as: hypoglycemia, ketoacidosis, coma, digestive problems and others[9,10].

Despite the fact that hypoglycemia agents are used as anti-diabetic medications, Diabetes and its complications are a serious challenge in diabetics' therapeutic care. As a result, one of the lines of research that continues to capture the attention of many researchers is the quest for novel safe and effective natural anti-diabetic medicines for the treatment of diabetes. Indeed, several medicinal herbs have been shown to have a hypoglycaemic impact on experimental diabetes in various recent research[2,11-13].

Ononis is a genus from the family of Fabaceae that includes some 75 species in the world, found in particular in the Canaries, Central Asia, the Mediterranean region, Europe[14] and North Africa. *Ononis natrix* is a perennial plant of 30-50 cm, herbaceous, under woody at the base, slimy, which can develop into small bushes with very branched stems at the base, with persistent branches, which after flowering becoming a little thorny. This species is very polymorphic and widely distributed in southeastern Morocco[15]. For centuries, *Ononis* species have been practiced as folk remedies for their antiseptic, antimicrobial and diuretic effects[16]. Decoctions of species *Ononis* is used to treat, skin disorders, problems of urinary tract as well as gout[17]. In light of this, *Ononis* species have been commercialized as a herbal tea, either alone or in combination with other diuretic plants.[18]. Many studies have shown that the genus *Ononis* has important biological actions, such as antioxidant[19,20], antimicrobial[19,21] wound healing[22], cytotoxic[23], analgesic[24] enzyme inhibitory, and DNA protection effect[25]. To our knowledge, no research on the anti-diabetic potential of the aqueous extract of *Ononis natrix* has been documented to date. We tested the possible antidiabetic action of *Ononis natrix* in type 1 diabetic mice because of the plant's safety and popularity as a traditional medicinal antidiabetic.

Materials and Methods

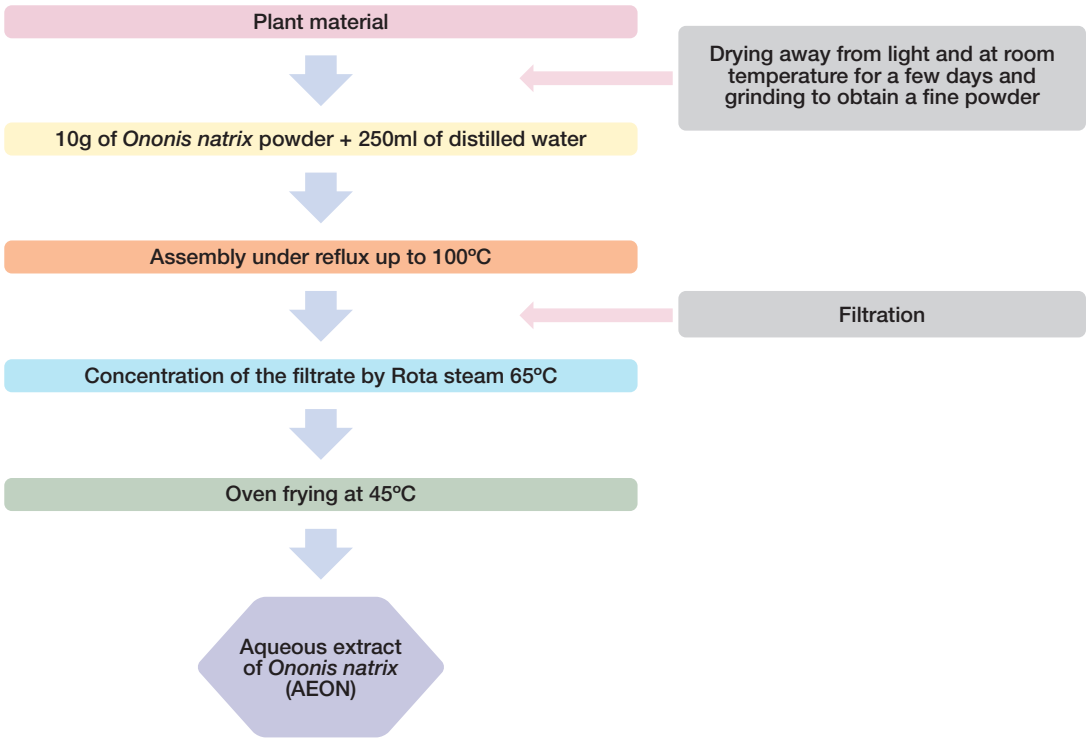
Plant material

The aerial parts (stems, leaves and flowers) of *Ononis natrix* were collected in their natural habitat in February 2019 in the region of Ouarzazate (southeastern Morocco). After cleaning, the aerial parts were dried for a few days in the shade at room temperature, in order to preserve the integrity of the molecules as much as possible (Boukal, 2015). They are then ground using an electric grinder (TAURUS-908503 Electric coffee grinder Aromatic 150 - Stainless steel) to obtain a powder to be extracted, the latter was carefully stored away from light and humidity. Professor Ouhammou Ahmed carries out the botanical identification of plant species, and a reference specimen (MARK 13792) was deposited in the MARK-Herbarium of the Science Faculty of Semlalia, Cady Ayyad University (Marrakech, Morocco).

Extraction procedure

Ten grammes of the prepared powder was boiled in 250 ml of distilled water for 30 minutes. The aqueous extract obtained was filtered on absorbent cotton then on Whatman paper and then evaporated to dryness under reduced pressure at 65°C on a rotavapor to remove the water. Thereafter, stored at +4°C in the dark until use[25] (**Figure 1**).

Figure 1: Experimental protocol for the aqueous extraction of Ononis natrix.



Assessment of mice's acute oral toxicity

The study for acute oral toxicity was carried out in accordance with the limit test procedure according to guideline 420 of the Organization for Economic Co-operation and Development (OECD, 2001). Adult male albino swiss strain mice (n = 20), weighing between (25 g to 33 g), were distributed in five groups of four mice each, previously placed in fasting overnight with access only to water. Animal groups were as follows: Group 1: control male mice, given only physiological water (9% NaCl), Group 2: male mice, given 50 mg / kg BW by gastric gavage of the extract, Group 3: male mice, given 150 mg / kg BW by gastric gavage of the extract, Group 4: male mice, given 250 mg / kg BW by gastric gavage of the extract, Group 5: male mice, given 500 mg / kg BW by gastric gavage of the extract. The effect of the different doses of the extract was checked periodically for the symptoms of toxicity (vomiting, hair loss, diarrhea, etc.), the behavior of the animal (motor activity), the variation in body weight and the rate mortality, during the initial two hours then four hours after force-feeding and then once a day for 14 days.

Antidiabetic assay

Animals

Male Swiss albino mice, weighing between 25 to 33g, were the animals used in the experiment. The mice were provided by the animal house of Cadi Ayyad University, Marrakech (UCAM) Morocco. All of the animals were maintained at a constant room temperature (25°C) and on a 12 hour light/12 hour dark cycle with unrestricted access to food and drink. Prior to the trial, A random process was used to divide the mouse groups depending on their body weight, and they underwent a week of acclimatization. The animals were handled and cared for respecting the European regulation on the ethical evaluation and approval of projects involving the use of animals in experimental research, the use of animals in experimental procedures, dated 1 February 2013, NOR: AGRG1238767A. The Moroccan Society for Ethics and Animal Research's Ethic Committee authorized the experimental protocol (MoSEAR).

Induction of experimental diabetes

It's worth noting that all animals' blood glucose levels were checked at the start of the trial, and those with high levels were removed from the groups. Animals were fasted for 14 hours after a week of acclimatization before one intraperitoneal dosage of alloxan monohydrate was given to develop type 1 diabetes. At a dose of 300 mg/kg BW, the diabetogenic dose of alloxan was newly produced in physiological saline solution (pH 4.5) at 1% concentration[26]. Blood samples were obtained from the end of the mice's tails twenty-four hours after they were infected with diabetes. An electronic glucometer (glucomètre Diab control TD-4279) was used to assess blood glucose levels, and animals with manifest hyperglycaemia (levels of blood glucose = 250 mg/dl) were classified diabetic and employed in the experiment[2].

Assessment of Ononis natrix aqueous extract

Four groups of mice were created, each containing four mice. Group 1: received the adequate volume of physiological saline solution (10 ml/kg BW), and was used as normal control Group 2: composed of diabetic mice not treated, Group 3: contains diabetic mice were administered *Ononis natrix* aqueous extract at 500 mg / kg of BW, Group 4: consisted of diabetic mice given Glibenclamide (Daonil) as a reference medication at a dosage of 20 mg per kg of BW. Mice were given orally an aqueous extract of *Ononis natrix* and monitored for 8 hours. For blood glucose assessment, blood samples were obtained before starting of therapy (t = 0), after the injection of Alloxane, and at 2-hour intervals after each gavage.

Histopathological study of pancreas

The histopathological methodology was implemented in accordance with the process outlined in our previous work[27,28]. After 8 h of therapy, all mice were sacrificed under anesthesia (Urethane anesthesia, (1 g/Kg, China, Lot & Filling #1, 373,588 43, 308,029, and the tissues of pancreas were retrieved and immediately fixed for 24 h at 4 C. After fixation, pancreatic tissue samples were processed to obtain thin ribbons (sections of 4 µm thick) using a semi-automated microtome (Leica Biosystems RM 2245). The samples were stained with hematoxylin-eosin (HE). They were then put on a glass slide, examined histopathologically with a Zeiss light microscope, and 400x photomicrographs of the pancreatic islets of Langerhans were shot using a camera (Nikon Coolpix, p7100). Using the ImageJ software, the average islet diameter for each part, the average for many segments, and finally the average for all mice belonging to the same group were calculated using photomicrographs of pancreatic islets.

Statistical analysis

The outcomes are reported as the mean ± ESM (standard error of the mean). They are subjected to ANOVA analysis of variance followed by Bonferroni's test using Sigma plot for Windows Version 14.0 software. Findings were regarded as statistically significant when the P-value was less than 0.05.

Results

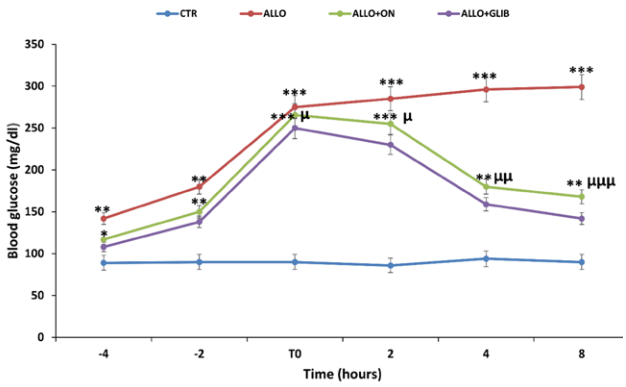
Acute toxicity in mice

The findings obtained showed that there is an absence of symptoms of toxicity (diarrhea, vomiting, cardiovascular disturbance, skin and mucous membrane damage, hair loss, etc.) during the 14 days after the single treatment. Thus, no case of mortality has been recorded. Indeed, the plant of Ononis natrix does not present acute toxicity with doses lower than 5000mg / kg; we can therefore conclude that LD50 of Ononis natrix is greater than 5000mg / kg.

Antidiabetic effect of Ononis natrix aqueous extract

In this study, the effect of aqueous extract of Ononis natrix on glucose levels in alloxan-treated mice blood is shown (**Figure 2**). In comparison to the normal control group, the administration of alloxan caused a substantial increase (p 0.01) in blood glucose levels in the alloxan group. In diabetic mice, the aqueous extract significantly reduced the levels of blood glucose (p = 0.006), especially 6-8 hours after treatment, compared to untreated diabetic mice. The impact was equivalent to that achieved with Glibenclamide (p= 0.06).

Figure 2: Effect of Ononis natrix aqueous extract on blood glucose levels in alloxan-induced diabetic mice after 8h of treatment. Group 1 (CTR), normal control mice treated with sterile normal saline. Group 2 (ALLO), diabetic mice treated with sterile normal saline alone. Group 3 (ALLO + ON), diabetic mice treated with 500 mg/kg body weight extract Ononis natrix aqueous extract. Group 4 (ALLO + GLIB), positive control mice treated with 20 mg/ kg body weight of glibenclamide.



Histopathological study of pancreas

The findings of the histopathological analysis of pancreas sections stained with hematoxylin and eosin (**Figure 3**) and the mean diameter of the islets of Langerhans (**Figure 4**) revealed a regular pancreas architecture with normal acini and islets of Langerhans population comprising α and β cells in the control group (**Figure 3A**). Alloxan-treated mice's pancreas showed signs of pancreatic tissue deterioration and necrosis, as well as damage to the Langerhans islets (**Figure 3B**). The outcomes revealed that giving an aqueous extract of *Ononis natrix* at a concentration of 500 mg/kg BW reduced the damaging effects of alloxan on the pancreatic islets and caused the β cell population to return to normal. (**Figure 3C**). The group given glibenclamide as a treatment showed slight restoration of islets of Langerhans cells and partial islet cells regeneration (**Figure 3D**).

According to morphometric examination of the pancreas. The delivery of alloxan resulted in a considerable decrease in the size of the islets, particularly in diameter (119,647± 4,177µm), compared to the normal control group (420,488± 3,549µm) (P < 0.001). While oral administration of aqueous extract of *Ononis natrix* significantly prevented alloxan-induced pancreatic injury by preserving islet diameter (261,269± 13,359 µm) (P = 0.001), and that this impact was more important than that of glibenclamide (P= 0.01) with an islet diameter of (185, 311± 8,963µm) (**Figure 4**).

Figure 3: Histopathological sections of pancreatic (hematoxylin and eosin staining). (A), pancreas of control group mice showing the exocrine region and islets of Langerhans, with scattered β cells. (B), pancreas of diabetic mice alloxan-inducted (300 mg/kg) showing the exocrine region and islets of Langerhans with damaged β cells due to necrosis and a decreased number of β cells. (C), pancreas of diabetic mice, treated with 500 mg/kg of Ononis natrix aqueous extract showing evenly distributed β cells and an increased number of β cells. (D), pancreas of diabetic mice, treated with 20 mg/kg of glibenclamide. EX: Exocrine pancreas, β cell: beta cells.

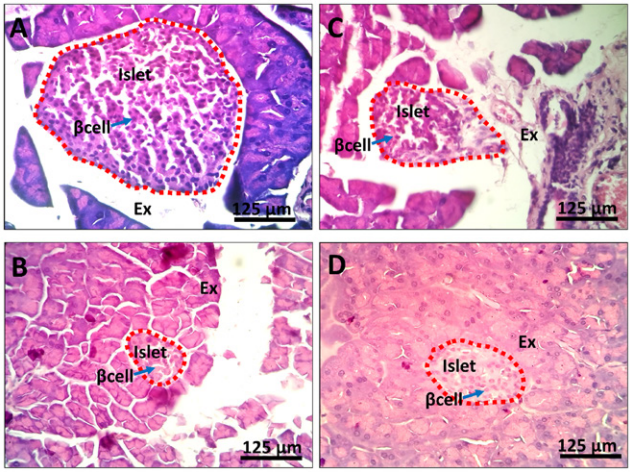
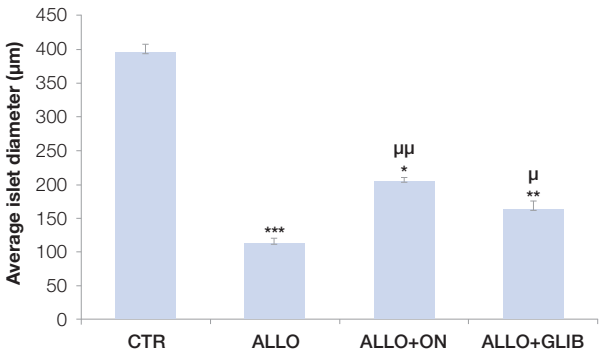


Figure 4: Graphical representation of the effects of Ononis natrix extract on islets diameter (µm) in type 1 diabetes alloxan-inducted. Microscope magnification (400 magnification). Values were expressed as means ± SEM, *p < 0.05; **P < 0.01; ***P < 0.001 compared to normal control group, µp < 0.05; µµp < 0, 01 compared to alloxan group.



Discussion

Alloxan-induced diabetes is a well-known model of experimental diabetes, we found very highly significant hyperglycaemia following administration of alloxan monohydrate to animals. This compound can cause severe necrosis of pancreatic β cells. This action is explained by the fact that Alloxane is endowed with a capacity to generate hydrogen peroxide and other free radicals which are at the origin of this cellular necrosis of β cells and consequently a significant drop in I insulinemia[29]. The sensitivity of these cells to oxidative stress is attributed to a low level of antioxidants in the pancreas compared to other tissues[30]. In recent studies, the phenolic compounds found in extracts of *Ononis natrix* have a variety of biological properties, including antimicrobial, antioxidant, anticancer, and inhibitory enzymes[31-33] .Furthermore, acute oral toxicity investigation demonstrated that the aqueous extract of *Ononis natrix* is non-toxic. Until the completion of the trial period, no mortality or adverse effects were observed with the chosen doses. ONAE's LD50 was calculated to be larger than 5000 mg/kg.

The hypoglycaemic action was most likely attributed to the existence of antioxidant chemicals in the analysed extract. Antioxidants act by preventing the generation of free radicals caused by Alloxane administration. Moreover, these antioxidant-rich chemicals helps pancreatic islets of Langerhans in diabetic rats to regenerate[34]. Flavonoids have long been known to help animals with alloxan diabetes rebuild their pancreatic β cells[35].

Our plant contains these families of molecules (flavonoids, saponosides, tri terpenes and tannins), and it is not known that one or the other or the synergy of all these compounds is responsible for the cellular "regeneration" of the islets from Langerhans. It should also be noted that the regeneration could be due to other active ingredients, which have not yet been identified. In addition, it has already been reported that polyphenols show their effect either through insulin-mimetic activity or through increased insulin secretion[36]. It's likely that these extracts cause diabetic mice to have hypoglycaemia effects by potentiating the insulin activity of the plasma, either by increasing pancreatic insulin secretion by existing β cells or by releasing the bound form[37]. Thus, phenolic compounds are known to help regulate blood sugar[38] and to possess marked anti-diabetic action[39] In one study, the most abundant phenolic compounds in the aqueous extract of *Ononis natrix* were shown to be benzoic acid and quercetin. During the phytochemical screening, coumarins, catechic tannins, saponins, and terpenes were found[25]. Quercetin is known for its antidiabetic potential[34,36]. Monoterpenes exhibit antihyperglycemic and anti-inflammatory properties. Tannins are an important indicator of hypoglycaemic or anti-diabetic activity for this plant species[40]. Other research has shown that tannins, in general, can affect glucose levels through a variety of ways, including improved glucose absorption in peripheral tissues, stimulation of insulin secretion of β cells in the pancreas, and decrease in glycation circulating proteins[41]. In addition, Tannins with anti-diabetic effect are indicated by their action on diabetes itself at the cellular level, by reinforcing insulin action (by reducing insulin resistance), and on diabetes problems due to their antioxidant and anti-enzymatic properties, which counteract the impact of free radicals and reduce inflammation in numerous tissues[40]. Apigenin, one of the constituents of *Ononis natrix*, also induces a moderate inhibitory effect on α-amylase and on α-glucosidase[25]. Mammalian -glucosidases are enzymes that catalyse the final step of the carbohydrate digestion process. They are found in the surface membrane of the brush border of intestinal cells. This mechanism significantly raises glucose levels in the blood, especially in diabetic

people. As a result, -glucosidase inhibitors may prolong this process in the gut, lengthen carbohydrate absorption time, lower the levels of postprandial plasma glucose and control postprandial hyperglycaemia[42].

Conclusions and future recommendation

The data provided on the variation of glycemia during the present study showed a clear and potent antihyperglycemic activity of our plant extract. Furthermore, histopathological examination of the islets revealed that, after treatment, the damaged islets were restored, and the diameter of the cells improved. It can therefore be assumed that the crude aqueous extract of *Ononis natrix* at a dose of 500 mg/kg has a therapeutic effect, which relieves diabetes mellitus. These preliminary results require further in-depth studies at different levels of the approach through a fine and extensive characterization on other compounds by other techniques, in order to establish a structure-activity relationship and to determine the actual chemical compound that produces this effect.

Interest Conflict declaration

The authors claim that no conflicts of interest have been reported.

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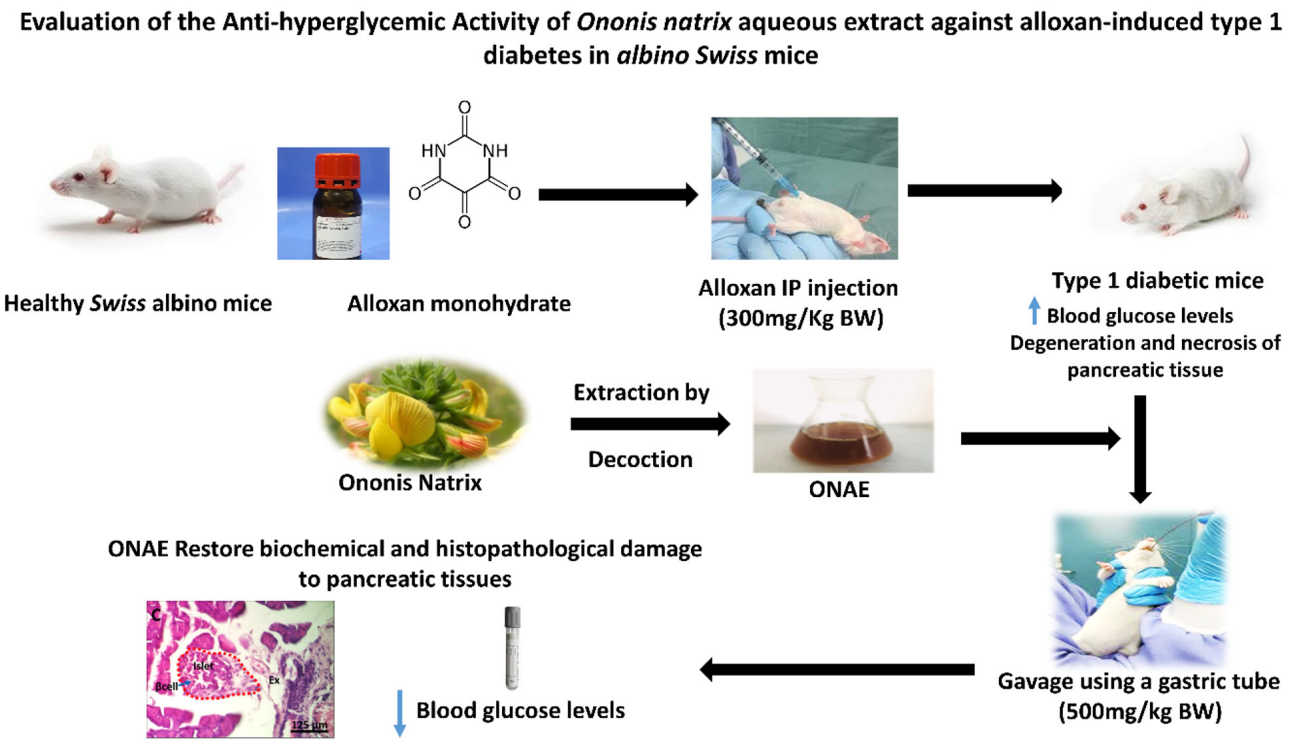
Graphical abstract



References

1. Wild S, Roglic G, Green A, Sicree R, King H. Global Prevalence of Diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care. 2004;27(5):1047-1053. doi:10.2337/diacare.27.5.1047

2. Chen T, Gao J, Xiang P, Chen Y, Ji J, Xie P, et al. Protective effect of platycodin D on liver injury in alloxan-induced diabetic mice via regulation of Treg/Th17 balance. Int Immunopharmacol. 2015 Jun;26(2):338-48. doi: 10.1016/j.intimp.2015.04.001.

3. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet (London, England). 2014;383(9911):69-82. doi:10.1016/S0140-6736(13)60591-7

4. Caillat-Zucman S, Garchon HJ, Timsit J, Assan R, Boitard C, Djilali-Saiah I, et al. Age-dependent HLA genetic heterogeneity of type 1 insulin-dependent diabetes mellitus. J Clin Invest. 1992 Dec;90(6):2242-50. doi: 10.1172/JCI116110.

5. Hajzadeh M, Rajaei Z, Pharmacologyonline GG-, 2011 undefined. The effect of Salvia officinalis leaf extract on blood glucose in streptozotocin-diabetic rats. researchgate.net. Published online 2010. Accessed April 25, 2022. https://www.researchgate.net/profile/Zahra-Rajaei/publication/268433692_The_effect_of_Salvia_officinalis_leaf_extract_on_blood_glucose_in_streptozotocin-diabetic_rats/links/5547481e0cf234bdb21dcc0f/The-effect-of-Salvia-officinalis-leaf-extract-on-blood-glucose-in-streptozotocin-diabetic-rats.pdf

6. Drouin P, Blickle JF, Charbonnel B, Eschwege E, Guillausseau PJ, Plouin PF, et al. Diagnostic et classification du diabète sucré: les nouveaux critères [Diagnosis and classification of diabetes mellitus: the new criteria]. Diabetes Metab. 1999 Mar;25(1):72-83. French.

7. EMC-Endocrinologie DR-, 2004 undefined. Epidémiologie et physiopathologie des complications dégénératives du diabète sucré. Elsevier. Accessed April 25, 2022. https://www.sciencedirect.com/science/article/pii/S1762565303000054

8. S Virdi J, Sivakami S, Shahani S, Suthar AC, Banavalikar MM, Biyani MK. Antihyperglycemic effects of three extracts from Momordica charantia. J Ethnopharmacol. 2003 Sep;88(1):107-11. doi: 10.1016/s0378-8741(03)00184-3.

9. Bailey CJ. Metformin: effects on micro and macrovascular complications in type 2 diabetes. Cardiovasc drugs Ther. 2008;22(3):215-224. doi:10.1007/S10557-008-6092-0

10. Grant PJ. Beneficial effects of metformin on haemostasis and vascular function in man. Diabetes Metab. 2003;29(4 II). doi:10.1016/s1262-3636(03)72787-6

11. Berraaouan A, Abid S, Bnouham M. Antidiabetic oils. Curr Diabetes Rev. 2013;9(6):499-505. doi:10.2174/15733998113096660081

12. Rathore K, Singh VK, Jain P, Rao SP, Ahmed Z, Singh VD. In-vitro and in-vivo antiadipogenic, hypolipidemic and antidiabetic activity of Diospyros melanoxylon (Roxb). J Ethnopharmacol. 2014;155(2):1171-1176. doi:10.1016/j.jep.2014.06.050

13. Khatun H, Nesa L, Islam R, Ripa FA, Mamum A, Kadir S. Antidiabetic and antidiarrheal effects of the methanolic extract of Phyllanthus reticulatus leaves in mice. Asian Pacific J Reprod. 2014;3(2):121-127. doi:10.1016/S2305-0500(14)60015-4

14. Wollenweber E, Dörr M, Rivera D, Roitman JN. Externally Accumulated Flavonoids in Three Mediterranean Ononis Species. Zeitschrift fur Naturforsch - Sect C J Biosci. 2003;58(11-12):771-775. doi:10.1515/ZNC-2003-11-1202/HTML

15. Fennane M, Ibn Tattou M. Statistiques et commentaires sur l'inventaire actuel de la flore vasculaire du Maroc. Flora. 2012;34(February 2016):1-9. Accessed April 25, 2022. http://ww2.bgbm.org/EuroPlusMed/query.asp

16. Al-Qudah MA, Al-Ghoul AM, Trawenh IN. Antioxidant Activity and Chemical Composition of Essential Oils from Jordanian Ononis Natrix L. and Ononis Sicula Guss. J Biol Act Prod from Nat. 2014;4(1):52-61. doi:10.1080/22311866.2014.890069

17. Liebezeit G. Ethnobotany and phytochemistry of plants dominant in salt marshes of the Lower Saxonian Wadden Sea, southern North Sea. Mar Biodivers. 2008;1(38):1-30. doi:10.1007/BF03043865

18. Gampe N, Darcsi A, Lohner S, Béni S, Kursinszki L. Characterization and identification of isoflavonoid glycosides in the root of Spiny restharrow (Ononis spinosa L.) by HPLC-QTOF-MS, HPLC-MS/MS and NMR. J Pharm Biomed Anal. 2016;123:74-81. doi:10.1016/j.jpba.2016.01.058

19. Mhamdi B, Abbassi F, Abdelly C. Chemical composition, antioxidant and antimicrobial activities of the edible medicinal Ononis natrix growing wild in Tunisia. Nat Prod Res. 2015;29(12):1157-1160. doi:10.1080/14786419.2014.981188

20. Mezrag A, Malafronte N, Bouheroum M, Travaglino C, Russo D, Milella L, et al. Phytochemical and antioxidant activity studies on Ononis angustissima L. aerial parts: isolation of two new flavonoids. Nat Prod Res. 2017 Mar;31(5):507-514. doi: 10.1080/14786419.2016.1195381

21. Sayari N, Najib Saidi M, Sila A, Ellouz-Chaabouni S, Bougatef A. Chemical composition, angiotensin I-converting enzyme (ACE) inhibitory, antioxydant and antimicrobial activities of Ononis natrix leaves extracts. Free Radicals Antioxidants. 2016;6(1):23-33. doi:10.5530/fra.2016.1.3

22. Süntar I, Baldemir A, Coşkun M, Keleş H, Akkol EK. Wound healing acceleration effect of endemic Ononis species growing in Turkey. J Ethnopharmacol. 2011;135(1):63-70. doi:10.1016/J.JEP.2011.02.023

23. Ghribi L, Ben Nejma A, Besbes M, Harzalla-Skhiri F, Flamini G, Ben Jannet H. Chemical Composition, Cytotoxic and Antibacterial Activities of the Essential Oil from the Tunisian Ononis angustissima L. (Fabaceae). J Oleo Sci. 2016;65(4):339-345. doi:10.5650/jos.ess15242

24. Yilmaz BS, Özbek H, Çitoğlu GS, Uğraş S, Bayram I, Erdoğan E. Analgesic and hepatotoxic effects of Ononis spinosa L. Phyther Res. 2006;20(6):500-503. doi:10.1002/PTR.1891

25. Yerlikaya S, Zengin G, Mollica A, Baloglu MC, Altunoglu YC, Aktumsek A. A multidirectional perspective for novel functional products: In vitro pharmacological activities and in silico studies on Ononis natrix subsp. hispanica. Front Pharmacol. 2017;8(SEP):600. doi:10.3389/FPHAR.2017.00600/PDF

26. Ahmadi S, Ebrahimi SS, Oryan S, Rafieenia F. Blockades of ATP-sensitive potassium channels and L-type calcium channels improve analgesic effect of morphine in alloxan-induced diabetic mice. Pathophysiology. 2012;19(3):171-177. doi:10.1016/j.pathophys.2012.04.007

27. El Khiat A, Tamegart L, Draoui A, El Fari R, Sellami S, Rais H, et al. Kinetic deterioration of short memory in rat with acute hepatic encephalopathy: Involvement of astroglial and neuronal dysfunctions. Behav Brain Res. 2019 Jul 23;367:201-209. doi: 10.1016/j.bbr.2019.03.046

28. El Khiat A, El Hiba O, Tamegart L, Rais H, Fdil N, Sellami S, et al. Time dependent alteration of locomotor behavior in rat with acute liver failure induced cerebellar neuroinflammation and neuro-astroglial damage. J Chem Neuroanat. 2022 Jan;119:102055. doi: 10.1016/j.jchemneu.2021.102055.

29. Tiwari P, Patel RK. Chances of reduction in cardiovascular risk by Draksharishta in induced diabetic condition. Pharmacologyonline. 2010;2:583-590. Accessed April 25, 2022. https://pharmacologyonline.silae.it/files/archives/2010/vol2/056.Preeti.pdf

30. Lenzen S, Tiedge M, Jörns A, Munday R. Alloxan derivatives as a tool for the elucidation of the mechanism of the diabetogenic action of alloxan. Lessons from Anim Diabetes VI. Published online 1996:113-122. doi:10.1007/978-1-4612-4112-6_8

31. Lopez-Lazaro M. Distribution and biological activities of the flavonoid luteolin. Mini Rev Med Chem. 2009;9(1):31-59. doi:10.2174/138955709787001712

32. Amoah SKS, Sandjo LP, Kratz JM, Biavatti MW. Rosmarinic Acid - Pharmaceutical and Clinical Aspects. Planta Med. 2016;82(5):388-406. doi:10.1055/S-0035-1568274

33. Anand David AV, Arulmoli R, Parasuraman S. Overviews of biological importance of quercetin: A bioactive flavonoid. Pharmacogn Rev. 2016;10(20):84-89. doi:10.4103/0973-7847.194044

34. hemmati mina, Saha SK, Vessal M, Hemmati M, Vasei M. Antidiabetic effects of quercetin in streptozocin-induced diabetic rats. Elsevier. 2003;135:357-364. Accessed April 25, 2022. https://www.sciencedirect.com/science/article/pii/S1532045603001406

35. Chakravarthy BK, Gupta S, Gambhir SS, Gode KD. Pancreatic beta-cell regeneration - a novel antidiabetic mechanism of Pterocarpus marsupium, Roxb. Indian J Pharmacol. 1980;12(2):123-127. Accessed April 25, 2022. https://ijp-online.com/article.asp?issn=0253-7613;year=1980;volume=12;issue=2;spage=123;epage=127;aulast=Chakravarthy;type=0

36. Hatware K, Annapurna A. The effect of quercetin on blood glucose levels of normal and streptozotocin induced diabetic (type i & type ii) rats. Int J Pharm Chem Biol Sci. 2014;4(3):613-619. Accessed April 25, 2022. http://search.ebscohost.com/login.aspx?direct=true&profile=ehost&scope=site&authtype=crawler&jrnl=22499504&AN=115933018&h=i107XFmFicWiKeQlOGdSmq85%2FDJJ0A7mh19G6gIQ1a%2BvMn%2B%2Bkx5tBFmk97XMxiUO4ME5vRgWPvH3qcA8pUSooQ%3D%3D&crl=c

37. Shirwaikar A, Rajendran K, Kumar CD, Bodla R. Antidiabetic activity of aqueous leaf extract of Annona squamosa in streptozotocin-nicotinamide type 2 diabetic rats. J Ethnopharmacol. 2004;91(1):171-175. doi:10.1016/j.jep.2003.12.017

38. Olmedilla B, Granado F, Gil-Martinez E, Blanco I, Rojas-Hidalgo E. Reference values for retinol, tocopherol, and main carotenoids in serum of control and insulin-dependent diabetic Spanish subjects. Clin Chem. 1997;43(6):1066-1071. doi:10.1093/clinchem/43.6.1066

39. Kumari S, Kumar P, Wanjari M, Palani S. Antidiabetic activity of Pandanus fascicularis Lamk - aerial roots in alloxan-induced hyperglycemic rats. Int J Nutr Pharmacol Neurol Dis. 2012;2(2):105. doi:10.4103/2231-0738.95943

40. Mangambu M, Mushagalusa K, Kadima N. Contribution à l'étude photochimique de quelques plantes médicinales antidiabétiques de la ville de Bukavu et ses environs (Sud-Kivu, R.D.Congo). J Appl Biosci. 2014;75(1):6211. doi:10.4314/jab.v75i1.7

41. Masunda TA, Mbala MB, Kayembe SJ, BF Longoma, KN Ngbolua, DST Tshibangu, et al. Activité anti-hyperglycémique et antiradicalaire des extraits des fruits de Raphia gentiliana De Wild.(Arecaceae). Ajol. info. Published online 2014. doi:10.4314/ijbcs.v8i6.7

42. Gao H, Huang YN, Gao B, Xu PY, Inagaki C, Kawabata J. α-Glucosidase inhibitory effect by the flower buds of Tussilago farfara L. Food Chem. 2008;3(106):1195-1201. doi:10.1016/J.FOODCHEM.2007.07.064

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ORIGINAL

Determination of the risk of fatty liver and hepatic fibrosis in the working population of the Balearic Islands

Determinación del riesgo de hígado graso y fibrosis hepática en la población trabajadora de Baleares

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Abstract

Introduction: The most common liver disease is fatty liver. The purpose of this study is to determine the prevalence of workers in the Balearic Islands with at high risk of fatty liver and liver fibrosis, as well as the variables it influences.
Methodology: Descriptive, retrospective and cross-sectional study, with a sample of 146,318 workers (83,602 men and 62,716 women), obtaining information related to medical examinations carried out during 2 consecutive years. Different formulas were used to predict fatty liver and liver fibrosis.
Results: The prevalence of high values in both men and women behaves similarly to the mean values, increasing with age and as we descend in social class. It is higher in smokers and rises in parallel with increasing body mass index and waist-to-height ratio is the same as the average values, that is, it increases with age and as we descend in social class, it is higher in smokers, and it rises in parallel as the index increases. body mass and waist-height perimeter. In all cases, the differences observed were statistically significant, seeing that all the variables (sex, age, social class, tobacco, body mass index, waist-height index) influence the appearance of high values of all the risk scales of non-alcoholic fatty liver, highlighting the body mass index and the waist-height index for presenting higher odds ratio.
Conclusion: The degree of correlation of the results of the different formulas is good, especially the Fatty Liver Disease, Hepatic Steatosis Index and Zhejian University index formulas, so these formulas could be included as another parameter when predicting risk. of fatty liver within health surveillance in workers with a probability of said pathology.

Key words: Fatty liver, non-alcoholic fatty liver disease, occupational health.

Resumen

Introducción: La enfermedad hepática más común es el hígado graso. El objetivo de este estudio es conocer la prevalencia de trabajadores de las Islas Baleares con alto riesgo de hígado graso y fibrosis hepática, así como las variables que influyen.
Metodología: Estudio descriptivo, retrospectivo y transversal, con una muestra de 146318 trabajadores (83602 hombres y 62716 mujeres), obteniendo la información relativa a los reconocimientos médicos realizados durante 2 años consecutivos. Se utilizaron distintas fórmulas para la predicción de hígado graso y de fibrosis hepática.
Resultados: La prevalencia de valores elevados tanto en hombres como en mujeres se comporta igual que los valores medios, es decir, aumenta con la edad y a medida que descendemos en la clase social, es mayor en fumadores, y se eleva paralelamente al incrementar el índice de masa corporal y perímetro cintura-altura. En todos los casos las diferencias observadas fueron estadísticamente significativas viendo que todas las variables (sexo, edad, clase social, tabaco, índice de masa corporal, índice cintura-altura), influyen en la aparición de valores elevados de todas las escalas de riesgo de hígado graso no alcohólico destacando el índice de masa corporal y el índice cintura-altura por presentar odds ratio más elevadas.
Conclusión: El grado de correlación de los resultados de las diferentes fórmulas es buena, especialmente las fórmulas Fatty Liver Disease, Hepatic Steatosis Index y *Zhejian University index*, por lo que se podrían incluir como un parámetro más a la hora de predecir el riesgo de hígado graso dentro de la vigilancia de la salud en trabajadores con probabilidad de dicha patología.

Palabras clave: hígado graso; hígado graso no alcohólico; salud laboral.

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Introducción

The most common hepatic disease is fatty liver, which encompasses a pathological spectrum ranging from steatosis, steatohepatitis with or without fibrosis, cirrhosis and hepatocellular carcinoma, and may have different etiologies. The main ones are[1]:

- Alcoholic fatty liver, caused by habitual daily consumption of more than 20 grams in women and 30 grams in men.
- Non-alcoholic fatty liver disease (NAFLD), associated with obesity, insulin resistance and metabolic syndrome, among others[2,3].

Liver-related pathology is a subject that is gaining special importance due to Due to its recent increase. The prevalence of NAFLD is currently 24% in the USA with Estimates projecting it to rise to 50% in the next decade[4]. It is highly prevalent in Western countries, particularly among obese individuals, affecting 82% of this population. In relation to other comorbidities, the prevalence is 72% in the case of hyperlipidemia, 72% in the case of metabolic syndrome, 68% in the case of arterial hypertension (AHT) and 44% in the case of type 2 diabetes mellitus (DM2)[5-9]. In spite of this, metabolic diseases and NAFLD have an intertwined and complex feedback relationship since one can favor the development of the other.

All of the above will lead to an increase in the medical and economic burden over time, as well as a deterioration in the quality of life of patients[10], since these diseases can increase mortality not only due to liver involvement, but also due to an increased risk of cardiovascular and infectious diseases[11].

In relation to the world of work, recent studies have shown that occupational and environmental chemical exposures may be associated with the development of NASH, with the liver being the target organ most affected by industrial chemicals, resulting in a wide range of liver pathologies from necrosis to cancer in both humans and animals[1].

Regarding the diagnosis of NASH, it is usually based on imaging tests, with abdominal ultrasound being the most accessible and innocuous. Then other tests can be used, such as computerized axial tomography (CAT), Fibroscan and Nuclear Magnetic Resonance (NMR), the latter being the best method for detecting and quantifying the amount of fat in the liver[12]. Finally, there is the hepatic biopsy as gold standard since it allows reaching a diagnosis of certainty and also allows differentiating if the origin is or not in the excessive consumption of alcohol[13].

The main concern regarding these tests is based on their cost and the risk involved in invasive tests in the absence of effective treatments[14]. There are multiple indicators and predictive formulas for NASH that could serve as initial screening tools for fibrosis risk, facilitating subsequent decisions regarding invasive strategies[15]. Among the prediction formulas in this study we highlight the Fatty Liver Index (FLI), Hepatic steatosis index (HSI), Lipid accumulation product (LAP), Fatty liver disease index (FLD), Zhejiang University index (ZJU), Korean steatosis index (KSI), Bard score[16-19].

For all these reasons, given that it is an increasingly prevalent disease in our society and that it can be actively addressed and provide a better quality of working life, we consider it an important area of research to be taken into account among the working population of the Balearic Islands in order to identify and prevent risk factors and thus promote protocols for action and promote healthy behaviors and habits that are accessible to this population from the prevention services.

Methods

Design

A descriptive and cross-sectional study was carried out based on the collection of information from an anonymized database owned by ADEMA Escuela Universitaria. Information related to medical examinations performed during 2 consecutive years will be taken into account.

Inclusion criteria:

- Age between 18 and 69 years (working age).
- Working population of the Balearic Islands.
- Workers who have all the variables necessary to calculate the scales of hepatic fibrosis and fatty liver.
- Workers who have undergone the mandatory medical check-ups.
- Workers who agree to participate in the study and give their data for epidemiological purposes.
- Not to be a heavy alcohol consumer.

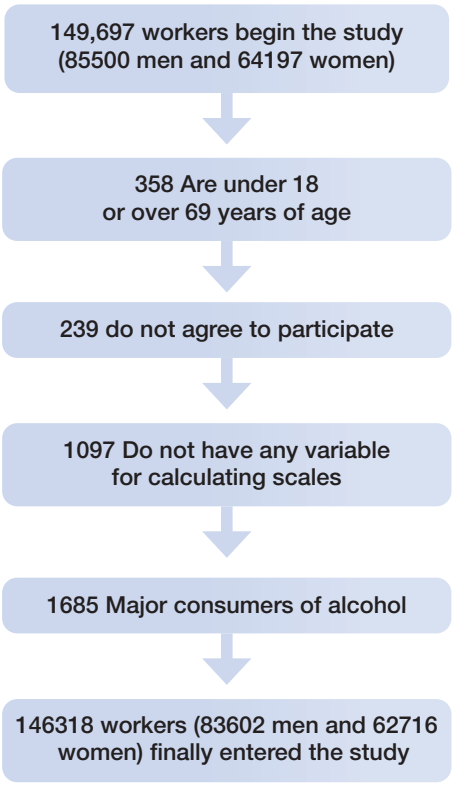
Determination of variables

The collection of information was carried out through medical examinations performed during two consecutive years, between January 2018 and December 2019.

The information was obtained from the clinical interviews and clinical analyses requested in said examinations as well as from the measurements taken in consultation using the appropriate instruments (SECA 700 model scale-measuring scale and tape measure).

In order to avoid inter-observer bias, considered the main one in this study, the information collection measures were homogenized, as well as the training of the health personnel necessary for data collection. In addition, all the workers underwent the examinations at the same prevention service.

Figure 1: Flow chart of the participants.



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The following formulas will be used for the prediction of fatty liver and liver fibrosis:

- Fatty liver index (FLI)[20]

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

An FLI result >60 indicates high probability of fatty liver, 30-59 intermediate probability, <30 low probability.

- Hepatic steatosis index (HSI)[21]
HSI= 8 ×(ALT / AST) + BMI + 2 (if DM type 2) + 2 (if women)

An HSI score <30 would rule out hepatic steatosis. If HSI >36 it is associated with such pathology.

- Zhejian University index (ZJU Index)[22]
ZJU = BMI + glucose + triglycerides + 3 x ALT/AST + 2 if women
ZJU >38 is associated with increased likelihood of fatty liver. Conversely, a score of <32 would indicate low probability.

- Fatty liver disease index (FLD Index)[23]
FLD = BMI+Triglycerides+3 × (AST/ALT) +2 × Hyperglycemia (present=1; absent=0). The cutoff point to consider high risk is 37.

- Korean steatosis index (KSI)[24]
BMI 23-25 (2 points), BMI > 25 (3 points), ALT/AST > 1.5 (1 point), GGT > 50 (1 point), Triglycerides >150.
A KSI score > 3 points is associated with a high probability of high fatty liver.

- Lipid accumulation product (LAP index)[25]
LAP index = [{waist (cm) - 65} x triglycerides (mmol/ L)] in men
[{waist (cm) - 58} x triglycerides (mmol/L)] in women.
LAP index >42, 7 high likelihood of fatty liver

- Bard Score[26]
BMI ≥ 28 (1 point), AST/ALT ≥ 0.8 (2 points), DM type 2 (1 point)

Obtaining a score of 2- 4 points indicates a high probability of fibrosis.

A person who has quit smoking less than a year ago or who has consumed at least one cigarette per day (or its equivalent in other forms of consumption) within the last thirty days is considered a smoker.

The social class was determined by adopting the social determinants group's suggestion from the Spanish Society of Epidemiology[27] based on the profession, creating three categories: Class I includes managers and directors, professionals from universities, athletes, and artists; Class II includes intermediate jobs and skilled independent contractors; Class III includes unskilled laborers.

Statistical analysis

In the data analysis, categorical variables are described by frequency and percentage, and quantitative variables by mean and standard deviation. The association between variables will be analyzed using Chi-square (χ^2) tests (with Fisher's exact test when conditions required) and Student's t test for independent samples. Multivariate analysis will be performed by multinomial logistic regression with the Wald statistic, with the calculation of odds ratios and their corresponding 95% confidence intervals (95%CI), and the Hosmer-Lemeshow goodness-of-fit test will be

performed. Pearson's correlation coefficient and Cohen's kappa index are applied to assess the concordance and correlation between the fatty liver and liver fibrosis scales. The statistical analysis was performed with the SPSS 28.0 program, with the accepted level of statistical significance being p<0.05.

Ethical aspects

The research team committed to always adhering to the ethical guidelines for health sciences research that have been established on a national and international level (the Declaration of Helsinki), with particular consideration paid to participant anonymity and data confidentiality. The Ethics and Research Committee of the Balearic Islands (CEI-IB) was consulted in order to acquire approval, which was accomplished using indicator IB 4383/20. The study was voluntary, meaning that after being fully informed about its purpose, the participants gave their written and verbal consent to take part in it. In order to do this, they were provided with an information sheet outlining the purpose of the study and an informed consent form. The codes used to identify the data collected for the study make it impossible for anybody other than the project's coordinator to link the data to the participants. There will be no publication of the participants' identities in any study report. Any information that could be used to identify them will not be shared by the investigators. The research team guarantees that the participant in this study may exercise his or her rights of access, rectification, cancellation, and opposition of the data collected. In any event, the team pledges to strictly adhere to Organic Law 3/2018, of December 5, on the protection of personal data and guarantee of digital rights.

Results

Of the 149,697 workers distributed in 85,500 men and 64,197 women, 146,318 met the inclusion criteria previously mentioned, distributed in 83,602 men and 62,716 women, who were those who finally participated in the study (**Figure 1**).

In relation to the characteristics of the sample, the mean age was 41.81 years in the case of men and 39.88 in the case of women, with a predominance of social class III (79.38%, 72.01%) and non-smokers (67.50%, 66.66%). The average BMI is overweight, especially in men, 42.86% with BMI 26.88 compared to 48.99% of women who are in normal weight, BMI 25.81, correlating with the high waist/height index, being a more reliable parameter that is increasing its use in recent years compared to BMI. Regarding total cholesterol levels, this is within the high limits of normality at the expense of LDL cholesterol and, in the case of triglycerides, they are higher in men than in women (34.85%, 33.42%).

Table I: Characteristics of the sample.

	Men n=83602 Mean (SD)	Women n=62716 Mean (SD)	p-value
Age	41.81 (10.45)	39.88 (10.48)	<0.001
Height	175.18 (6.85)	162.28 (6.34)	<0.001
Weight	82.58 (14.99)	67.98 (14.70)	<0.001
Body mass index	26.88 (4.47)	25.81 (5.36)	<0.001
Waist	87.61 (10.19)	75.13 (10.49)	<0.001
Waist to height ratio (WtHR)	0.50 (0.06)	0.46 (0.06)	<0.001
Systolic blood pressure	126.11 (15.62)	115.38 (15.52)	<0.001
Diastolic blood pressure	77.32 (11.10)	72.33 (10.47)	<0.001
Total cholesterol	195.55 (37.86)	192.11 (35.53)	<0.001
HDL-cholesterol	52.05 (9.75)	57.15 (10.26)	<0.001
LDL-cholesterol	118.68 (34.85)	116.37 (33.42)	<0.001
Triglycerides	125.73 (75.96)	93.13 (45.59)	<0.001
Glucose	93.42 (21.51)	88.26 (16.02)	<0.001
ALT	29.01 (17.52)	18.69 (11.60)	<0.001
AST	24.42 (13.30)	18.15 (7.91)	<0.001
GGT	32.70 (31.83)	18.78 (16.31)	<0.001
	n (%)	n (%)	p
18-29 years	12004 (14.36)	12180 (19.42)	<0.001
30-39 years	22274 (26.64)	18126 (28.90)	
40-49 years	28128 (33.65)	20082 (32.02)	
50-59 years	17970 (21.49)	10516 (16.77)	
60-69 years	3226 (3.86)	1812 (2.89)	
Social class I	5082 (6.08)	4696 (7.49)	<0.001
Social class II	12158 (14.54)	12856 (20.50)	
Social class III	66362 (79.38)	45164 (72.01)	
Non smokers	56428 (67.50)	41804 (66.66)	<0.001
Smokers	27174 (32.50)	20912 (33.34)	
Underweight	624 (0.75)	1896 (3.02)	<0.001
Normal weight	29986 (35.87)	30722 (48.99)	
Overweight	35834 (42.86)	18060 (28.80)	
Obesity	17158 (20.52)	12038 (19.19)	
WtHR normal	45802 (54.79)	48088 (76.68)	<0.001
WtHR high	37800 (45.21)	14628 (23.32)	

Glycemia and hepatic profile are in range, a little higher in the case of males (**Table I**).

Table II shows the values of the nonalcoholic fatty liver disease risk scales in men. These mean values increase in all cases with increasing age. An increase in these mean values is also observed when the socioeconomic level decreases. The risk scales show more unfavorable values in smokers. There is also a progressive increase in the values as BMI and waist-to-height ratio increase.

With respect to the prevalence of high values of the fatty liver risk scales in both men and women, it behaves in the same way as the mean values, that is, it increases with age, increases as we descend in social class, is higher in smokers, and rises in parallel with increasing BMI and waist-height circumference. All the data can be seen in **tables IV** and **V**. In all cases the differences observed are statistically significant.

In the multivariate analysis of multinomial logistic regression (**Table VI**) it can be seen that all the variables (sex, age, social class, smoking, BMI, waist-height index) influence the appearance of elevated values of all the non-alcoholic fatty liver disease risk scales. Of all these, the most influential in presenting higher odds ratios were BMI and waist-to-height ratio.

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

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

Table II: Mean values of scales assessing nonalcoholic fatty liver disease and liver fibrosis according to sociodemographic variables, smoking and scales of overweight and obesity in men.

		FLI	HSI	ZJU	FLD	KSI	LAP	BARD
Men	n	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
18-29 years	12004	26.88 (24.21)	34.55 (6.70)	34.64 (5.34)	29.81 (5.22)	2.09 (1.55)	23.81 (21.20)	1.55 (0.96)
30-39 years	22274	36.38 (26.38)	36.41 (6.82)	36.50 (5.53)	31.57 (5.35)	1.69 (1.51)	31.99 (29.38)	1.56 (1.03)
40-49 years	28128	43.33 (26.65)	37.45 (6.75)	37.79 (5.61)	32.65 (5.32)	3.07 (1.42)	36.71 (30.98)	1.68 (1.07)
50-59 years	17970	45.49 (25.95)	37.59 (6.44)	38.32 (5.57)	32.93 (5.15)	3.17 (1.39)	37.07 (28.86)	1.86 (1.12)
60-69 years	3226	46.02 (25.17)	37.70 (6.12)	38.79 (5.35)	33.16 (4.92)	3.23 (1.30)	37.42 (26.20)	2.13 (1.16)
Social class I	5082	38.05 (25.52)	36.64 (6.55)	36.84 (5.24)	31.73 (4.95)	2.83 (1.52)	32.37 (27.96)	1.60 (1.08)
Social class II	12158	39.70 (25.50)	36.75 (6.83)	37.14 (5.77)	32.03 (5.47))	2.89 (1.45)	33.34 (27.22)	1.63 (1.09)
Social class III	66362	39.81 (27.10)	37.13 (6.43)	37.29 (5.25)	32.17 (4.96)	2.98 (1.52)	33.83 (29.44)	1.70 (1.06)
Non smokers	56428	39.47 (26.68)	36.76 (6.86)	37.10 (5.66)	31.99 (5.35)	2.85 (1.50)	33.36 (29.25)	1.68 (1.07)
Smokers	27174	39.79 (26.83)	36.81 (6.70)	37.17 (5.68)	32.06 (5.37)	2.86 (1.49)	33.82 (28.94)	1.69 (1.07)
Underweight	624	5.41 (4.57)	25.65 (2.98)	26.59 (2.01)	21.74 (1.44)	0.21 (0.43)	8.08 (8.01)	1.47 (0.92)
Normal weight	29986	16.84 (11.54)	31.79 (4.19)	32.32 (2.64)	27.38 (2.42)	1.40 (1.21)	17.37 (12.56)	1.58 (0.83)
Overweight	35834	41.90 (18.51)	37.34 (4.58)	37.61 (2.79)	32.49 (2.49)	3.61 (0.79)	34.56 (22.99)	1.62 (1.11)
Obesity	17158	76.24 (15.66)	44.80 (5.87)	44.98 (4.65)	39.58 (4.26)	3.92 (0.89)	61.22 (38.47)	2.19 (1.07)
WtHR normal	45802	23.27 (16.28)	33.68 (5.15)	34.12 (3.71)	29.12 (3.47)	2.25 (1.53)	20.27 (14.73)	1.49 (0.99)
WtHR high	37800	59.58 (23.30)	40.57 (6.54)	40.81 (5.47)	35.57 (5.13)	3.60 (1.06)	49.90 (33.49)	1.92 (1.12)

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

Table III: Mean values of scales assessing nonalcoholic fatty liver disease and liver fibrosis according to sociodemographic variables, smoking and scales of overweight and obesity in women.

		FLI	HSI	ZJU	FLD	KSI	LAP	BARD
Women	n	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
18-29 years	12180	14.28 (19.74)	34.42 (6.53)	35.12 (5.84)	28.40 (5.7)	1.53 (1.47)	15.86 (15.85)	1.81 (0.93)
30-39 years	18126	18.03 (22.48)	35.91 (7.13)	36.46 (6.34)	29.68 (6.18)	1.85 (1.50)	18.23 (17.79)	1.83 (0.85)
40-49 years	20082	20.11 (22.20)	36.68 (6.60)	37.24 (5.83)	30.35 (5.61)	2.12 (1.46)	19.69 (18.08)	1.86 (0.98)
50-59 years	10516	25.35 (24.06)	38.04 (6.80)	38.71 (6.06)	31.61 (5.75)	2.51 (1.44)	23.47 (20.62)	1.92 (1.04)
60-69 years	1812	26.91 (23.69)	38.60 (6.58)	39.40 (5.88)	32.13 (5.51)	2.66 (1.39)	24.16 (19.19)	2.08 (1.09)
Social class I	4696	12.97 (17.45)	34.20 (5.58)	34.95 (4.98)	28.17 (4.83)	1.58 (1.48)	14.54 (15.78)	1.75 (0.95)
Social class II	12856	16.96 (20.88)	35.73 (6.63)	36.20 (5.71)	29.38 (5.53)	1.89 (1.53)	17.24 (16.86)	1.78 (0.87)
Social class III	45164	20.84 (23.22)	36.68 (7.02)	37.32 (6.31)	30.42 (6.07)	2.09 (1.49)	20.37 (18.74)	1.89 (0.97)
Non smokers	41804	19.18 (22.41)	36.17 (6.77)	36.81 (6.09)	29.94 (5.86)	1.98 (1.50)	19.12 (18.26)	1.85 (0.95)
Smokers	20912	19.59 (22.55)	36.37 (6.94)	36.96 (6.17)	30.09 (5.94)	2.02 (1.51)	19.37 (18.24)	1.86 (0.96)
Underweight	1896	2.16 (1.30)	27.13 (2.98)	27.90 (1.48)	21.22 (1.41)	0.10 (0.33)	4.69 (4.24)	1.62 (0.81)
Normal weight	30722	5.97 (4.47)	32.19 (3.88)	32.82 (2.42)	26.08 (2.27)	0.86 (1.06)	10.19 (7.21)	1.68 (0.75)
Overweight	18060	19.12 (11.29)	37.87 (3.91)	38.46 (2.36)	31.54 (2.13)	3.25 (0.51)	20.73 (12.53)	1.86 (1.01)
Obesity	12038	57.07 (21.65)	45.87 (5.68)	46.44 (4.80)	39.30 (4.54)	3.38 (0.61)	42.63 (23.91)	2.47 (0.99)
WtHR normal	48088	9.92 (9.59)	33.89 (4.98)	34.52 (3.89)	27.72 (3.72)	1.61 (1.46)	12.90 (9.80)	1.71 (0.88)
WtHR high	14628	50.80 (24.22)	44.22 (6.31)	44.79 (5.58)	37.69 (5.32)	3.34 (0.60)	40.28 (23.19)	2.35 (1.02)

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

Table IV: Prevalence of high values of scales assessing nonalcoholic fatty liver disease and liver fibrosis according to sociodemographic variables, smoking and overweight and obesity scales in men.

		FLI	HSI	ZJU	FLD	KSI	LAP	BARD
Men	n	%	%	%	%	%	%	%
18-29 years	12004	12.90	33.86	21.86	48.51	49.00	24.31	10.78
30-39 years	22274	21.47	45.83	32.32	59.94	65.11	37.50	15.74
40-49 years	28128	28.99	53.62	42.66	64.60	74.59	45.60	21.65
50-59 years	17970	31.56	56.32	47.18	65.13	78.59	49.24	37.32
60-69 years	3226	31.87	59.14	52.45	67.33	81.34	49.54	39.71
Social class I	5082	22.27	49.20	35.93	60.07	68.89	38.02	17.67
Social class II	12158	23.84	49.35	38.26	64.90	69.93	41.46	19.97
Social class III	66362	25.83	51.21	38.45	66.33	72.68	41.92	20.91
Non smokers	56428	25.06	49.29	38.24	60.87	69.16	40.79	20.59
Smokers	27174	25.44	49.60	38.33	61.46	69.67	41.51	20.67
Underweight	624	0.00	0.05	0.01	0.03	0.00	0.02	1.56
Normal weight	29986	0.90	11.71	1.93	11.19	17.07	10.50	2.85
Overweight	35834	18.42	58.48	39.92	30.83	65.55	46.62	21.58
Obesity	17158	83.32	98.59	99.71	95.17	88.99	85.57	50.11
WtHR normal	45802	3.91	27.04	13.48	60.67	49.24	16.31	7.47
WtHR high	37800	51.26	76.72	68.31	60.00	94.06	71.62	36.46

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

Table V: Prevalence of high values of scales assessing nonalcoholic fatty liver disease and liver fibrosis according to sociodemographic variables, smoking and overweight and obesity scales in women.

		FLI high	HSI high	ZJU high	FLD high	KSI high	LAP high	BARD high
Women	n	%	%	%	%	%	%	%
18-29 years	12180	5.57	32.55	23.91	34.75	37.78	20.10	15.25
30-39 years	18126	8.29	40.64	31.56	39.90	46.66	25.58	18.87
40-49 years	20082	8.65	47.51	37.80	48.15	53.69	29.42	21.93
50-59 years	10516	11.81	57.44	48.00	53.99	63.90	37.90	27.16
60-69 years	1812	12.03	62.91	54.42	60.71	70.09	39.85	34.22
Social class I	4696	4.09	30.24	21.34	37.22	36.93	16.06	12.61
Social class II	12856	6.72	40.73	30.24	42.53	45.82	23.12	16.10
Social class III	45164	9.57	47.37	38.45	45.82	53.60	30.94	23.24
Non smokers	41804	8.58	43.89	34.79	44.38	50.08	27.83	20.70
Smokers	20912	8.59	45.14	35.83	44.51	51.10	28.42	21.12
Underweight	1896	0.00	0.09	0.01	0.01	0.00	0.01	1.27
Normal weight	30722	0.15	12.63	0.18	18.93	5.64	4.41	1.45
Overweight	18060	5.69	67.31	54.05	37.44	48.65	34.32	25.06
Obesity	12038	43.61	99.67	99.56	95.23	85.19	84.27	67.82
WtHR normal	48088	0.26	30.07	18.86	43.15	36.85	12.11	9.50
WtHR high	14628	35.92	92.93	90.16	49.21	99.55	81.20	58.72

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

Table VI: Regresión logística multinomial.

	FLI high	HSI high	ZJU high	FLD high	KSI high	LAP high	BARD high
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Women	1	1	1	1	1	1	1
Men	7.07 (6.73-7.44)	1.34 (1.32-1.36)	1.05 (1.01-1.10)	1.68 (1.64-1.73)	3.51 (3.31-3.72)	1.15 (1.11-1.18)	1.41 (1.35-1.47)
18-29 years	1	1	1	1	1	1	1
30-39 years	1.06 (1.02-1.10)	1.06 (1.03-1.10)	1.25 (1.14-1.36)	1.07 (1.03-1.12)	1.08 (1.05-1.12)	1.03 (1.01-1.06)	1.51 (1.40-1.62)
40-49 years	1.11 (1.07-1.16)	1.18 (1.09-1.27)	1.56 (1.43-1.70)	1.12 (1.04-1.22)	1.26 (1.18-1.35)	1.10 (1.02-1.18)	2.00 (1.86-2.15)
50-59 years	1.26 (1.14-1.39)	1.38 (1.28-1.49)	2.23 (2.05-2.43)	1.37 (1.26-1.48)	1.71 (1.57-1.85)	1.34 (1.24-1.45)	2.43 (2.25-2.61)
60-69 years	1.95 (1.75-2.18)	1.75 (1.61-1.90)	3.03 (2.75-3.33)	1.80 (1.65-1.95)	3.23 (3.01-3.45)	1.94 (1.79-2.11)	2.66 (2.46-2.89)
Social class I	1	1	1	1	1	1	1
Social class II	1.08 (1.05-1.12)	1.09 (1.06-1.12)	1.07 (1.02-1.12)	1.05 (1.02-1.09)	1.05 (1.01-1.09)	1.06 (1.02-1.10)	1.17 (1.12-1.22)
Social class III	1.23 (1.17-1.29)	1.21 (1.18-1.24)	1.15 (1.07-1.23)	1.14 (1.08-1.20)	1.23 (1.17-1.30)	1.23 (1.15-1.30)	1.21 (1.14-1.30)
Non smokers	1	1	1	1	1	1	1
Smokers	1.06 (1.02-1.10)	1.03 (1.01-1.05)	1.04 (1.01-1.08)	1.04 (1.02-1.07)	1.04 (1.01-1.07)	1.03 (1.00-1.07)	1.09 (1.05-1.14)
Underweight	1	1	1	1	1	1	1
Normal weight	4.79 (4.56-5.03)	4.72 (4.60-4.85)	4.63 (4.33-4.94)	1.82 (1.72-1.93)	5.81 (5.60-6.03)	3.53 (3.38-3.68)	3.12 (3.01-3.24)
Overweight	17.19 (16.79-17.60)	19.12 (18.70-19.56)	17.86 (17.51-18.29)	5.84 (5.60-6.05)	19.20 (18.78-19.63)	18.01 (17.09-18.98)	33.78 (31.55-36.16)
Obesity	1	1	1	1	1	1	1
WtHR normal	5.36 (5.06-5.67)	1.71 (1.65-1.77)	2.05 (1.98-2.13)	1.40 (1.36-1.45)	3.21 (2.98-3.45)	4.93 (4.76-5.10)	2.01 (1.93-2.09)

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

Table VII: Pearson correlation coefficient of the seven scales.

	FLI	HSI	ZJU	FLD	FSI	LAP	BARD SCORE
FLI	1	0.712	0.813	0.864	0.809	0.809	0.731
HSI		1	0.923	0.928	0.590	0.513	0.587
ZJU			1	0.978	0.768	0.649	0.647
FLD				1	0.781	0.681	0.669
FSI					1	0.774	0.649
LAP						1	0.617
BARD SCORE							1

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

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

	FLI	HSI	ZJU	FLD	LAP	BARD SCORE
FLI	1	0.350	0.504	0.130	0.532	0.524
HSI		1	0.731	0.273	0.458	0.401
ZJU			1	0.098	0.585	0.530
FLD				1	0.086	0.025
LAP					1	0.471
BARD SCORE						1

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

Discussion

The pathology in relation to NAFLD covers a diverse pathological spectrum that evolves from steatosis, steatohepatitis with or without fibrosis, cirrhosis to hepatocellular carcinoma. The progression to one or the other has been shown to be non-linear, depending on certain factors, both internal, specific to the individual, and external or environmental. It is a disease that is increasingly present in our environment and a substantial increase is expected in the coming years.

In terms of occupational health, cases of steatohepatitis linked to chemical exposures in the workplace and environment have emerged. Hence, our study investigates the prevalence of fatty liver and hepatic fibrosis among the working population of the Balearic Islands, along with the variables influencing this prevalence, as assessed by primary prediction formulas and scales.

In our sample there is a predominance of men and women of average age (41.81 and 39.88 years), with overweight in the case of men as opposed to women who are mostly normal weight, smokers, social class III, normal waist/height with an average of the analytical profiles within the normal range except for LDL cholesterol which is elevated in both sexes.

We observed higher mean values and prevalence of elevated values in non-alcoholic fatty liver disease and liver fibrosis risk scales with advancing age and descending social class, they are also lower in women and somewhat lower in smokers. An increase is also observed in parallel to the increase in BMI and waist/height index values.

The multivariate analysis showed that the variable that most increased the risk of presenting high values of the different nonalcoholic fatty liver disease and liver fibrosis risk scales were the scales that assessed excess weight, followed by age and, to a lesser extent, sex, social class, and smoking.

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

Different studies have assessed the prevalence of NASH according to age, with the conclusion that as age increases, the prevalence of NASH also increases, a result that agrees with that obtained by us in this study. Data from the Third National Health and Nutrition Examination Survey (NHANES III) conducted in the United States in 3,270 persons showed very high rates of NASH, especially in older persons, even exceeding 40%[28] as in our work. Similar data are found in the studies of Alqahtani et al[29] and Bertolotti et al[30], the latter also showing a greater number of complications derived from NASH in older persons.

A study conducted in a Spanish working population of more than 30,000 workers also found an increase in the prevalence of a risk scale, in this case FLI, with age[31]. The study by Abeysekera et al[32] conducted in more than 10,000 people in Bristol showed a higher prevalence of liver fibrosis determined by FibroScan in older people.

The work of Fresneda et al[31] found, as we did, a higher prevalence of elevated FLI values in males and in people from the most disadvantaged social classes. Data from

5,272 middle-aged adults who participated in the 2014-2018 Korean National Health and Nutrition Examination Surveys (KNHANES)[33] also showed a higher prevalence of elevated values of an EHGNA risk scale, in this case HSI, in people with lower socioeconomic status. A paper by Ramirez-Manent et al[34] in 15,057 Spanish workers showed that the risk of developing nonalcoholic fatty liver disease and liver fibrosis was much higher in men than in women.

The role of smoking in the development of NAFLD remains controversial, some authors such as Jung et al[35] found an increased prevalence in smokers. Other authors such as Zein et al[36] observed an increased possibility of hepatic fibrosis associated with smoking. This cross-sectional study in 160,862 persons showed that smoking was associated with an increased risk of NAFLD (adjusted odds ratio 1.10; 95% confidence interval, 1.06-1.14). Furthermore, among smokers, the risk of NASH increased with the number of cigarettes (<10 and ≥10 pack-years vs. never smokers; odds ratios 1.04 and 1.11; 95% CI, 1.01-1.08 and 1.05-1.16, respectively.

Strengths and limitations

As strengths of the study, we can highlight the large sample size (more than 146,000 persons) and the large number of NASH and liver fibrosis risk scales used. The main limitation is that no diagnostic techniques for NASH or liver fibrosis other than the risk scales were used.

Conclusions

Taking into account the results obtained in our study, we can conclude that in this Spanish working population there is a direct relationship between the values of the different NASH and liver fibrosis risk scales as well as overweight and obesity scales, BMI and waist/height index, in addition to sociodemographic variables such as age, sex and social class and tobacco consumption.

The degree of correlation of the different scales is good, especially between FLD with ZJU and HSI and between ZJU and HSI. The degree of agreement, however, is not as good except between ZJU and HSI.

This is important since, within the health surveillance carried out through medical examinations, the FLD, HSI and ZJU scales could be included as another parameter when predicting the risk of fatty liver disease in workers, highlighting those with a probability of NAFLD, thus influencing their health from a preventive point of view.

Another thing to be highlighted from this study is the need to promote health promotion within companies through medical check-ups, since this is a fundamental pillar to avoid the development of pathologies of this type, favoring awareness and concern for the health of the workers themselves on an individualized basis.

Interest conflict

The authors claim that no conflicts of interest have been reported.

References

1. Wahlang B, Beier JI, Clair HB, Bellis-Jones HJ, Falkner KC, McClain CJ, et al. Toxicant-associated steatohepatitis. Toxicol Pathol 2013;41(2):343-60.

2. Martínez-Almoyna-Rifá E, Tomás-Gil1 P, Coll Villalonga JLL , Ramírez-Manent JI, Martí-Lliteras P, López-González AA. Relationship between nonalcoholic fatty liver disease and liver fibrosis risk scales with overweight and obesity scales in 219,477 spanish workers. Academic Journal of Health Sciences 2023;38(4):92-100 doi: 10.3306/AJHS.2023.38.04.92

3. Martínez-Almoyna-Rifá E, Tomás-Gil1 P, Coll Villalonga JLL , Ramírez-Manent JI, Martí-Lliteras P, López-González AA. Relationship between nonalcoholic fatty liver disease and liver fibrosis risk scales and various cardiometabolic risk scales in 219.477 Spanish workers. Academic Journal of Health Sciences 2023;38(5):138-45 doi: 10.3306/AJHS.2023.38.05.138

4. Saiman Y, Duarte-Rojo A, Rinella ME. Fatty Liver Disease: Diagnosis and Stratification. Annu Rev Med 2022;73:529-44.

5. Huang X, Xu M, Chen Y, Peng K, Huang Y, Wang P, et al. Validation of the Fatty Liver Index for Nonalcoholic Fatty Liver Disease in Middle-Aged and Elderly Chinese. Medicine (Baltimore) 2015;94(40):e1682.

5. Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. Hepatol Baltim Md 2023;77(4):1335-47.

6. Cariou B, Byrne CD, Loomba R, Sanyal AJ. Nonalcoholic fatty liver disease as a metabolic disease in humans: A literature review. Diabetes Obes Metab. 2021;23(5):1069-83.

7. Buzzetti E, Linden A, Best LM, Madden AM, Roberts D, Chase TJG, et al. Lifestyle modifications for nonalcohol-related fatty liver disease: a network meta-analysis. Cochrane Database Syst Rev. 2021;2021(6):CD013156.

8. Meneses D, Olveira A, Corripio R, Méndez MDC, Romero M, Calvo-Viñuelas I, et al. Prevalence and predictors of non-alcoholic steatohepatitis in patients with morbid obesity. Endocrinol Diabetes Nutr. 2022;69(3):178-88.

9. Cotter TG, Rinella M. Nonalcoholic Fatty Liver Disease 2020: The State of the Disease. Gastroenterology. 2020;158(7):1851-64.

10. Zhu Y, Liu H, Zhang M, Guo GL. Fatty liver diseases, bile acids, and FXR. Acta Pharm Sin B. 2016;6(5):409-12.

11. Wahlang B, Jin J, Beier JI, Hardesty JE, Daly EF, Schnegelberger RD, et al. Mechanisms of Environmental Contributions to Fatty Liver Disease. Curr Environ Health Rep. 2019;6(3):80-94.

12. Ajmera V, Loomba R. Imaging biomarkers of NAFLD, NASH, and fibrosis. Mol Metab. 2021;50:101167.

13. Amernia B, Moosavy SH, Banookh F, Zoghi G. FIB-4, APRI, and AST/ALT ratio compared to FibroScan for the assessment of hepatic fibrosis in patients with non-alcoholic fatty liver disease in Bandar Abbas, Iran. BMC Gastroenterol. 2021;21(1):453.

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

15. Ebrahimi, M., Seyedi, S.A., Nabipoorashrafi, S.A. et al. Lipid accumulation product (LAP) index for the diagnosis of nonalcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis. Lipids Health Dis 22, 41 (2023). https://doi.org/10.1186/s12944-023-01802-6

16. Ruffillo G, Fassio E, Alvarez E, Landeira G, Longo C, Domínguez N, et al. Comparison of NAFLD fibrosis score and BARD score in predicting fibrosis in nonalcoholic fatty liver disease. J Hepatol. 2011;54(1):160-3.

17. Fennoun H, Mansouri SE, Tahiri M, Haraj NE, Aziz SE, Hadad F, et al. Interest of hepatic steatosis index (HSI) in screening for metabolic steatopathy in patients with type 2 diabetes. Pan Afr Med J. 2020;37:270.

18. Ebrahimi M, Seyedi SA, Nabipoorashrafi SA, Rabizadeh S, Sarzaeim M, Yadegar A, et al. Lipid accumulation product (LAP) index for the diagnosis of nonalcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis. Lipids Health Dis. 2023;22(1):41.

19. Wang J, Xu C, Xun Y, Lu Z, Shi J, Yu C, Li Y. ZJU index: a novel model for predicting nonalcoholic fatty liver disease in a Chinese population. Sci Rep. 2015;5:16494. doi: 10.1038/srep16494.

20. Martínez-Almoyna-Rifá E, Tomás-Gil1 P, Coll Villalonga JLL , Ramírez-Manent JI, Martí-Lliteras P, López-González AA. Relationship between values of 7 NAFLD scales and different RCV scales in 219,477 Spanish workers. Academic Journal of Health Sciences 2023;38(4):52-9 doi: 10.3306/AJHS.2023.38.04.52

21. Preveden T, Veres B, Ruzic M, Pete M, Bogic S, Kovacevic N, et al. Triglyceride-Glucose Index and Hepatic Steatosis Index for the assessment of liver steatosis in HCV patients. Minerva Gastroenterol (Torino). 2023 Jun;69(2):254-260. doi: 10.23736/S2724-5985.22.03168-0.

22. Zheng K, Yin Y, Guo H, Ma L, Liu R, Zhao T,et al. Association between the ZJU index and risk of new-onset non-alcoholic fatty liver disease in non-obese participants: a Chinese longitudinal prospective cohort study. Front Endocrinol (Lausanne). 2024 Feb 9;15:1340644. doi: 10.3389/fendo.2024.1340644

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

24. Yip TC, Lee HW, Chan WK, Wong GL, Wong VW. Asian perspective on NAFLD-associated HCC. J Hepatol. 2022 Mar;76(3):726-734. doi: 10.1016/j.jhep.2021.09.024

25. Chen ZY, Liu L, Zhuang XX, Zhang YC, Ma YN, Liu Y, et al. Lipid accumulation product is a better predictor of metabolic syndrome in Chinese adolescents: a cross-sectional study. Front Endocrinol (Lausanne). 2023 Jun 23;14:1179990. doi: 10.3389/fendo.2023.1179990.

26. Xiong S, Yin S, Deng W, Zhao Y, Li W, Wang P, et al. Predictive value of liver fibrosis scores in cardiovascular diseases among hypertensive population. J Hypertens. 2023 May 1;41(5):741-750. doi: 10.1097/HJH.0000000000003394.

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

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

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

30. Bertolotti M, Lonardo A, Mussi C, Baldelli E, Pellegrini E, Ballestri S, Romagnoli D, Loria P. Nonalcoholic fatty liver disease and aging: epidemiology to management. World J Gastroenterol. 2014;20(39):14185-204. doi: 10.3748/wjg.v20.i39.14185.

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

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

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

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

35. Jung HS, Chang Y, Kwon MJ, Sung E, Yun KE, Cho YK, et al. Smoking and the Risk of Non-Alcoholic Fatty Liver Disease: A Cohort Study. Am J Gastroenterol. 2019;114(3):453-463. doi: 10.1038/s41395-018-0283-5. PMID: 30353055.

36. Zein CO, Unalp A, Colvin R, Liu YC, McCullough AJ. Smoking and severity of hepatic fibrosis in nonalcoholic fatty liver disease. J Hepatol. 2011;54(4):753-9.

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ORIGINAL

Subcutaneous ring block and dorsal penile nerve block effectiveness in male circumcision: A cross-sectional study

Eficacia del bloqueo subcutáneo del anillo y del bloqueo del nervio dorsal del pene en la circuncisión masculina: Un estudio transversal

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Abstract

Background: Our aim was to compare the effectiveness and postoperative implications of two regional anesthesia techniques, namely the subcutaneous ring block (SRB) and the dorsal penile nerve block (DPNB), when applied during routine circumcision in children.

Patients and methods: This comparative retrospective study was conducted between the years 2021 and 2022. The subjects were patients who underwent circumcision during this period. The techniques compared were the subcutaneous ring block (SRB) (group 1) and the deep dorsal penile nerve block (DPNB) (group 2).

Results: We observed that neither group had any instances of comorbidity or infection, rendering these factors statistically identical between the two groups (p=1.000 in both cases). Group 1 showed edema in 4 patients (21.2%) while it was reported in 12 patients (63.2%) in Group 2 (p =0.009). Similarly, bleeding was observed in 4 patients (21.2%) in group 1, but there were no instances of bleeding in group 2 (p =0.034). In terms of postoperative pain, group 1 had a higher average pain score (6.02±1.33) compared to Group 2 (4.68±3.12) (p =0.040). In Group 1, 18 patients (94.7%) required postoperative analgesia, whereas in Group 2, only 3 patients (15.8%) needed it (p <0.001).

Conclusions: Our comparative analysis demonstrates that the deep dorsal penile nerve block (DPNB) was associated with fewer postoperative complications, lower pain scores, and less need for postoperative analgesia than the subcutaneous ring block (SRB) in pediatric circumcision.

Key words: deep dorsal penile nerve block, subcutaneous ring block, circumcision, children.

Resumen

Antecedentes: Nuestro objetivo fue comparar la eficacia y las implicaciones postoperatorias de dos técnicas de anestesia regional, a saber, el bloqueo subcutáneo del anillo (BSR) y el bloqueo del nervio dorsal del pene (BNDP), cuando se aplican durante la circuncisión rutinaria en niños.

Pacientes y métodos: Este estudio retrospectivo comparativo se realizó entre los años 2021 y 2022. Los sujetos fueron pacientes sometidos a circuncisión durante este periodo. Las técnicas comparadas fueron el bloqueo subcutáneo en anillo (BSR) (grupo 1) y el bloqueo profundo del nervio dorsal del pene (BDPN) (grupo 2).

Resultados: Se observó que en ninguno de los dos grupos hubo comorbilidad ni infección, por lo que estos factores fueron estadísticamente idénticos entre los dos grupos (p =1,000 en ambos casos). El Grupo 1 presentó edema en 4 pacientes (21,2%), mientras que en el Grupo 2 se registró en 12 pacientes (63,2%) (p =0,009). Del mismo modo, se observó hemorragia en 4 pacientes (21,2%) del grupo 1, pero no hubo casos de hemorragia en el grupo 2 (p =0,034). En cuanto al dolor postoperatorio, el grupo 1 tuvo una puntuación media de dolor más alta (6,02±1,33) en comparación con el grupo 2 (4,68±3,12) (p =0,040). En el Grupo 1, 18 pacientes (94,7%) precisaron analgesia postoperatoria, mientras que en el Grupo 2 sólo la necesitaron 3 pacientes (15,8%) (p <0,001).

Conclusiones: Nuestro análisis comparativo demuestra que el bloqueo profundo del nervio dorsal del pene (BDPP) se asoció con menos complicaciones postoperatorias, puntuaciones de dolor más bajas y menor necesidad de analgesia postoperatoria que el bloqueo subcutáneo en anillo (BSR) en la circuncisión pediátrica.

Palabras clave: bloqueo profundo del nervio peneano dorsal, bloqueo subcutáneo en anillo, circuncisión, niños.

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Introduction

Circumcision refers to the surgical elimination of the male foreskin. This procedure is commonplace amongst approximately 30% of the male population worldwide, reaching peak prevalence of 87% in regions like sub-Saharan Africa. Notably, the operation often takes place with inadequate or no pain management for neonates, contradicting the established understanding that the procedure can be distressing and painful for the child. Ensuring optimal pain relief not only soothes the patient but also allows the surgeon to operate with greater care and precision, thereby enhancing the overall outcome[1-3].

Various methods have been employed to alleviate the pain associated with routine circumcision in neonates[4-7]. General anesthesia, while effective, carries considerable relative risks. Regional techniques, including caudal and pudendal blocks, are also efficient, but their invasive nature raises concerns[4,7-9]. The dorsal penile nerve block (DPNB) and subcutaneus ring block (SRB) are commonly used safer alternatives. A wealth of research demonstrates that DPNB is superior to topical LPC in terms of efficacy. Nonetheless, it's worth noting that there are painful stages in its application, and there are documented instances of partial block up to 13% and complete block failures up to 7%. The needle prick when administering the DPNB can induce pain at the outset. Moreover, it is significantly less effective when the circumcision procedure involves trauma to the ventral part of the penis, as this area partially draws its nerve supply from the perineal nerve, which is unaffected by the block[9-11].

In this study, we aimed to compare the effectiveness and postoperative implications of two regional anesthesia techniques, namely the subcutaneous ring block (SRB) and the dorsal penile nerve block (DPNB), when applied during routine circumcision in children.

Patients and methods

This cross-sectinal study was conducted between the years 2021 and 2022 after obtained ethical approval from local ethical commite with date-no 11.05.2023-4797. The subjects were patients who underwent circumcision during this period. The techniques compared were the subcutaneous ring block (SRB) (group 1) and the deep dorsal penile nerve block (DPNB) (group 2). All procedures were performed by experienced surgeons adhering to established protocols.

Data for each patient was retrospectively retrieved from hospital records. The data included patient age at the time of surgery, weight, any existing comorbidities, and the occurrence of edema, infection, or bleeding post-operation. In addition, data on post-operative pain scores at the time of surgery and 24 hours later were also collected. Furthermore, information regarding the need for postoperative analgesia immediately after surgery and within the 24-hour postoperative period was recorded.

To objectively evaluate pain experienced by the subjects, we utilized the FLACC scale, an acronym for Face, Legs, Activity, Cry, Consolability. The FLACC scale is a validated, comprehensive tool that has been developed to quantify pain in children ranging from 2 months to 7 years of age, as well as in individuals incapable of effectively communicating their pain[9].

The FLACC scale operates on a numerical range of 0 to 10, with 0 symbolizing a complete absence of pain. The scale consists of five distinctive criteria: facial expression (Face), leg movements (Legs), activity level (Activity), vocal expression (Cry), and response to comforting measures (Consolability). Each of these categories is allotted a score of 0, 1, or 2 based on the observed behavior, posture, or response of the patient. These individual scores are then summed to provide a comprehensive pain score for each patient. Higher scores on the FLACC scale represent a higher intensity of perceived pain (**Table I**)[9,11].

Statistical analysis

The information we collected for our study was analyzed using SPSS software (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL), version 24. We expressed the descriptive data as n, % values for classifiable variables, and as mean and standart deviation for continuous variables. We used the Pearson Chi-square test to determine differences between groups for classifiable variables. To assess the normality of the distribution for continuous variables, we employed the Kolmogorov-Smirnov test. Than two variables, were tested by the independet t- test. A p-value below 0.05 was considered the cut-off for statistical relevance.

Table I: FLACC score[9,11].

Behaviour	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant quivering chin, clenched jow
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting, back and forth, tense	Arched, rigid or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams, sobs, frequent complaints
Consolability	Content, relaxed	Reassured by touching, hugging or being talked to, distractible	Difficult to console or comfort

*Total score between 0-10. (0 = Relaxed and comfortable); (1-3 = Mild discomfort); (4-6 = Moderate pain); (7-10 = Severe discomfort/pain)

Results

Our study comprised two groups, Group 1 (n=19) and Group 2 (n=19). On analyzing various parameters, we found differences as well as similarities between the groups. The mean age in Group 1 was 5.68±2.69 years, and in Group 2 it was 7.53±3.47 years. This difference was not statistically significant (p =0.076). Similarly, the mean weight was 24.37±8.45 kg and 28.16±10.83 kg in Groups 1 and 2, respectively, with no significant statistical difference (*p* =0.237). When we looked at the comorbidity and infection rates in both groups, we observed that neither group had any instances of comorbidity or infection, rendering these factors statistically identical between the two groups (*p* =1.000 in both cases). The occurrence of edema was significantly different between the two groups. Group 1 showed edema in 4 patients (21.2%) while it was reported in 12 patients (63.2%) in Group 2 (p =0.009). Similarly, bleeding was observed in 4 patients (21.2%) in group 1, but there were no instances of bleeding in group 2 (*p* =0.034). In terms of postoperative pain, group 1 had a higher average pain score (6.02±1.33) compared to Group 2 (4.68±3.12) (*p* =0.040). However, the 24-hour pain scores were not significantly different between the two groups (Group 1: 1.89±0.93; Group 2: 1.21±2.15 (*p* =0.561). Notably, there was a striking difference between the two groups when comparing the postoperative need for analgesia. In Group 1, 18 patients (94.7%) required postoperative analgesia, whereas in Group 2, only 3 patients (15.8%) needed it—a highly significant statistical difference (*p* <0.001). Regarding the need for analgesia 24 hours after surgery, there were no significant differences between the groups (*p* =0.418). Specifically, in Group 1, 6 patients (31.6%) reported no need for analgesia, compared to 2 patients (10.5%) in Group 2. For the use of analgesia once, twice, three times, and four times in 24 hours, the figures for Group 1 were 2 (10.5%), 6 (31.6%), 4 (21.2%), and 1 (5.3%), respectively. For Group 2, these numbers were 3 (15.8%), 9 (47.4%), 5 (26.3%), and 0 (0%), respectively (**Table II**).

Discussion

Circumcision is a prevalent surgical procedure conducted by pediatric surgeons. Unlike past practices, contemporary methods aim for effective pain management during and after circumcision[8,12]. This is done to enhance the child's comfort and minimize the psychological impact during this period. Successfully achieving postoperative pain relief can help mitigate potential adverse effects of pain. This approach can lower patient anxiety, reduce morbidity, decrease the duration of hospital stay, and curtail costs. There are several strategies in practice to ensure analgesia post circumcision, including caudal epidural block, dorsal penile block, subcutaneous ring block, and the use of intravenous, oral, or rectal paracetamol. To evaluate pain levels in children, various assessment tools are utilized, such as the Neonatal Infant Pain Scale (NIBPS), FLACC, and CHEOPS[9,11]. In our study, we employed the FLACC method.

In regular pediatric medical practices, the use of intravenous paracetamol to provide analgesia, postoperative or otherwise, is quite common. Potential rare side effects associated with paracetamol usage include anaphylaxis, liver disorders, hypotension, and tachycardia. Similarly, intravenous Tramadol HCl is another pain reduction tool often used in postoperative periods, although it too can induce side effects such as sweating, nausea, anaphylaxis, and liver disorders[1-4].

With recent advancements in anesthesia, regional anesthesia techniques have been safely and effectively employed alongside general anesthesia in pediatric cases. Caudal epidural block, dorsal penile block, and subcutaneous ring block are commonly utilized for managing circumcision pain. These methods can occasionally result in mechanical side effects like hematoma development. Moreover, due to the chemical nature of the local anesthetics used, complications such as methemoglobinemia, convulsion, and cardiac arrest might occur, especially with anesthetics containing adrenaline[12,13]. Notably, there have been no

Table II: Comparison of the penil block techniques.

	Group 1 (n=19)	Group 2 (n=19)	*p* -value
Age	5.68±2.69	7.53±3.47	0.076
Weight	24.37±8.45	28.16±10.83	0.237
Comorbidity	0 (0%)	0 (0%)	1.000
Edema	4 (21.2%)	12 (63.2%)	**0.009**
Infection	0 (0%)	0 (0%)	1.000
Bleeding	4 (21.2%)	0 (0%)	**0.034**
Post-op pain score	6.02±1.33	4.68±3.12	**0.040**
24-h pain score	1.89±0.93	1.21±2.15	0.561
Post-op need for analgesia	18 (94.7%)	3(15.8%)	**<0.001**
24h need for analgesia			0.418
Never	6 (31.6%)	2 (10.5)	
Once	2 (10.5)	3 (15.8%)	
Twice	6 (31.6%)	9 (47.4)	
Three times	4 (21.2%)	5 (26.3%)	
Four times	1 (5.3%)	0 (0%)	

significant complications reported in association with ring-shaped superficial infiltration anesthesia, or subcutaneous ring block.

In the larger context of research on postoperative analgesia following circumcision, our results contribute an important piece to the puzzle. Previous studies have yielded diverse and sometimes contradictory results. For instance, while Vater et al[14] found the caudal epidural block more advantageous, Weksler et al[15] did not discern any difference between the methods they examined. Similarly, White et al[16] proposed the dorsal penile block had more benefits, but Tutuncu et al[17] found it less advantageous compared to other methods.

Against this backdrop, our findings add another perspective. In our research, we observed a significant difference in postoperative complications and pain management needs between two groups of patients. Group 1, who had undergone deep dorsal penile nerve block (DPNB), had lower rates of edema and bleeding compared to Group 2. The average pain score was also lower in Group 1, and far fewer patients in this group required postoperative analgesia.

These results indicate that, in our study, the deep dorsal penile nerve block demonstrated superior outcomes. However, does not negate the results of the previously mentioned studies but rather adds to the growing body of evidence that the best method of postoperative analgesia is likely dependent on a variety of factors. It underscores the need for more research to develop a more comprehensive understanding of the most effective and patient-friendly methods of pain management following circumcision.

Limitations

The study's limitations include its retrospective nature, potentially introducing selection bias. The small sample size may not represent the broader pediatric population. The use of only the FLACC scale may miss some pain nuances. Hospital record dependence could overlook unrecorded complications. The two groups had different mean ages and weights, potentially influencing results. There's no mention of operator variability, which might affect outcomes. The generalizability to different cultural or regional practices is uncertain.

Conclusions

Our comparative analysis demonstrates that the deep dorsal penile nerve block (DPNB) was associated with fewer postoperative complications, lower pain scores, and less need for postoperative analgesia than the subcutaneous ring block (SRB) in pediatric circumcision. This indicates its potential superior efficacy in managing postoperative outcomes in this setting, further research is needed.

Conflict of interest

The authors report no conflict of interest.

Funding source

No funding was required.

Informed consent

Written informed consent was obtained from all individual participants and/or their gaurdians.

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No

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

1. Aydoğdu B, Azizoğlu M, Okur MH. Social and psychological effects of circumcision: A narrative review. Janh 2022; 4: 264-71.

2. Sağır S, Azizoğlu M, Ergün M. Fewer knots in circumcision are associated with less postoperative pain: A retrospective comparative study. Neonatol Hir Perinat Med 2023; 8: 25-30.

3. Osorio W, Ceballos C, Moyano J. Effectiveness of acute post-operative pain management by the acute pain service Cir Cir 2022; 90: 197-201.

4. Okut G, Turgut E, Kaplan K, Bag YM, Akbas S, Sumer F, Kayaalp C. Does laparoscopic-guided transversus abdominis plane block have an effect on postoperative pain and recovery after sleeve gastrectomy? Eur Rev Med Pharmacol Sci 2022; 26: 5406-5412.

5. Sagir S. Post-operative complications of subcoronal hypospadias repair in patients receiving caudal block vs. penil block: A comparative study. J Clin Trials Exp Investig 2023; 2: 159-63.

6. Melgar-Bieberach RE. Methodological proposal for the development and validation of a scale of pain assessment in the critically burned patient. Cir Cir 2022; 90: 365-71.

7. Fernández-Cuadros M, Robles-López M, Martin-Lardies MªY, Laborda Delgado A, López-Fernández J, Albaladejo-Florín MªJ. Enfermedad de la Peyronie y radiofrecuencia capacitiva resistiva: estudio piloto y evaluación preliminar. Academic Journal of Health Sciences 2024; 39 (3):129-33.

8. Munevveroglu C, Gunduz M. Postoperative pain management for circumcision; Comparison of frequently used methods. Pak J Med Sci 2020; 36: 91-5.

9. Rybojad B, Sieniawski D, Rybojad P, Samardakiewicz M, Aftyka A. Pain Evaluation in the Paediatric Emergency Department: Differences in Ratings by Patients, Parents and Nurses. Int J Environ Res Public Health 2022; 19: 2489.

10. Sharara-Chami R, Lakissian Z, Charafeddine L, Milad N, El-Hout Y. Combination Analgesia for Neonatal Circumcision: A Randomized Controlled Trial. Pediatrics 2017; 140: e20171935.

11. Willis MH, Merkel SI, Voepel-Lewis T, Malviya S. FLACC behavioral pain assessment scale: a comparison with the child's self-report. Pediatric Nursing 2003; 29: 195-8.

12. Lv BD, Zhang SG, Zhu XW, Zhang J, Chen G, Chen MF, Shen HL, Pei ZJ, Chen ZD. Disposable circumcision suture device: clinical effect and patient satisfaction. Asian J Androl 2014; 16: 453-6.

13. American Academy of Pediatrics. Circumcision policy statement. Task Force on Circumcision. Pediatrics 1999; 103: 686.

14. Vater M, Wandless J. Caudal or dorsal nerve block?Comparison of two local anesthetic techniques for postoperative analgesia following day-case circumcision. Acta Anesthesiol Scand 1985; 29: 175-9.

15. Weksler N, Attas I, Klein M, Rosenztsveig V, Ovaida L, Gurman GM. Is penil block better than caudal epidural block for postcircumcision analgesia? J Anesth 2005; 19: 36-9.

16. White J, Harrison B, Richmond P, Procter A, Curran J. Postoperative analgesia for circumcision. Br Med J (Clin Res Ed) 1983; 286: 1934.

17. Tutuncu AC, Kendigelen P, Ashyyeralyeva G, Altintas F, Emre S, Ozcan R, et al. Pudendal Nerve Block Versus Penile Nerve Block in Children Undergoing Circumcision. Urol J 2018; 15: 109-15.

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ORIGINAL

Estimation of D-dimer reference range in a low-risk Kurdish pregnant women: A cross sectional study

Estimación del intervalo de referencia del dímero D en embarazadas kurdas de bajo riesgo: Un estudio transversal

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Abstract

Objectives: To measure D-dimer levels during the three trimesters of pregnancy in a sample of low-risk pregnant Kurdish women and to determine a D-dimer reference range (cut-off value) for each trimester.
Methods: From May 2022 to May 2023, 240 healthy pregnant women participated in a cross-sectional study within Maternity Teaching Hospital in Erbil city, Kurdistan Region, Iraq. Every woman in any trimester of pregnancy had her D-dimer levels measured once using an automated immunoturbidimetric method.
Results: Significant differences were detected between and within the three trimesters of pregnancy regarding the mean D-dimer and cut-off value at 95th centile CI was (497, 850 and 1311) ng/dl in first, second and third trimester respectively. A significant positive correlation was seen between gestational age and D-dimer levels ($r = 0.81$, $p < 0.001$). There was a modest positive correlation between D-dimer concentration and body mass index (BMI), indicating that D-dimer concentration rises with rising BMI. A relatively weak positive correlation was detected between age and D-dimer level ($r = 0.384$, $p < 0.001$). The correlation between D-dimer level and parity was also relatively weak ($r = 0.360$, $p < 0.001$).
Conclusion: The current study revealed a linear increase in D-dimer levels across the three trimesters of pregnancy.

Key words: cut-off point D-dimer, venous thromboembolism, low risk pregnancy, reference range.

Resumen

Objetivos: Medir los niveles de dímero D durante los tres trimestres del embarazo en una muestra de mujeres kurdas embarazadas de bajo riesgo y determinar un intervalo de referencia del dímero D (valor de corte) para cada trimestre.
Métodos: De mayo de 2022 a mayo de 2023, 240 mujeres embarazadas sanas participaron en un estudio transversal dentro del Hospital Docente de Maternidad en la ciudad de Erbil, Región del Kurdistán, Irak. A cada mujer en cualquier trimestre de embarazo se le midieron los niveles de dímero D una vez utilizando un método inmunoturbidimétrico automatizado.
Resultados: Se detectaron diferencias significativas entre los tres trimestres de embarazo y dentro de cada uno de ellos con respecto a la media del dímero D y el valor de corte en el IC del centil 95 fue de (497, 850 y 1311) ng/dl en el primer, segundo y tercer trimestre, respectivamente. Se observó una correlación positiva significativa entre la edad gestacional y los niveles de dímero D ($r = 0,81$, $p < 0,001$). Se observó una modesta correlación positiva entre la concentración de dímero D y el índice de masa corporal (IMC), lo que indica que la concentración de dímero D aumenta con el incremento del IMC. Se detectó una correlación positiva relativamente débil entre la edad y el nivel de dímero D ($r = 0,384$, $p < 0,001$). La correlación entre el nivel de dímero D y la paridad también fue relativamente débil ($r = 0,360$, $p < 0,001$).
Conclusiones: El presente estudio reveló un aumento lineal de los niveles de dímero D a lo largo de los tres trimestres del embarazo.

Palabras clave: punto de corte del dímero D, tromboembolismo venoso, embarazo de bajo riesgo, intervalo de referencia.

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Introduction

Pregnancy-related venous thromboembolism (VTE) is widely established to be one of the primary causes of maternal morbidity and mortality[1]. Also, with increasing maternal mortality rate prenatal mortality will increase[29]. Women are five times more likely than nonpregnant women to develop thromboembolism during pregnancy[2]. However in the postpartum period, the risk of venous thromboembolism increases 21fold to 84-fold within the first 6 weeks after delivery[3]. Pregnancy induces different physiological changes, with anatomic and hemostatic components both contributing to VTE diagnostic challenges. These diagnostic issues stem from concerns about testing methodologies, limitations, and the management of proven VTE patients, which must account for placental drug transport and the impact on fetal growth[4]. D-dimer is a tiny protein particle known as a cross-linked fibrin degradation product that is produced as a byproduct of blood coagulation and breakdown. D-dimer is typically not detectable in blood or can be detected in very low amounts; however, when blood clotting or clot disintegration is more common, D-dimer can be detected in significant quantities in the blood[5]. Normal physiological changes during pregnancy cause the maternal plasma D-dimer concentration to increase progressively from conception until delivery[6].

Although D-dimer testing is frequently used to rule out VTE outside of pregnancy[7], its accuracy in discriminating against VTE during pregnancy is questionable[8]. Due to its high negative probability ratio, the D-dimer test should not be used for clinical assessment of pulmonary embolism (PE) during pregnancy, according to a 2018 study by Goodacre et al[9]. According to another study, normal D-dimer levels are efficient at detecting that VTE does not develop throughout pregnancy or the postpartum period , according to Choi et al[10]. A systematic meta-analysis was also conducted to examine the safety of D-dimer levels for ruling out acute VTE in pregnant women. The pooled estimated values for sensitivity and negative predictive value were 99.5% and 100%, respectively. one study concluded that D-dimer levels enable the safe exclusion of VTE in pregnant women with suspected VTE[8].

Concerning the variation in the cut-off point of the D-dimer normal range, there are disagreements in the reference ranges and interpretation during pregnancy between nations, and even between healthcare facilities or laboratories within the same country. The reference range may vary depending on the population being tested, the testing methods used, and the protocols followed by the healthcare providers[11-13,14].

This study was carried out to measure D-dimer levels during the three trimesters of pregnancy in a sample of pregnant women, and to estimate the D-dimer range in the study sample, which may be beneficial in the future for identifying specific D-dimer cut- off limits during pregnancy in our population.

Methods

Study design

A cross-sectional investigation of D-dimer levels in low-risk pregnant women.

Setting

This study was conducted at the outpatient clinic of Maternity Teaching Hospital, Erbil city, Kurdistan region, Iraq from May 2022 to May 2023.

The Maternity Teaching Hospital is a large tertiary care hospital that serves approximately 13000 births annually. This hospital is Erbil's principal public maternity facility. The hospital provides obstetric and gynecological emergency care around the clock.

Participants

Healthy low-risk women who attend the outpatient clinic for antenatal checkup were considered for participation in the study.

Low-risk pregnant patients were classified as singleton, term, vertex or pregnant with no medical or surgical complications, no active complications, or no maternal or fetal factors that placed the pregnancy at a higher risk for obstacles[15,16].

Pregnant women aged 18 to 40 years, with a singleton vertex pregnancy, a gestation period of 6 to 42 weeks, no obstetric complications, or medical or surgical conditions, who agreed to participate in the research were included in the study.

All women with a history of VTE, diabetes, preeclampsia, ischaemic heart disease, smoking, anticoagulant and antiplatelet use, a history of 3 or more miscarriages, recent COVID-19 infection (6 months before sampling); a recent history of acute infection and fever; or a history of amniotic membrane rupture, who refused to participate were excluded from this study.

Study size

The sample size was 240 pregnant women as estimated by the following equation[17]:

n = (z^2 * σ^2) / (δ^2 * 1 - r^2)[17]

n = the sample size

z = the z-score for the desired confidence level (typically 1.96 for a 95% confidence interval)

σ = the standard deviation of the population = the desired precision of the estimate (typically 10% or 0.1)

r = the intraclass correlation coefficient (ICC), which measures the similarity of measurements within individuals

For this study, we assumed the following:

Confidence level = 95% Precision = 10% ICC = 0.7

Standard deviation = 0.1(for the desired margin of error, 10% should be the standard deviation)

n = (1.96^2 * 0.1^2) / (0.1^2 * 1 - 0.7^2) = 75.325

The minimum sample size for this study was75-120 to identify the reference interval with the desired confidence and precision, However, to obtain more significant results, a larger number of participants was used.

Data collection

The Women who satisfied the study's inclusion criteria provided information regarding their age, parity, occupation and gestational age, which was confirmed by the last menstrual period and first trimester ultrasonography. Participants were categorized according to their gestational age into 3 groups: first trimester 13+6 weeks, and second trimester 14 –27+6[27].

Quantitative variables

Blood was sampled once from each woman, and blood was withdrawn from them for laboratory tests.

Three milliliters of venous blood were drawn into a sodium citrate tube, and the sample was filled with exactly 3 ml of the marketed area on the citrated tube (tube containing 0.11 molar sodium citrate solution) to avoid over, or underfilling the=*) tubes.

Within 24 hours of collection, the samples were examined in the same private laboratory close to the hospital. To ensure stability until processing, each sample was kept between 2 and 8 degrees Celsius.

All the samples were analyzed via an automated immunoturbidimetric assay (the autodimer assay uses latex particles coated with an antibody against D-dimer). In the presence of D-dimer, particles join to form larger aggregates. The increase in scattered light is proportional to the amount of D-dimer in the sample.

With a Cobas Roche c111 (Tina Quant D-dimer Gen.2) machine manufactured by ROCHE DIAGNOSTICS GMBH at MANNHEIM GERMANY. The Sensitivity of the device was 100%, the specificity was 60% and the limit of detection was 0.15 µg/ml.

The D-dimer concentration was measured with 500 ng/ml or 0.50 µg/ml as cut-off D- dimer level for nonpregnant people; a level above this cut-off was considered high.

Statistical methods

The data were analyzed using the Statistical Package for Social Sciences (SPSS, version 26). One way analysis of variance (ANOVA) was used to compare the means of the three groups. A post hoc test (LSD) was used to determine whether the difference between two groups was significant (after ANOVA). The Pearson correlation coefficient was used to determine the strength of the correlation between two numerical variables. A multiple regression model was used to predict D-dimer levels (based on the values of the studied variables). The formula of the straight line (Y = a + bX) was used in the prediction of D-dimer (Y), where 'Y' is the dependent variable, 'X' (gestational age) is the predictor of D-dimer, 'a' is a constant and 'b' is the regression coefficient. (Reference below)[17]. A p value of ≤ 0.05 was considered to indicate statistical significance.

Ethics approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Research Protocol Ethics Committee / Kurdistan higher council of medical specialties on August 14th 2022 (no. 1391). Written informed consent was obtained from each woman who agreed to participate in the study at the time of the first interview. All participants were assured that their information would be kept confidential and would be used for research purposes only.

Results

Participants

300 women were interviewed for involvement in the study. 28 were excluded due to a lack of inclusion criteria, 15 declined to participate, and 17 blood samples were destroyed because there was insufficient blood in the tube. At the conclusion, 240 ladies took part in the research. Among the 240 women, one-third were in their first semester, 38.3% in their second, and 28.3% in their third trimester.

Main results

- The mean D-dimer of the women was 255.9 ng/ml in the first trimester, 539.1 ng/ml in the second trimester, and 955 ng/ml in the third trimester. Other details are presented in **table I**.

- After removing the variables that were not significantly correlated with D-dimer, **table II** presents the correlation between D-dimer and gestational age. The D-dimer level could be predicted from the following equation: Y = a + bx (equation of the straight line). Accordingly, the predicted D-dimer = -26.451 + 28.041 gestational age.

- Note that all the differences between each two means were significant by LSD post-hoc test. Positive strong significant correlation was detected between the D-dimer and gestational age ($r = 0.875$, $p < 0.001$). The more the weeks of gestation, the more the D-dimer (**Figure 1**).

- The cut off point of D-dimer (500 ng/ml) in non-pregnant population is presented as a straight line in **figure 4**, where it is evident that the majority of the D-dimer readings of early weeks of gestation were below the line, while the majority of the readings of

Table I: Descriptive statistics of D-dimer by trimesters of pregnancy.

D-dimer (ng/ml)	Trimesters		
	First (n = 80)	Second (n = 92)	Third (n = 68)
Mean	255.9	539.1	955.0
Standard deviation	106.3	185.1	217.8
Standard error	11.9	19.3	26.4
95% Confidence Interval for Mean			
Lower Bound	232.3	500.8	902.2
Upper Bound	279.6	577.4	1007.7
Median	230.5	547.5	963.0
Minimum	100.0	121.0	269.0
Maximum	600.0	950.0	1660.0
Percentiles			
5th	100.0	235.3	597.7
25th	194.0	410.0	837.5
50th	230.5	547.5	963.0
75th	309.3	666.8	1086.0
95th	497.0	850.5	1311.0

Significant differences were detected between and within the three trimesters of pregnancy ($p < 0.001$ by ANOVA test) regarding the mean D-dimer in the table I.

Table II: Regression analysis between D-dimer and gestational age.

	Unstandardized Coefficients		Standardized Coefficients			95.0% Confidence interval for B	
	B*	SE**	Beta	T	P	Lower Bound	Upper Bound
(Constant)	-26.451	23.453		-1.128	0.261	-72.653	19.750
Gestation weeks	28.041	1.006	0.875	27.875	0.000	26.059	30.023

*B: Regression coefficient. **SE: Standard error.

Figure 1: Correlation between D-dimer and gestational age.

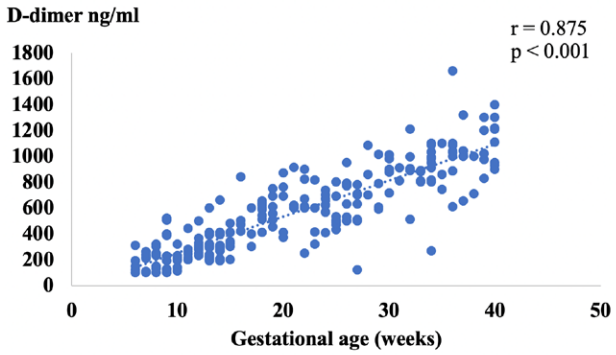


Figure 2: dimer values of pregnant ladies compared with the cut-off point of d dimer of non-pregnant population.

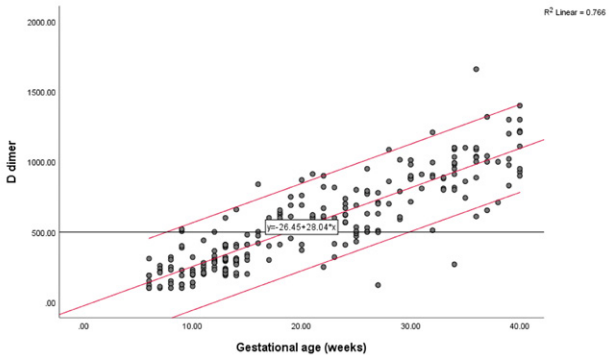


Figure 3: Correlation between the actual and predicted D-dimer.

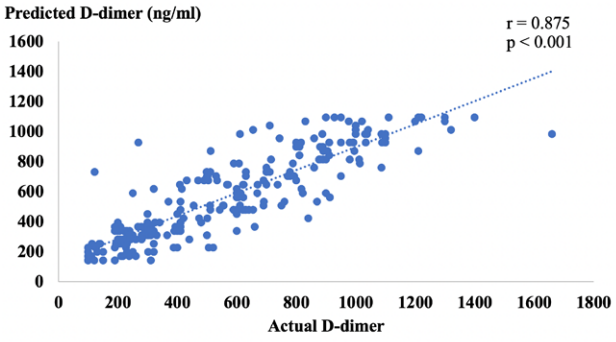
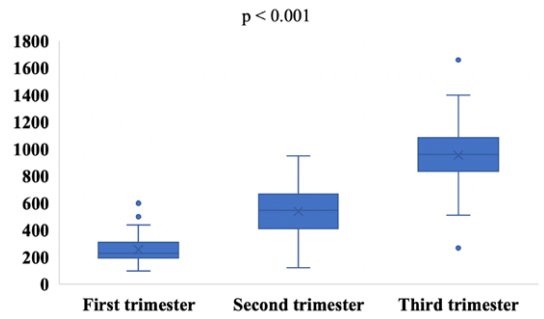


Figure 4: differences between D-dimer means and each trimester of pregnancy, note that all the differences between each two means were significant by LSD post-hoc test.



the late weeks of gestation were above the line. Three slopped lines are present in the mentioned figure, where the line in the middle is the line of the best fit to the points (values). The upper and lower slopped lines represent the 95% confidence interval of the D-dimer readings (**Figure 2**).

- Significant, positive and strong correlation was detected between the actual and the predicted D-dimer (that was calculated according to the equation above) (**Figure 3**).

- The post-hoc test showed also that there were significant differences between each two means. The mean D-dimer of the third trimester was significantly higher than the mean of the second trimester, which was significantly higher than the mean of the first trimester as presented in **figure 4**.

- We also could get the result that there is a relatively weak positive significant correlation was detected between age and D-dimer ($r = 0.384$, $p < 0.001$) if we draw a scatter plot and putting D-dimer (ng/dl) on Y axis while putting age on X axis. Same test done of D-dimer relation with BMI and Parity too which we got the correlation between D-dimer and parity was also relatively weak, positive significant correlation ($r = 0.360$, $p < 0.001$). and positive correlation between d-dimer levels and BMI by which Each point on the graph represents a pregnant woman. The x-axis shows her BMI, and the y-axis shows her D-dimer, The general trend of the data points is upward from left to right. This indicates a positive correlation between BMI and D-dimer levels, greater BMI in women correlates with greater D-dimer levels, while lower BMI correlates with lower levels.

Discussion

Key results

The current study revealed a linear increase in D-dimer levels across the three trimesters of pregnancy and established a new D-dimer reference range for each trimester.

According to other published studies, the D-dimer levels increase linearly during pregnancy[13,11]. However, these elevated levels were comparable to the typical D-dimer levels in nonpregnant women. because D-dimer concentrations increase above the nonpregnant cut-off concentration, it is difficult to diagnose VTE during pregnancy.

In nonpregnant populations, the cut-off value of D-dimer is often less than 500 ng/ml; however, during pregnancy, all of the physiological changes occur throughout the pregnancy and each trimester has its own threshold[13,14,19].

The current study revealed that the 1st trimester 95% CI cut-off was 497, in the second trimester it was 850 and in the 3rd trimester it was 1311. These cut-off values were less than those of other study which was conducted on 71 pregnant women at the Prenatal Research Outpatient Clinic of Obstetrics and Gynecology at the Pomeranian Medical University (PMU) in Szczecin, Poland[14]. but is very similar to the result of research conducted in Türkiye on 460 pregnant women[12].

These variations could be attributable to differences in sample size or regional considerations. This disparity could be attributed to the methodology employed to estimate D-dimer levels.

In this study, the Cobas Roche c111 was utilized, which has a sensitivity of 100%, a specificity of 60%, and a limit of detection of 150 ng/ml. We used this type of device since it is commonly available and inexpensive and was featured in a well-published journal[13,21].

Other procedures such as latex immunology nephelometry[19], ELISA[20], and latex agglutination assay[22] have been used in other studies which will make determining exact cut-off value of each trimester during pregnancy complex worldwide.

Furthermore, there may be different levels in different countries. Therefore, each region should use the same method for laboratory estimation of D-dimer levels and determination of the cut-off value during pregnancy and during each trimester.

We also detected a positive association between D-dimer concentration and BMI, which suggested that D-dimer concentration increases with increasing body mass index. A study was conducted by Nishii A. et al. at the mother and Child Center, Japan, on 1131 women where D-dimer levels were measured throughout the three trimesters, this also build up on obesity complications during pregnancy as it adds increase D-dimer level to long list of (preeclampsia, gestational diabetes, poor birth outcome) as it declares by a study conducted Baftiu et al[28]. The sample was classified into three groups according to BMI: 18.5-24.9, 25-29, and >30[27], and according to the relation between D-dimer and BMI. The mean D-dimer levels were significantly greater in each group than the third trimester[19]. The relationship between D-dimer levels and parity was not particularly strong, as was the case in the study conducted by Wenping Sun et al[26].

Strength and limitations

This is the first study in our locality, and at the same time, this is regarded as a limitation of the study; that is, we cannot generalize the findings. Therefore, in this study, we calculated the D-dimer cut-off point in low-risk pregnant woman. we identified a new cut- off point that is generally physiological and can be used as a

reference for other pregnant people; however, other published articles have mostly compared a control group with another high-risk group to calculate D-dimer levels[23,24,25].

One of the limitations of this study was that it was a cross-sectional study, and a prospective design involving the same pregnant women is more valuable. This design was used because the participants were less likely to volunteer for such a study if it required them to attend follow-up appointments and additional hospital visits. Additionally, this study had a small sample size of 240 women therefore, we recommend conducting this study in other hospitals in the Kurdistan region, and in Iraq as a whole.

Conclusion

A linear increase in D-dimer concentration throughout pregnancy was conducted in a sample of pregnant women in one tertiary care center in the Kurdistan region, Iraq. and a reference interval for D-dimer levels in each trimester of pregnancy was established.

A larger sample size including all the cities in the region is needed to determine the cut-off point for each trimester.

Conflict of interest

The authors declare that they have no conflict of interest.

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Author contributions

All authors contributed to the study conception and design. [LI Adullah]: Material preparation, data collection, and analysis, manuscript writing, drafting of manuscript. [SK Alalaf]: Design of the study, drafting of the study, confirming the last version of the study, the first draft of the manuscript was written by [LI Abdullah] and authors commented on previous version of the manuscript. Both authors read and approved the final manuscript.

References

1. Urato AC, Jaoude EA, Abramson J, Alter H, Andrew LB, Antonuccio D, et al. National Partnership for Maternal Safety: Consensus Bundle on Venous Thromboembolism. Obstet Gynecol 2019;134(5):1115-1117. DOI: 10.1097/AOG.0000000000003540

2. Kearsley R, Stocks G. Venous thromboembolism in pregnancy-diagnosis, management, and treatment. BJA Educ2021; 21(3):117-123. doi:10.1016/j.bjae.2020.10.003.

3. Jackson E, Curtis KM, Gaffield ME. Risk of venous thromboembolism during the postpartum period: a systematic review. Obstet Gynecol 2011 117(3):691-703. doi:10.1097/AOG.0b013e31820ce2db.

4. Langer AL, Connell NT. Update on pregnancy-associated venous thromboembolism. Thromb Update 2022 8:100-107. doi:10.1016/j.tru.2022.100107.

5. Lim W, Le Gal G, Bates SM, Righini M, Haramati LB, Lang E, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: diagnosis of venous thromboembolism. Blood Adv 2018 2(22):3226-3256. doi:10.1182/bloodadvances.2018024828.

6. Hedengran KK, Andersen MR, Stender S, Szecsi PB. Large D-Dimer Fluctuation in Normal Pregnancy: A Longitudinal Cohort Study of 4,117 Samples from 714 Healthy Danish Women. Obstet Gynecol Int 2016:3561675. doi:10.1155/2016/3561675.

7. Koch V, Biener M, Müller-Hennessen M, Vafaie M, Staudacher I, Katus HA, et al. Diagnostic performance of D-dimer in predicting venous thromboembolism and acute aortic dissection. Eur Heart J Acute Cardiovasc Care 2016 10(5):559-66. doi:10.1177/2048872620907322.

8. Bellesini M, Robert-Ebadi H, Combescure C, Dedionigi C, Le Gal G, Righini M. D-dimer to rule out venous thromboembolism during pregnancy: a systematic review and meta-analysis. J Thromb Haemost 2021 19(10):2454-2467. doi:10.1111/jth.15432.

9. Goodacre S, Horspool K, Nelson-Piercy C, Knight M, Shephard N, Lecky F, et al. The DiPEP study: an observational study of the diagnostic accuracy of clinical assessment, D-dimer and chest x-ray for suspected pulmonary embolism in pregnancy and postpartum. BJOG 2019 126(3):383-392. doi:10.1111/1471-0528.15286.

10. Choi H, Krishnamoorthy D. The diagnostic utility of D-dimer and other clinical variables in pregnant and post-partum patients with suspected acute pulmonary embolism. Int J Emerg Med. 2018 ;11(1):10. doi: 10.1186/s12245-018-0169-8.

11. Gutiérrez García I, Pérez Cañadas P, Martínez Uriarte J, García Izquierdo O, Jódar Pérez MA, García de Guadiana Romualdo L. D-dimer during pregnancy: establishing trimester-specific reference intervals. Scandinavian Journal of Clinical and Laboratory Investigation, 2018 78(6), 458-463. https://doi.org/10.1080/00365513.2018.1488177

12. Ercan Ş, Özkan S, Yücel N, Orçun A. Establishing reference intervals for D-dimer to trimesters. J Matern-Fetal Neonatal Med 2014 28(8):983-987. doi:10.3109/14767058.2014.940891

13. Murphy N, Broadhurst D, Khashan A, Gilligan O, Kenny L, O'Donoghue K. Gestation-specific D-dimer reference ranges: a cross-sectional study. BJOG 2014 122(3):395-400. doi:10.1111/1471-0528.12855

14. Siennicka A, Kłysz M, Chełstowski K, Tabaczniuk A, Marcinowska Z, Tarnowska P, et al. Reference Values of D-Dimers and Fibrinogen in the Course of Physiological Pregnancy: the Potential Impact of Selected Risk Factors-A Pilot Study. BioMed Res Int 2020:3192350. doi:10.1155/2020/3192350

15. Board on Children, Youth, and Families; Institute of Medicine; National Research Council. (2013, September 23). An Update on Research Issues in the Assessment of Birth Settings: Workshop Summary. National Academies Press. DOI: 10.17226/18368: doi:10.17226/18368

16. UCSFHealth. (n.d.)(2017) Low-risk pregnancies. https://obgyn.ucsf.edu/sites/obgyn.ucsf.edu/files/UCSF_PregGuidebook_June2017.pdf

17. Chow SC, Shao J, Wang H, Lokhnygina Y. Sample size calculations in clinical research (3rd ed.) 2017. CRC Press

18. American College of Obstetricians and Gynecologists. How your fetus grows during pregnancy. Retrieved January 2020;22, 2024, from https://www.acog.org/womens-health/faqs/how-your-fetus-grows-during-pregnancy

19. Nishi A, Noda Y, Nemoto R, Ushiro K, Ohno T, Mochizuki Y, et al. Evaluation of D-dimer during pregnancy. J Obstet Gynaecol Res2009 35(4):689-93. doi:10.1111/j.1447-0756.2008.01007.x

20. Francalanci I, Comeglio P, Alessandrello Liotta A, Cellai AP, Fedi S, Parretti E, et al. D-Dimer plasma levels during normal pregnancy measured by specific ELISA. International Journal of Clinical & Laboratory Research1997 27, 65-67. Springer-Verlag. doi:10.1007/BF02827245

21. Parammeswaran A, Chappell P, Kulkarani S,Shirley J. Evaluation of an immunoturbidimetric D-dimer assay and pretest probability score for suspected venous thromboembolism in a district hospital setting. Hematology 2009 14(5):305-10. https://doi.org/10.1179/102453309X446162

22. Chan WS, Lee A, Spencer FA, Chunilal S, Crowther M, Wu W, et al. D-dimer testing in pregnant patients: towards determining the next "level" in the diagnosis of venous thrombosis. Journal of Thrombosis and Haemostasis 2010 8(5), 1004-1011. https://doi.org/10.1111/j.1538-7836.2010.03783.x

23. Chen DQ, Cheng E. Correlation between serum D-dimer and risk of gestational diabetes mellitus. Indian J Chem Technol 2022 29(6):805-809.

24. Zaitoun MM, Elbhiedy TM, Alarabi Jama II, Wasfy MA. Study of Plasma D-Dimer Level in Normal Pregnancy and Complicated Pregnancy. Egypt J Hosp Med 2023 90(2):3266-3272. DOI: 10.21608/EJHM.2023.291015

25. Shams N, Taimoor A, Nazir A, Zaman U, Shams H, Javed S. Comparison of d-dimer levels in preeclampsia and normal pregnancy. Pak J Physiol 2022 18(1):20-22. https://pjp.pps.org.pk/index.php/PJP/article/view/1415.

26. Sun W, Zhuang Y, Liu Z, Liu H. Reference intervals for D-dimer and fibrinogen in theChinese population during the third trimester of pregnancy. Clin Exp Obstet Gynecol 48(6):1345-1349. https://doi.org/10.31083/j.ceog4806213

27. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004 10 January;363(9403):157-63

28. Baftiu D, Abazaj E, Shundi L, Nikolla L. Pregnancy obesity, weight gain during pregnancy, and its association with birth outcomes. Academic Journal of Health Sciences: Medicina Balear, 2023 38(1), 139-146. doi: 10.3306/AJHS.2023.38.01.139

29. Abdelmounaim B, Soumia M, Hajar A, Yassine BM, Nadia O, Abdelghafour M. Factors Associated with Perinatal Mortality in Pregnant Women in Marrakech: Case Control Study. Academic Journal of Health Sciences 2023; 38 (6):50-6 doi: 10.3306/ AJHS.2023.38.06.50

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ORIGINAL

Is tumor size a prognostic factor in lymph node-negative stage 1 endometrioid endometrial cancer recurrence?

¿Es el tamaño del tumor un factor pronóstico en la recurrencia del cáncer endometrial endometrioide en estadio 1 con ganglios linfáticos negativos?

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Abstract

Background: To investigate whether tumor size is a prognostic factor in lymph node-negative stage 1 endometrioid-type endometrial cancer recurrence.

Methods: A total of 294 patients diagnosed with stage I (FIGO 2009) endometrioid-type endometrial cancer (EEC) were included in the study. The cases were evaluated in terms of age, histologic grade, tumor diameter, myometrial invasion, lymphovascular space invasion (LVSI), adjuvant radiotherapy, overall (OS) and disease-free (DFS) survival time. The data for the cases were analyzed according to median tumor diameter.

Results: For the 294 patients, the mean age was 63.7±10.0 years. Among patients, 65.3% were ≥60 years, 86.1% were stage 1A, 74.1% were grade 1, 1.7% (5 cases) had malignant peritoneal fluid and 8.5% had LVSI positivity. Recurrence was detected in 21 (7.1%) cases and adjuvant radiotherapy was administered to 36.4% of cases. The median DFS was calculated as 36 months (1-167). OS and DFS durations were 155.1±4.3 and 155.2±4.2 months, respectively. A statistically significant difference was found between 149 patients with median tumor diameter of ≤35 mm and 145 patients with diameter of >35 mm in terms of ≥50% myometrial invasion, grade 2, LVSI positivity, OS and DFS durations (respectively, p=0.001, p=0.001, p=0.014, p=0.021 and p=0.027). In terms of OS and DFS times, only tumor diameter was found to be a significant factor in Cox regression analysis (p=0.039, OR=5.611 95% CI 1.090-28.880 and p=0.044, OR 5.406 95% CI 1.050-27.838). The rates for OS and DFS at 5 years were calculated as 97.6% and 94.9%, respectively.

Conclusions: Median tumor diameter of 35 mm is a prognostic factor in terms of OS and DFS durations in stage 1 endometrioid type endometrial cancer. Myometrial invasion ≥50%, grade 2 and LVSI positivity were significant prognostic factors based on tumor diameter.

Key words: Endometrioid, endometrial cancer, recurrence, tumor size.

Resumen

Antecedentes: Investigar si el tamaño tumoral es un factor pronóstico en la recidiva del cáncer de endometrio de tipo endometrioide en estadio 1 con ganglios linfáticos negativos.

Métodos: Se incluyeron en el estudio un total de 294 pacientes diagnosticadas de cáncer de endometrio de tipo endometrioide (CEE) en estadio I (FIGO 2009). Los casos fueron evaluados en términos de edad, grado histológico, diámetro tumoral, invasión miometrial, invasión del espacio linfovascular (LVSI), radioterapia adyuvante, tiempo de supervivencia global (SG) y libre de enfermedad (SLE). Los datos de los casos se analizaron según la mediana del diámetro tumoral.

Resultados: Para los 294 pacientes, la edad media fue de 63,7±10,0 años. Entre los pacientes, el 65,3% eran ≥60 años, el 86,1% estaban en estadio 1A, el 74,1% eran de grado 1, el 1,7% (5 casos) tenían líquido peritoneal maligno y el 8,5% presentaban positividad de LVSI. Se detectó recurrencia en 21 (7,1%) casos y se administró radioterapia adyuvante al 36,4% de los casos. La mediana de la SSE se calculó en 36 meses (1-167). Las duraciones de la SG y la SSE fueron de 155,1±4,3 y 155,2±4,2 meses, respectivamente. Se encontró una diferencia estadísticamente significativa entre 149 pacientes con diámetro tumoral medio ≤35 mm y 145 pacientes con diámetro >35 mm en términos de ≥50% de invasión miometrial, grado 2, positividad de LVSI, SG y duración de la SSE (respectivamente, p=0,001, p=0,001, p=0,014, p=0,021 y p=0,027). En cuanto a los tiempos de SG y SSE, sólo el diámetro del tumor resultó ser un factor significativo en el análisis de regresión de Cox (p=0,039, OR=5,611 IC 95% 1,090-28,880 y p=0,044, OR 5,406 IC 95% 1,050-27,838). Las tasas de SG y SSE a 5 años se calcularon en 97,6% y 94,9%, respectivamente.

Conclusiones: La mediana del diámetro tumoral de 35 mm es un factor pronóstico en términos de SG y SSE duraciones en el cáncer de endometrio tipo endometrioide en estadio 1. La invasión miometrial ≥50%, el grado 2 y la positividad del LVSI fueron factores pronósticos significativos en función del diámetro tumoral.

Palabras clave: Endometrioide, cáncer de endometrio, recurrencia, tamaño tumoral.

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Introduction

Endometrial cancer (EC) is the most prevalent gynecologic cancer in developed countries[1]. EC is subdivided into two groups by histopathology: estrogen-induced type 1 (grade 1 and 2 EEC) and non-estrogen-induced type 2 EC including non-endometrioid EC and grade 3 EEC[2]. EEC occurs in 75-80% of EC cases[3]. In the International Federation of Gynecology and Obstetrics (FIGO) staging system, <50% myometrial invasion is defined as stage 1A, and ≥50% myometrial invasion is defined as stage 1B EC[4]. Besides, FIGO staging system alone is insufficient for treatment decision in cases diagnosed with stage 1 EEC. According to the guidelines, it is recommended to evaluate risk factors such as age ≥60 years, histological grade, and LVSI during treatment decisions, as well as myometrial invasion. In stage 1A cancer, postoperative observation or brachytherapy is recommended according to risk factors[5]. The National Comprehensive Cancer Network (NCCN) guidelines recommend post-surgical brachytherapy ± external beam radiotherapy or radiotherapy ± chemotherapy treatment in stage 1B cases[5]. Follow-up procedures for adjuvant therapy and EC cases after adjuvant therapy are debatable in the guidelines[6,7].

Recurrence is detected in 5-10% of cases with stage IA grade 1 EEC[8]. Although approximately 75% of cases diagnosed with early stage EC, comparatively early, prognosis can include recurrence in cases treated with surgery and adjuvant therapy[9]. Recurrent cancers lead to a significantly lower survival rate, with 5-year OS falling to 17% for extra pelvic recurrence, and 55% for pelvic recurrence[9].

Studies identified a number of prognostic parameters for survival and recurrence, including histological type, grade, depth of myometrial invasion, LVSI, and stage[10-13]. In addition, different recurrence behavior was demonstrated in cases receiving different radiotherapy modalities[10]. Because early stage EC cases have longer survival time and relapse detection varies significantly over time, assessment of relapse profiles is important for predicting prognosis and guiding surveillance[14]. However, relapse-related risk factors for this group have not yet been identified. Studies about tumor diameter affecting recurrence in low risk stage 1 grade 1 and 2 EEC cases are limited in the literature. Therefore, we aimed to investigate the prognostic effect of tumor size on recurrence of stage 1 grade 1 and 2 EEC.

Materials and Methods

This clinical study was conducted by Selcuk University Faculty of Medicine Ethics Committee on 04.10.2022 with decision numbered 2022/403. Cases diagnosed with stage 1 EEC between December 2010 and January 2022 in Selcuk University Obstetrics and Gynecology Clinic were included. The cases were staged according to the FIGO-2009 classification[4]. Age, FIGO stage, histological grade, myometrial invasion, LVSI, tumor size, DFS and OS times were evaluated statistically. Tumor size was not found to be significant in ROC analysis for the evaluation of recurrence, group distribution was heterogeneous when tumor diameter was taken as 2 cm according to the Mayo criteria, and survival was statistically insignificant. Hence, cases were divided into two groups according to the median value of tumor size. Inclusion criteria included stage 1, grade 1 and 2, and EEC cases. The exclusion criteria were accepted as endometrioid type grade 3, stage 2, 3 and 4 and non-endometrioid EC cases. Probe curettage was performed and imaging methods (computerized tomography, positron emission tomography or magnetic resonance) were used in all cases during preoperative clinical examination.

Standard treatment for early stage EC includes total hysterectomy, bilateral salpingo-oophorectomy, and lymph node dissection, depending on risk factors[15]. OS was defined as time to last follow-up after treatment or death, and DFS as time to diagnosis of post-treatment local recurrence or metastasis. The decision to initiate adjuvant treatment was made by a multidisciplinary council based on international guidelines and treatment included vaginal brachytherapy and/or external beam radiotherapy, and/or chemotherapy[16]. Postoperative check-ups including physical examination and imaging methods (computerized tomography, positron emission tomography-computerized tomography, magnetic resonance, and or ultrasonography) were performed every three months for the first two years, every six months for the next three years, and once a year after five years. Routine follow-up schedules included physical exams, and imaging[17].

Statistical analysis

IBM SPSS Statistics V21.0 (IBM Corporation, Armonk, NY, USA) was used for all statistical data analysis. A number of descriptive features (median, percentage mean, and standard deviation) included in the present study were analyzed with the help of descriptive statistical tests. Mann-Whitney test and Student's t-test were used for non-parametric and parametric continuous variables, respectively. Categorical variables were assessed using Chi-square test or Fisher's Exact test. OS, and DFS were analyzed by the Kaplan-Meier method and differences between OS and DFS were calculated using the log-rank test. Cox regression analysis of HR ratios was performed for variables significant for recurrence. The p value of less than 0.05 was considered statistically significant.

Results

A total of 294 cases were included in the present study and the mean age was 63.7±10.0 years. Of them, 65.3% were≥60 years, 86.1% were stage 1A, 74.1% were grade

1, 1.7% (5 cases) had malignant peritoneal fluid and 8.5% had LVSI positivity. Recurrence was detected in 21 (7.1%) cases and adjuvant radiotherapy was administered in 36.4%. Median follow-up time of cases was calculated as 38 (1-167) months. The median DFS was calculated as 36 months (1-167). OS and DFS were calculated as 155.2±4.2 and 155.1±4.3 months, respectively (**Table I**, **figure 1** and **figure 2**). The median value of tumor diameter for the cases was calculated as 35 mm. There was no significant difference in age, age interval, parity, malignant peritoneal fluid and adjuvant radiotherapy between 149 cases with tumor diameter of ≤35 mm and 145 cases with tumor diameter of >35 mm. However, there was found a statistically significant difference in terms of ≥50% myometrial invasion (p=0.001), grade 2 (p=0.001), LVSI positivity (p=0.004), OS (p=0.021), and DFS (p=0.027) (**Table II**, **figure 3** and **figure 4**).

In the Cox regression analysis for the OS and DFS times, only tumor diameter (≤35 mm and >35 mm) was found to be a significant factor (OS p=0.039, OR=5.611, 95% CI 1.090-28.880 and DFS p=0.044, OR=5.406, 95% CI 1.050-27.838, **table III**). The 5-year DFS and OS rates were calculated as 94.9% and 97.6%, respectively.

Table I: Characteristics of cases with lymphnode negative stage 1 endometrioid type endometrial cancer.

Parameters		(n=294)	%
Age, (year)		63.7±10.0	
Age interval	<60 ≥60	102 192	34.7 65.3
Parity		3 (0-11)	
Stage	IA IB	253 41	86.1 13.9
Grade	1 2	218 76	74.1 25.9
Peritoneum fluid	Malignant Benign	5 289	1.7 98.3
LVSI	Yes No	25 269	8.5 91.5
Tumor size, mm		35 (0-130)	
Tumor interval, mm	≤35 >35	149 145	50.7 49.3
Tumor interval, mm	≥2 < 2	246 48	83.7 16.3
Adjuvant radiotherapy	Yes No	107 187	36.4 63.6
Recurrence	Yes No	21 273	7.1 92.9
DFS, months		155.1±4.3 (146.8-163.5)	
OS, months		155.2±4.2 (147.0-163.5)	

LVIS: Lymphovascular space invasion, **DFS:** Disease-free survival, **OS:** Overall survival.

Table II: Comparison of characteristic factors according to tumor size in cases with stage 1 endometrioid type endometrial cancer.

Parameters		Tumor size ≤35 mm		Tumor size >35 mm		P value
		(n=149)	(%)	(n=145)	(%)	
Age, year		64.1±10.2		63.2±9.8		0.436
Age interval	<60 ≥60	49 100	32.9 67.1	53 92	36.6 63.4	0.295
Parity		3 (0-8)		3 (0-11)		0.975
Myometrial invasion	≤50% >50%	140 9	94.0 6.0	113 32	77.9 22.1	**0.001***
Grade	1 2	123 26	82.6 17.4	95 50	65.5 34.5	**0.001***
Peritoneum fluid	Malignant Benign	2 147	1.3 98.7	3 142	2.1 97.9	0.487
LVSI	Yes No	6 143	4.0 96.0	19 126	13.1 86.9	**0.004***
Adjuvant radiotherapy	Yes No	51 98	34.2 65.8	56 89	38.6 61.4	0.254
DFS, month		161.0±4.3 (152.5-169.4)		122.5±5.0 (112.7-132.4)		**0.027***
OS, month		161.5±4.0 (153.8-169.2)		122.4±5.0 (112.5-132.3)		**0.021***

LVIS: Lymphovascular space invasion, **DFS:** Disease-free survival, **OS:** Overall survival.

Table III: Cox regression analysis of DFS and OS times based on tumor size (≤35 mm vs. >35 mm).

Parameters	DFS				OS			
			95% CI				95% CI	
	P value	OR	Lower	Upper	P value	OR	Lower	Upper
Tumor size (≤35 mm vs>35 mm)	0.044*	5.406	1.050	27.838	0.039*	5.611	1.090	28.880
Myometrial invasion	0.838	0.845	0.168	4.261	0.870	0.873	0.173	4.401
Grade	0.646	0.671	0.123	3.672	0.683	0.704	0.130	3.798
LVSI	0.813	1.311	0.139	12.386	0.847	1.246	0.134	11.537

DFS: Disease-free survival, **OS:** Overall survival, **LVIS:** Lymphovascular space invasion, *A p value less than 0.05 means statistically significant.

Figure 1: Kaplan-Meier analysis for OS in stage 1 endometrioid type endometrial cancer cases.

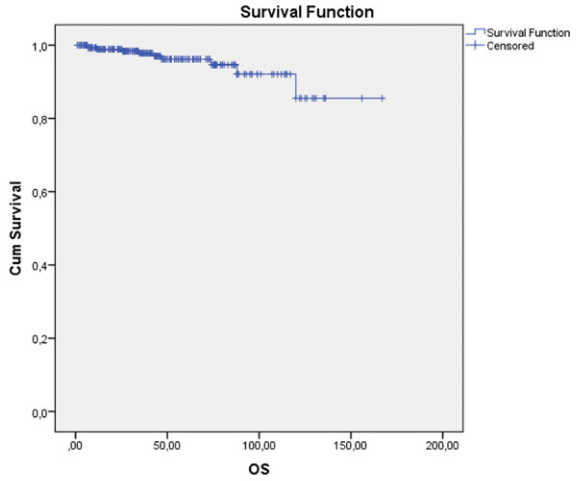


Figure 2: Kaplan-Meier analysis for DFS in stage 1 endometrioid type endometrial cancer cases.

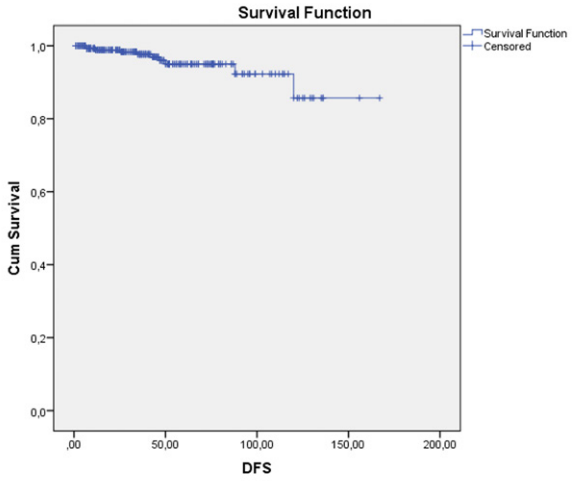


Figure 3: Kaplan-Meier analysis for tumor diameter 35 mm on OS.

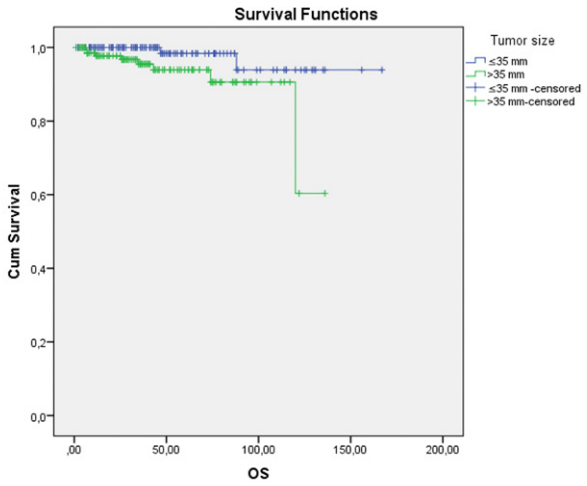
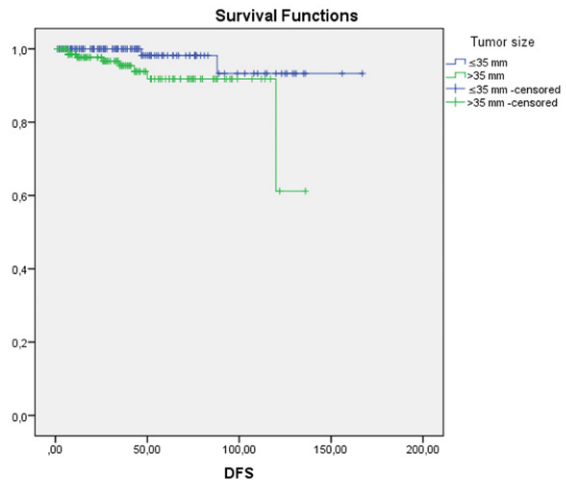


Figure 4: Kaplan-Meier analysis for tumor diameter of 35 mm on DFS



Discussion

Different results were reported in the literature about whether tumor size is a prognostic factor in low risk EEC recurrence. While there are studies showing that it is not a prognostic factor[18-21], there are studies showing that it is a prognostic factor in the opposite direction[22]. In addition, the overall recurrence rate for early stage EC was reported to be approximately 15%[23,24]. However, cases with tumor aggressiveness, various pathological types, and responsiveness to treatment were reported to be heterogeneous, especially in the early stage case group[10,25]. Therefore, we planned to investigate whether tumor size is a prognostic factor in recurrence for low risk EEC cases. In this study, a median tumor diameter of 35 mm was detected to be an independent prognostic

factor in terms of OS and DFS. Myometrial invasion ≥50%, grade 2 and LVSI positivity were evaluated to be significant risk factors for tumor diameter.

Zhu et al.[18] compared two groups with stage 1A, grade 1 and 2, including 1009 cases with EEC tumor diameter ≥2 cm in the intermediate-risk group and 818 cases with tumor diameter of <2 cm in the low risk group. Median recurrence time was recorded as 23 months (5-62) months. The 5-year OS and DFS were calculated as 100% and 95.2%. Ozkan et al.[19] reported median recurrence time of 23 months in a multicenter study of factors associated with survival after relapse in 67 cases diagnosed with low-risk EEC, grade 1, stage 1A, who could only be treated surgically. The 5-year OS rate was 51.2% for loco-regional recurrence and 35.9% for extra pelvic recurrence. Dos Reis et al.[20] including 240 grade 1 and 2, stage 1A cases, recurrence was found at a rate of 5%. Median tumor size was 30 mm (3-160). Imoboden et al.[21] examined stage 1A and 1BEEC in a recurrence group (n=20) and control group (n=21), 41 cases in total, and found mean recurrence of 39.3 months and mean tumor size of 18.6 mm. While no correlation was found between recurrence and tumor size in these four studies, in the study by Nwachukwu et al.[22] about stage IA, grade 1, EEC recurrence risk factors, 205 cases without recurrence and 17 cases with recurrence (7.65%) were compared for a total of 222 cases. Tumor diameter ≥2cm was determined to be a prognostic factor. Median recurrence time was recorded as 15 months. The 5-year OS was calculated as 92%. Nwachukwu et al.[22], similar to this study, showed that a statistically significant difference was found between cases in terms of tumor size for the recurrence of EEC. A total of 294 cases with diagnosis of stage 1 EEC were enrolled in the present study. For median tumor diameter, 149 cases with tumor diameter ≤35 mm and 145 cases with >35 mm tumor diameter were evaluated. The median DFS was calculated as 36 months (1-167). The rates for 5-year OS and DFS were calculated as 97.6% and 94.9%. Differences between the studies may be due to the inclusion of cases in stage 1A and 1B and lymph node negative cases.

The degree of myometrial invasion, which is one of the risk factors for EEC, is used in the staging of EC[4]. The relationship between tumor diameter with myometrial invasion, tumor grade and LVSI positivity was evaluated in studies. Myometrial invasion was a significant factor according to tumor size in the studies by Zhu et al.[18] and Nwachukwu et al.[22], while a significant correlation was found between tumor size and myometrial invasion in this study as well.

While a significant relationship was found in terms of tumor diameter and tumor grade in the study by Zhu et al.[18], it was found to be insignificant in the study by Ozkan et al[19]. In present study, a significant correlation was found between tumor diameter and tumor grade. The relationship between LVSI and tumor diameter was a significant factor in the study by Zhu et al.[18] but not in the study by Nwachukwu et al[22]. In present study, there was a significant correlation between tumor size and LVSI. Differences in studies may be due to the design of the studies and differences in the groups.

In terms of tumor recurrence, Ozkan et al.[19], Dos Reis et al.[20] and Imoboden et al.[21] found no significant difference in histologic grades 1 and 2. Similarly, no significant difference was found in terms of grade in present study. In the study by Dos Reis et al.[20] and Imoboden et al.[21], there was a significant difference in the presence of LVSI in terms of DFS. Contrary to this, no significant difference was found in the study by Ozkan et al.[19] and Nwachukwu et al[22]. Similarly, no significant difference was found in terms of the presence of LVSI in this study. While Nwachukwu et al.[22] showed that myometrial invasion was a significant factor, contrarily, Imoboden et al.[21] found that myometrial invasion was not a significant factor. In the present study, myometrial invasion was not found to be significant.

Limitations

The limitations of the study are that it was retrospective, the number of cases was low, and the size of the preoperative tumor was unknown. Pathological assessment of tumor size and exclusion of positive lymph node cases are the strengths of this study. The study is also important in evaluating the relationship between tumor size with histological grade, myometrial invasion and LVSI in stage 1 EEC.

Conclusion

Median tumor diameter of 35 mm is a prognostic factor in terms of DFS and OS in stage 1 EEC. Myometrial invasion, grade and LVSI positivity are significant prognostic factors based on tumor diameter. Future studies may be helpful for the management of low-risk EEC cases.

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Conflict of interests

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References

1. Yaminifar L, Altisench-Jané, Tárraga-López PJ, Doudaran PJ, Endo-Milan JY, Hivechi N. A review on endometrial cancer; artificial intelligence, imaging modalities. Academic Journal of Health Sciences Medicina Balear 2022;37(3):102-7.

2. Felix AS, Weissfeld JL, Stone RA, Bowser R, Chivukula M, Edwards RP, Linkov F. Factors associated with Type I and Type II endometrial cancer. Cancer Causes Control. 2010 Nov;21(11):1851-6.

3. Kurman RJ, Carcangiu ML, Young RH, Herrington CS. WHO classification of tumours of female reproductive organs International Agency for Research on Cancer. World Health Organization Lyon: International Agency for Research on Cancer. 2014: 126-8.

4. Pecorelli S. Revised FIGO staging for carcinoma of the vulva and endometrium. Int J Gynaecol Obstet Off Organ Int Fed Gynaecol Obstet. 2009;105(2):103–4. https://doi.org/10.1016/j.ijgo.2009.02.012. Erratum in: Int J Gynaecol Obstet. 2010;108(2):176.

5. National Comprehensive Cancer Network. Uterine Neoplasms, Version 1.2021. https://www.nccn.org/professionals /physician_gls/pdf/uterine. pdf (2021.01.10).

6. Fung-Kee-Fung M, Dodge J, Elit L, Lukka H, Chambers A, Oliver T. Cancer Care Ontario Program in Evidence-based Care Gynecology Cancer Disease Site Group. Follow-up after primary therapy for endometrial cancer: a systematic review. Gynecol Oncol. 2006;101(3):520-9.

7. Concin N, Matias-Guiu X, Vergote I, Cibula D, Mirza MR, Marnitz S, et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Int J Gynecol Cancer. 2021 Jan;31(1):12-39. doi: 10.1136/ijgc-2020-002230.

8. Esselen KM, Boruta DM, del Carmen M, Schorge JO, Goodman A, Growdon WB. Defining prognostic variables in recurrent endometrioid endometrial cancer: a 15-year single-institution review. Int J Gynecol Cancer 2011;21:1078-83.

9. Connor EV, Rose PG. Management Strategies for Recurrent Endometrial Cancer. Expert Rev Anticancer Ther. 2018;18(9):873-885.

10. Xiang M, Kidd EA. Survival benefit of radiation in high-risk, early-stage endometrioid carcinoma. J Gynecol Oncol. 2020;31(4):e39.

11. Bendifallah S, Ouldamer L, Lavoue V, Canlorbe G, Raimond E, Coutant C, et al. Patterns of recurrence and outcomes in surgically treated women with endometrial cancer according to ESMO-ESGO-ESTRO Consensus Conference risk groups: Results from the FRANCOGYN study Group. Gynecol Oncol. 2017 Jan;144(1):107-112. doi: 10.1016/j.ygyno.2016.10.025.

12. Nomura H, Aoki D, Susumu N, Mizuno M, Nakai H, Arai M, et al. Analysis of the relapse patterns and risk factors of endometrial cancer following postoperative adjuvant chemotherapy in a phase III randomized clinical trial. Gynecol Oncol. 2019 Dec;155(3):413-419. doi: 10.1016/j.ygyno.2019.09.023.

13. Dabi Y, Uzan J, Bendifallah S, Ouldamer L, Lavoué V, Canlorbe G, et al. Prognostic value of local relapse for patients with endometrial cancer. Eur J Surg Oncol. 2017 Nov;43(11):2143-2149. doi: 10.1016/j.ejso.2017.08.004.

14. Hunn J, Tenney ME, Tergas AI, Bishop EA, Moore K, Watkin W, et al. Patterns and utility of routine surveillance in high grade endometrial cancer. Gynecol Oncol. 2015 Jun;137(3):485-9. doi: 10.1016/j.ygyno.2015.03.047. Gynecol Oncol. 2015;137(3):485-9.

15. Abu-Rustum N, Yashar C, Arend R, Barber E, Bradley K, Brooks R, et al. Uterine Neoplasms, Version 1.2023, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2023 Feb;21(2):181-209. doi: 10.6004/jnccn.2023.0006.

16. Colombo N, Preti E, Landoni F, Carinelli S, Colombo A, Marini C, et al. Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2011 Sep;22 Suppl 6:vi35-9. doi: 10.1093/annonc/mdr374.

17. Koh WJ, Abu-Rustum NR, Bean S, Bradley K, Campos SM, Cho KR, et al. Uterine Neoplasms, Version 1.2018, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2018;16(2):170-99.

18. Zhu M, Jia N, Huang F, Liu X, Zhao Y, Tao X, et al. Whether intermediate-risk stage 1A, grade 1/2, endometrioid endometrial cancer patients with lesions larger than 2 cm warrant lymph node dissection? BMC Cancer. 2017 Oct 23;17(1):696. doi: 10.1186/s12885-017-3671-0.

19. Topfedaisi Ozkan N, Meydanlı MM, Sarı ME, Demirkiran F, Kahramanoglu I, Bese T, et al. Factors associated with survival after relapse in patients with low-risk endometrial cancer treated with surgery alone. J Gynecol Oncol. 2017;28(5):e65.

20. dos Reis R, Burzawa JK, Tsunoda AT, Hosaka M, Frumovitz M, Westin SN, et al. Lymphovascular Space Invasion Portends Poor Prognosis in Low-Risk Endometrial Cancer. Int J Gynecol Cancer. 2015 Sep;25(7):1292-9. doi: 10.1097/IGC.0000000000000490.

21. Imboden S, Tapia C, Scheiwiller N, Kocbek V, Altermatt HJ, Janzen J, et al. Early-stage endometrial cancer, CTNNB1 mutations, and the relation between lymphovascular space invasion and recurrence. Acta Obstet Gynecol Scand. 2020 Feb;99(2):196-203. doi: 10.1111/aogs.13740.

22. Nwachukwu C, Baskovic M, Von Eyben R, Fujimoto D, Giaretta S, English D, et al. Recurrence risk factors in stage IA grade 1 endometrial cancer. J Gynecol Oncol. 2021 Mar;32(2):e22. doi: 10.3802/jgo.2021.32.e22.

23. Francis SR, Ager BJ, Do OA, Huang YJ, Soisson AP, Dodson MK, et al. Recurrent early stage endometrial cancer: Patterns of recurrence and results of salvage therapy. Gynecol Oncol. 2019 Jul;154(1):38-44. doi: 10.1016/j.ygyno.2019.04.676.

24. Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Wárlám-Rodenhuis CC, et al. Survival after relapse in patients with endometrial cancer: results from a randomized trial. Gynecol Oncol. 2003 May;89(2):201-9. doi: 10.1016/s0090-8258(03)00126-4.

25. Li L, Pan M, Chen L. Spontaneous hemoperitoneum during pregnancy: three case reports and literature review. Cir Cir. 2023;91(3):422-426.

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ORIGINAL

Effectiveness of Super Brain Yoga Practice Timing on Stress, Anxiety, and Aggression Levels among College Students: A Randomized Controlled Trial

Eficacia de la sincronización de la práctica de Super Brain Yoga en los niveles de estrés, ansiedad y agresividad entre estudiantes universitarios: Un ensayo controlado aleatorizado

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Abstract

Background and Aim: Yoga, an ancient practice originating from the Indian subcontinent, has gained global recognition for its holistic approach to well-being. Super Brain Yoga (SBY), a specialized form of yoga focusing on cognitive enhancement, presents a promising avenue for addressing mental health concerns, particularly among college students. The aim of this study was to investigate the impact of SBY practice timing on stress, anxiety, and aggression levels in college students, thereby contributing to the growing body of evidence supporting yoga-based interventions for mental well-being.

Material and Methods: Sixty male students aged 18-23 from SRM Institute of Science and Technology, Tamil Nadu, were randomly assigned to three groups: Morning (GI), Evening (GII), and Control (GIII). Pre- and post-tests were conducted using standardized psychological questionnaires to assess stress, anxiety, and aggression levels. The experimental groups underwent twelve weeks of SBY training, while the control group maintained their regular routine. Statistical analysis was performed using Analysis of Covariance (ANCOVA) to compare pretest and post-test scores among the groups, adjusting for baseline differences. Scheffe's post-hoc test determined the significance of paired mean differences.

Results: Significant reductions in stress, anxiety, and aggression levels were observed in both Morning and Evening SBY groups compared to controls. Participants in the Morning group exhibited decreased stress from 26.73 to 22.47, anxiety from 45.80 to 42.00, and aggression from 83.07 to 77.73. Similarly, the Evening group showed reductions in stress from 25.73 to 22.87, anxiety from 46.00 to 42.60, and aggression from 82.40 to 77.80. The control group displayed minimal changes.

Conclusions: Super Brain Yoga practice, regardless of timing, significantly reduced stress, anxiety, and aggression levels among college students. These results highlight the potential of SBY as an accessible and effective intervention for enhancing mental health in educational settings. Integrating SBY into college curricula could provide students with valuable tools for managing psychological challenges and improving overall well-being.

Key words: Super Brain Yoga, stress, anxiety, aggression, college students, mental well-being.

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Resumen

Antecedentes y objetivo: El yoga, una antigua práctica originaria del subcontinente indio, ha ganado reconocimiento mundial por su enfoque holístico del bienestar. El Super Brain Yoga (SBY), una forma especializada de yoga centrada en la mejora cognitiva, presenta una vía prometedora para abordar los problemas de salud mental, especialmente entre los estudiantes universitarios. El objetivo de este estudio fue investigar el impacto del tiempo de práctica de SBY en los niveles de estrés, ansiedad y agresión en estudiantes universitarios, contribuyendo así al creciente cuerpo de evidencia que apoya las intervenciones basadas en el yoga para el bienestar mental.

Material y métodos: Sesenta estudiantes varones de entre 18 y 23 años del Instituto de Ciencia y Tecnología SRM, Tamil Nadu, fueron asignados aleatoriamente a tres grupos: Matutino (GI), Vespertino (GII) y Control (GIII). Se realizaron pruebas previas y posteriores utilizando cuestionarios psicológicos estandarizados para evaluar los niveles de estrés, ansiedad y agresividad. Los grupos experimentales se sometieron a doce semanas de entrenamiento SBY, mientras que el grupo de control mantuvo su rutina habitual. El análisis estadístico se llevó a cabo mediante un análisis de covarianza (ANCOVA) para comparar las puntuaciones de los grupos antes y después de la prueba, ajustando las diferencias iniciales. La prueba post-hoc de Scheffe determinó la significación de las diferencias de medias emparejadas.

Resultados: Se observaron reducciones significativas en los niveles de estrés, ansiedad y agresividad en los grupos de SBY matutino y vespertino en comparación con los controles. Los participantes del grupo Matinal mostraron una disminución del estrés de 26,73 a 22,47, de la ansiedad de 45,80 a 42,00 y de la agresividad de 83,07 a 77,73. Del mismo modo, el grupo de la tarde mostró una reducción del estrés de 25,73 a 22,87, de la ansiedad de 46,00 a 42,60 y de la agresividad de 82,40 a 77,80. El grupo de control mostró cambios mínimos. El grupo de control mostró cambios mínimos.

Conclusiones: La práctica de Super Brain Yoga, independientemente del momento, redujo significativamente los niveles de estrés, ansiedad y agresión entre los estudiantes universitarios. Estos resultados destacan el potencial del SBY como una intervención accesible y eficaz para mejorar la salud mental en entornos educativos. La integración del SBY en los planes de estudios universitarios podría proporcionar a los estudiantes herramientas valiosas para gestionar los retos psicológicos y mejorar el bienestar general.

Palabras clave: Super Brain Yoga, estrés, ansiedad, agresión, estudiantes universitarios, bienestar mental.

Introduction

Yoga, an ancient practice originating from the Indian subcontinent, has transcended cultural boundaries to become a global phenomenon celebrated for its profound impact on physical, mental, and spiritual well-being[1]. Among the myriad forms of yoga, Super Brain Yoga (SBY) stands out as a practice specifically tailored to enhance cognitive functioning and mental clarity. Rooted in the wisdom of ancient yogic traditions, SBY offers a unique approach to nurturing the mind, body, and spirit[2,3]. The essence of yoga lies in its holistic philosophy of unity – the union of body, mind, and spirit. Derived from the Sanskrit word "Yuj," meaning to join or unite, yoga embodies a harmonious integration of physical postures (asanas), breath control (pranayama), and meditation (dhyana) to cultivate a state of balance and harmony within oneself and with the universe. In the Bhagavad Gita, a revered Hindu scripture, yoga is elucidated as the attainment of equilibrium – a balanced state of being where the individual aligns with the cosmic order, transcending the confines of the egoic mind[1,4,5].

SBY, as a subset of yoga, delves into the intricacies of mental cultivation, emphasizing the optimization of cognitive faculties for enhanced mental acuity and emotional stability. Unlike conventional yoga practices that encompass a broader spectrum of physical, mental, and spiritual dimensions, SBY zooms in on the cognitive aspect, offering a targeted approach to mental well-being. The genesis of SBY can be traced back to ancient yogic texts and oral traditions, where sages and seers elucidated the intricate connections between body, mind, and consciousness[6]. Drawing inspiration from these timeless teachings, SBY encapsulates a simple yet potent technique that harnesses the body's energy flow to stimulate the brain's cognitive functions. At its core, SBY involves a series of physical movements combined with specific breath control and mental focus. The practice typically begins with a preparatory phase, wherein practitioners assume a squatting position and engage in controlled breathing exercises. The key elements of SBY include hand placements on the earlobes, tongue placement on the upper palate, and contraction of the perineum muscles – all synchronized with inhalation and exhalation[4,7].

The rationale behind SBY lies in its ability to facilitate the circulation of subtle energy (prana) within the body, particularly towards the brain's frontal lobes – the seat of higher cognitive functions such as concentration, memory, and emotional regulation. By channeling pranic energy through specific energy pathways (nadis) and energy centers (chakras), SBY aims to optimize neuronal connectivity and neurotransmitter balance, thereby enhancing overall cognitive performance. The benefits of SBY extend beyond cognitive enhancement to encompass emotional resilience, stress reduction, and mental clarity. In an age marked by pervasive stressors and cognitive overload, SBY offers a sanctuary for the mind – a sanctuary wherein individuals can cultivate inner peace, clarity of thought, and emotional equilibrium amidst life's myriad challenges[8,9].

As the prevalence of mental health disorders continues to rise globally, there is a growing recognition of the importance of holistic approaches to mental well-being. While conventional interventions such as medication and psychotherapy play a crucial role in addressing mental health concerns, complementary practices like SBY offer a valuable adjunctive tool for promoting resilience, self-awareness, and self-regulation[3,10]. Against this backdrop, this study seeks to explore the impact of SBY on psychological parameters among college students, focusing specifically on stress, anxiety, and aggression. By elucidating the effects of SBY on these key variables, we aim to contribute to the growing body of evidence supporting the efficacy of yoga-based interventions in enhancing mental health and well-being. SBY represents a fusion of ancient wisdom and modern science – a testament to the enduring relevance of yogic teachings in the contemporary world. As we embark on this journey of exploration, let us delve deeper into the transformative potential of SBY and its capacity to awaken the latent powers of the human mind[11,12,13].

Purpose of the research study: The aim of this study was to investigate the impact of Super Brain Yoga's practice timing on stress, anxiety, and aggression levels in college students, thereby contributing to the growing body of evidence supporting yoga-based interventions for mental well-being.

Materials and methods

Participants

Sixty male students, aged 18-23, from various departments of the SRM Institute of Science and Technology, Tamil Nadu, were randomly selected. They were divided into three groups of 20 participants: Experimental Group I (Super Brain Yoga practice in the morning), Experimental Group II (Super Brain Yoga practice in the evening), and Control Group (no intervention).

Procedure

A true random group design was employed, with pretests conducted on all subjects using standardized psychological questionnaires to assess stress, anxiety, and aggression levels. Experimental groups underwent twelve weeks of Super Brain Yoga training, while the control group maintained their regular routine. Post-tests were administered immediately following the trial period. Stress was assessed using the Perceived Stress Scale, anxiety using Spielberger's Trait Anxiety questionnaire, and aggression using Buss and Perry's aggression questionnaire[14,15,16].

Statistical Analysis

Analysis of covariance (ANCOVA) was utilized to compare pretest and post-test scores among the groups, adjusting for baseline differences. Scheffe's post-hoc test was employed to determine the significance of paired mean differences if the adjusted post-test results were significant. This statistical approach allowed for the evaluation of the effects of different Super Brain Yoga practice timings on stress, anxiety, and aggression levels among college students.

Results

The **table I** presents the effects of Super Brain Yoga (SBY) on stress levels among participants in three different groups: Morning (GI), Evening (GII), and Control Group (GIII). Before the intervention, the mean stress levels were relatively similar across all groups, ranging from 25.40 to 26.73. The variance between these groups was statistically significant ($F = 2.44$, $p < 0.05$). After the intervention, noticeable reductions in stress levels were observed in both the Morning and Evening groups, with post-test means of 22.47 and 22.87, respectively. In contrast, the Control Group's stress levels remained relatively unchanged, with a post-test mean of 24.60. The differences in post-test means were statistically significant ($F = 13.12$, $p < 0.05$). The adjusted post-test means, which consider covariates, further support the significant reduction in stress levels in both the Morning and Evening groups compared to the Control Group ($F = 11.84$, $p < 0.05$) (**Table I**).

Table II displays the impact of practicing Super Brain Yoga in the morning (GI) versus evening (GII) on anxiety levels among participants, compared to a Control Group (GIII), analyzed using Analysis of Covariance (ANCOVA). Before the intervention, the mean anxiety scores were 45.80 for the Morning group, 46.00 for the Evening group, and 46.26 for the Control group. The between-group variance was 9.25, indicating no significant difference in pre-test anxiety levels among the groups (F-ratio = 1.42, $p > 0.05$). The standard deviations within groups ranged from 1.39 to 1.57, suggesting similar variability in pre-test anxiety levels across all groups. After the intervention, the mean anxiety scores decreased to 42.00 for the Morning group, 42.60 for the Evening group, and 45.47 for the Control group. The between-group variance significantly differed at 158.83 (F-ratio = 26.17, $p < 0.05$), indicating a notable impact of Super Brain Yoga practice timing on post-test anxiety levels.

The adjusted post-test mean anxiety scores, accounting for pre-test differences, were 42.00 for the Morning group, 42.60 for the Evening group, and 45.07 for the Control group. The between-group variance remained significant at 117.40 (F-ratio = 21.51, $p < 0.05$), reaffirming the efficacy of Super Brain Yoga practice timing in reducing anxiety levels (**Table II**).

Table III presents the influence of practicing Super Brain Yoga in the morning (GI) versus evening (GII) on aggression levels among participants, compared to a Control Group (GIII), and analyzed using Analysis of

Table I: Effects of super brain yoga practice timing on stress levels among participants using analysis of covariance (ANCOVA).

	Morning (GI)	Evening (GII)	Control Group (GIII)	Sources of Variance	Sum of Squares	Degrees of Freedom	Mean Squares	F – Ratio
Pre Test Mean	26.73	25.73	25.40	Between	14.45	3	4.82	
Standard Deviation	1.39	1.33	1.50	Within	110.40	56	1.97	2.44
Post Test Mean	22.47	22.87	24.60	Between	91.93	3	30.64	
Standard Deviation	1.51	1.51	1.91	Within	130.80	56	2.34	13.12*
Adjusted Post Test Mean	22.46	22.86	24.35	Between	76.467	3	25.49	11.84*

Table II: Effects of super brain yoga practice timing on anxiety levels among participants using analysis of covariance (ANCOVA).

	Morning (GI)	Evening (GII)	Control Group (GIII)	Sources of Variance	Sum of Squares	Degrees of Freedom	Mean Squares	F – Ratio
Pre Test Mean	45.80	46.00	46.26	Between	9.25	3	3.08	
Standard Deviation	1.57	1.56	1.39	Within	121.73	56	2.17	1.42
Post Test Mean	42.00	42.60	45.47	Between	158.83	3	52.84	
Standard Deviation	1.31	1.50	1.51	Within	113.07	56	2.02	26.17*
Adjusted Post Test Mean	42.00	42.60	45.07	Between	117.40	3	39.13	21.51*

Table III: Effects of super brain yoga practice timing on aggression levels among participants using analysis of covariance (ANCOVA).

	Morning (GI)	Evening (GII)	Control Group (GIII)	Sources of Variance	Sum of Squares	Degrees of Freedom	Mean Squares	F – Ratio
Pre Test Mean	83.07	82.40	81.00	Between	36.07	3	12.02	
Standard Deviation	2.91	2.82	2.80	Within	455.87	56	8.14	1.48
Post Test Mean	77.73	77.80	80.86	Between	172.18	3	57.39	
Standard Deviation	3.08	2.65	2.69	Within	457.47	56	8.17	7.02*
Adjusted Post Test Mean	77.73	77.80	80.57	Between	142.77	3	47.59	5.9*

Covariance (ANCOVA). Prior to the intervention, the mean aggression scores were 83.07 for the Morning group, 82.40 for the Evening group, and 81.00 for the Control group. The between-group variance was 36.07, indicating no significant difference in pre-test aggression levels among the groups (F-ratio = 1.48, $p > 0.05$). The standard deviations within groups ranged from 2.80 to 2.91, suggesting similar variability in pre-test aggression levels across all groups. After the intervention, the mean aggression scores decreased to 77.73 for the Morning group, 77.80 for the Evening group, and 80.86 for the Control group. The between-group variance significantly differed at 172.18 (F-ratio = 7.02, $p < 0.05$), indicating a notable impact of Super Brain Yoga practice timing on post-test aggression levels. The adjusted post-test mean aggression scores, considering pre-test differences, were 77.73 for the Morning group, 77.80 for the Evening group, and 80.57 for the Control group. The between-group variance remained significant at 142.77 (F-ratio = 5.9, $p < 0.05$), suggesting that Super Brain Yoga practice timing contributes to reducing aggression levels compared to the Control group (**Table III**).

Discussion

The study investigated the effects of Super Brain Yoga practice timing on stress, anxiety, and aggression levels among college students. Results from the analysis of covariance (ANCOVA) revealed significant differences in post-test scores among the Morning (GI), Evening (GII), and Control Group (GIII) across all three psychological variables.

In terms of stress levels, both Morning and Evening Super Brain Yoga practices led to significant reductions compared to the Control Group. Participants in the Morning group showed a decrease from a pre-test mean of 26.73 to a post-test mean of 22.47, while those in the Evening group decreased from 25.73 to 22.87. The Control Group, however, exhibited a slight increase in stress levels from 25.40 to 24.60. These findings suggest that Super Brain Yoga practice, regardless of timing, effectively mitigated stress among college students [9,17]. Similarly, the study found notable decreases in anxiety levels following Super Brain Yoga practice. Both Morning and Evening groups showed significant reductions in anxiety compared to the Control Group. The Morning group decreased from a pre-test mean of 45.80 to a post-test mean of 42.00, and the Evening group decreased from 46.00 to 42.60. In contrast, the Control Group exhibited a smaller reduction from 46.26 to 45.47. These results underscore the beneficial impact of Super Brain Yoga practice on alleviating anxiety among college students[18]. Regarding aggression levels, participants in both Morning and Evening Super Brain Yoga groups demonstrated significant decreases compared to the Control Group. The Morning group decreased from a pre-test mean of 83.07 to a post-test mean of 77.73, and the Evening

group decreased from 82.40 to 77.80. Conversely, the Control Group's aggression levels increased slightly from 81.00 to 80.86. These findings indicate that Super Brain Yoga practice timing plays a crucial role in reducing aggression among college students[1,19].

The study provides empirical evidence supporting the effectiveness of Super Brain Yoga in reducing stress, anxiety, and aggression levels among college students. Both Morning and Evening practice timings yielded positive outcomes, highlighting the versatility and accessibility of this intervention for promoting mental well-being. These findings have significant implications for implementing Super Brain Yoga practices in educational settings to support students' psychological health and academic success[20,21]. Further research could explore the long-term effects and mechanisms underlying the observed improvements to enhance our understanding of Super Brain Yoga's therapeutic potential[22,23,24].

Conclusions

This study demonstrates the effectiveness of Super Brain Yoga in reducing stress, anxiety, and aggression levels among college students. Both Morning and Evening practice timings yielded significant improvements, highlighting the potential of this intervention for enhancing mental well-being. These findings underscore the importance of integrating yoga-based practices into educational settings to support students' psychological health.

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Conflict of Interest Statement

The authors declare no conflict of interest regarding the publication of this study.

References

1. Cerdá A, Boned-Gómez S, Baena-Morales S. Exploring the mind-body connection: Yoga, mindfulness, and mental well-being in adolescent physical education. Education Sciences. 2023; 13 (11):1104. doi.org/10.3390/educsci13111104

2. Nemeroff R, Harden A, Kowalsky B. Yoga classes as an early intervention for college students reporting high levels of stress and anxiety: A pilot study. Journal of American College Health. 2024;72(1):4-10. doi.org/10.1080/07448481.2021.2008401

3. Akdeniz Ş, Kaştan Ö. Perceived benefit of yoga among adults who have practiced yoga for a long time: A qualitative study. BioPsychoSocial Medicine. 2023;17(19):1-10. doi.org/10.1186/s13030-023-00276-3

4. Jois SN, D'Souza L, Moulya R. Beneficial effects of super brain yoga on short-term memory and selective attention of students. Indian Journal of Traditional Knowledge. 2017; 16 (Suppl): S35–S39.

5. Farahani PV, Hekmatpou D, Khonsari AH, Gholami M. Effectiveness of super brain yoga for children with hyperactivity disorder. Perspectives in Psychiatric Care. 2019; 55(2): 140–146. doi.org/10.1111/ppc.12266

6. Murat ZH, Muhsin AFM, Kadir RSA, Ahmad FH. Intervention of super brain yoga towards brainwave balancing index, brainwave dominance and short term memory. AIP Conference Proceedings, 2306, 020037. 2020. doi.org/10.1063/5.0033359

7. Premalatha BR, Sudhir J, Hegde U, Sreeshyla HS, Chandavarkar V, Mishra MN. Effectiveness of super brain asana on the academic performance in dental students -an interventional study. Journal of Natural Remedies. 2021; 21(4): 291–295. doi.org/10.18311/jnr/2021/25874

8. Thomas JI, & Venkatesh D. A comparative study of the effects of superbrain yoga and aerobic exercise on cognitive functions. National Journal of Physiology, Pharmacy and Pharmacology. 2017; 7(9): 895–900. doi.org/10.5455/njppp.2017.7.0309126062017

9. Zoogman S, Goldberg SB, Vousoura E, Diamond MC, Miller L. Effect of yoga-based interventions for anxiety symptoms: A meta-analysis of randomized controlled trials. Spiritual Clinical Practice. 2019; 6(4): 256–278. doi.org/10.1037/scp0000202

10. Abbouyi S, Bouazza S, El Kinany S, El Rhazi A, Zarrouq B. Depression and anxiety and its association with problematic social media use in the MENA region: A systematic review. Egypt Journal of Neurology Psychiatry Neurosurgery 2024; 60(15) doi.org/10.1186/s41983-024-00793-0

11. Vuelvas-Olmos CR, Sánchez-Vidaña DI, Cortés-Álvarez NY. Gender-Based Analysis of the Association between Mental Health, Sleep Quality, Aggression, and Physical Activity among University Students during the COVID-19 Outbreak. 2023; Psychological Reports, 126(5), 2212–2236. doi.org/10.1177/00332941221086209

12. Bentley TGK, D'Andrea-Penna G, Rakic M, Arce N, LaFaille M, Berman R, et al. Breathing practices for stress and anxiety reduction: Conceptual framework of implementation guidelines based on a systematic review of the published literature. Brain Sciences. 2023; 13(12): 1612. doi.org/10.3390/brainsci13121612

13. Michl LC, McLaughlin KA, Shepherd K, Nolen-Hoeksema S. Rumination as a mechanism linking stressful life events to symptoms of depression and anxiety: Longitudinal evidence in early adolescents and adults. Journal of Abnormal Psychology. 2013; 122(2): 339–352. doi.org/10.1037/a0031994

14. Reyna C, Ivacevich MGL, Sanchez A, Brussino S. The buss-perry aggression questionnaire: Construct validity and gender invariance among Argentinean adolescents. International Journal of Psychological Research. 2011; 4(2): 30–37. doi.org/10.21500/20112084.775

15. Gubac DB, Foster KM. Is practicing yoga an effective alternative treatment for anxiety. Evidence-Based Practice. 2023; 26(12): 23–24. doi.org/10.1097/EBP.0000000000001913

16. Barnes LLB, Harp D, Jung WS. Reliability generalization of scores on the Spielberger State-Trait Anxiety Inventory. Educational Psychology Measurement. 2002; 62(4): 603–618. doi.org/10.1177/0013164402062004005

17. Ibrahim D, Ahmed RM, Mohammad AZ, Ibrahim B, Mohammed T, Mohamed ME, et al. Prevalence and correlates of generalized anxiety disorder and perceived stress among Sudanese medical students. BMC Psychiatry.2024; 24(68) doi.org/10.1186/s12888-024-05510-y

18. Theobald M, Breitwieser J, Brod G. Test anxiety does not predict exam performance when knowledge is controlled for: Strong evidence against the interference hypothesis of test anxiety. Psychological Science. 2022; 33(12): 2073–2083. doi.org/10.1177/09567976221119391

19. Sundstrom MJ, Asplund AL, Nguyen-Feng VN. Evaluation of online adaptive yoga for psychological well-being in adults with disabilities. Rehabilitation Psychology. 2024; 69(1): 55–60. doi.org/10.1037/rep0000520

20. Nemeroff R, Harden A, Kowalsky B. Yoga classes as an early intervention for college students reporting high levels of stress and anxiety: A pilot study. Journal of American College Health. 2024; 2(1): 4–10. doi.org/10.1080/07448481.2021.2008401

21. Kanchibhotla D, Gupte P, Harsora P, Kulkarni S. Impact of Prajñā yoga on cognition in adolescents with congenital and adventitious visual impairment. EXPLORE. 2022 May-Jun; 18 (3):313-318. doi.org/10.1016/j.explore.2021.05.010

22. Haverkamp B, Wiersma R, Vertessen K, van Ewijk H, Oosterlaan J, Hartman, E. Effects of physical activity interventions on cognitive outcomes and academic performance in adolescents and young adults: A meta-analysis. Journal of Sports Sciences.2020; 38(23): 2637–2660. doi.org/10.1080/02640414.2020.1794763

23. Ko E, Jang E, Sim J, Jeong M, Park S. Development of a campus-based intervention program to strengthen food literacy among university students: A qualitative formative study. Korean Journal of Community Nutrition. 2023; 28(6): 495–508. doi.org/10.5720/kjcn.2023.28.6.495

24. Wannapaschaiyong P, Vajrabhaya P, Rojmahamongkol P, Sutchritpongsa, S. A Computer-Based Early Intervention for Thai Preschool Children at Risk of Dyslexia: A Pre-and Postintervention Study. Journal of Child Science. 2023;13(01):e28-e34

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ORIGINAL

Trasplante renal en pacientes testigos de Jehová: Revisión de complicaciones de la serie histórica de un centro de referencia nacional

Kidney transplant in Jehovah's Witnesses: A review of complications in the historical series of a national reference centre

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Resumen

Introducción y objetivos: El trasplante renal (TR) en Testigos de Jehová (TJ) supone un desafío médico y ético, requiriendo concentración en centros especializados y cuidados perioperatorios específicos. Se analiza la serie histórica de TR en TJ de un hospital de tercer nivel para conocer las complicaciones postquirúrgicas más frecuentes y el perfil de aceptación de hemoderivados/alternativas.
Materiales y métodos: Estudio retrospectivo de pacientes TJ trasplantados (marzo 2000-2022). Analizamos variables demográficas de donantes/receptores; características del injerto; aceptación de hemoderivados/alternativas; aspectos quirúrgicos; hemoglobina pre/postoperatoria; días de ingreso; complicaciones; supervivencia del paciente/injerto.
Resultados: Se realizaron 15 TR en 13 TJ (40% de comunidades autónomas diferentes al centro receptor). El perfil de aceptación de hemoderivados/alternativas fue: 13.4% transfusiones alogénicas (urgencia vital), 13.4% autotransfusiones, 26.7% plasma fresco congelado, 33.3% hemodilución preanestésica, 33.3% recuperador de sangre. Perfil de donantes: 80% muerte encefálica, 13,3% asistolia controlada, 6,7% asistolia no controlada. Los tiempos de isquemia y quirúrgicos medios fueron 21.4 (14- 29) horas y 180.9 (120-284) minutos respectivamente. Datos de hemostasia: 100% reversión de heparinización, 20% uso de material hemostático. La tasa de complicaciones inmediatas fue 66.7% (hemorrágicas las más frecuentes, 60% Clavien-Dindo ≥ III), precisando 1 caso transfusión y 33% reinfusión de sangre recuperada. Se registraron complicaciones diferidas en el 26.6% (media de ingreso 26 días), todas Clavien Dindo ≤III. El injerto continúa funcionante en el 66.7% (seguimiento medio 94 meses). Ningún fallecimiento como consecuencia directa de cirugía.
Conclusiones: El TR en TJ es factible bajo protocolos estrictos de actuación, presentando complicaciones quirúrgicas y resultados funcionales similares al resto de la población.

Palabras clave: Testigos de Jehová, Trasplante renal, Cirugía sin sangre, Estrategias ahorradoras de sangre.

Abstract

Introduction and objectives: Kidney transplant (KT) in patients who refuse blood products poses a medical and ethical challenge, requiring concentration of the cases in specialized centers and specific peri-operative care. Jehovah's Witnesses (JWs) represent a significant subgroup among these patients. All cases of renal transplant in JWs performed since the beginning of the transplant program in a tertiary level hospital are analyzed to determine updated information about post-operative complications and acceptance rate of blood products/blood-saving strategies.
Materials and methods: Retrospective, descriptive study of JW renal transplant recipients (March 2000-2022). We analyzed: donor/recipient demographic variables; graft characteristics; blood products/blood-saving strategies acceptance; surgical aspects; pre/post-operative hemoglobin; length of hospital stay; complications; patient/graft survival.
Results: 15 KTs were performed in 13 JWs. Blood products/blood-saving strategies acceptance rate: 13.4% allogeneic transfusions (vital emergency), 13.4% autotransfusions, 26.7% fresh frozen plasma, 33.3% pre-operative normovolemic hemodilution, 33.3% cell salvage. Donor profile: 80% brain death, 13.3% controlled non-beating heart donation, 6.7% uncontrolled non-beating heart donation. Mean ischemia: 21.4 (14-29) hours. Surgical time: 80.9 (120-284) minutes. Hemostasis: 100% reversal of heparin anticoagulation, 20% use of hemostatic material. Immediate complications: 66.7% (hemorrhagic complications were the most frequent ones, 60% Clavien-Dindo ≥ III), requiring transfusion in 1 case, and 33% reinfusion of intra-operative cell salvage. Deferred complications: 26.6% (mean hospital stay 26 days), all of them Clavien Dindo ≤III. Kidney graft remained functional in 66.7% of the cases (mean follow-up 94 months). No deaths as a direct consequence of surgery.
Conclusions: KT in patients who refuse blood transfusions is feasible under strict protocols, although it has risks and complications. It requires specialized care in referral centers.

Key words: Jehovah's Witnesses, Kidney transplant, Bloodless surgery, Blood-saving strategies.

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Introducción

El trasplante de riñón (TR) se trata de la terapia de sustitución renal que ha demostrado un mayor beneficio en cuanto a la supervivencia y la calidad de vida de los pacientes, además de tratarse del tratamiento más coste-efectivo para la insuficiencia renal crónica terminal[1,2].

Los testigos de Jehová (TJ) son una denominación cristiana que basan sus creencias en los textos sagrados de la Biblia. Representan un porcentaje no desdeñable de la población española, con aproximadamente 120000 miembros de esta comunidad en nuestro país, suponiendo esto una proporción de 1 por cada 393 habitantes. A nivel mundial en 2021 se estimaban un total de 8.686.980, predicando su fe en un total de 239 países[3]. Sus pautas de actuación en cuanto a la negativa a la administración de hemoderivados se basa en las enseñanzas bíblicas "Hechos 15:28-29", "Levítico 17:11" y "Génesis 9:3-5", en cuyos textos se trata el consumo de sangre por parte del ser humano[4].

La cirugía del TR en TJ supone un desafío tanto a nivel médico como ético. Con el fin de minimizar en lo posible las complicaciones hemorrágicas de dicho procedimiento, es necesaria una planificación prequirúrgica, intraoperatoria y postoperatoria. El cuidado de este perfil de pacientes comienza por un correcto manejo de la anemia preoperatoria[5] y puede verse apoyado en alternativas a la transfusión de hemoderivados como pueden ser las transfusiones autólogas, la recuperación de sangre y la transfusión de derivados sanguíneos como la albúmina, las globulinas, la trombina o diferentes factores de la coagulación[6]. Sin embargo, desde las organizaciones internacionales y nacionales de TJ no existen instrucciones específicas en cuanto a dichas estrategias, por lo que a menudo su aceptación se trata de una decisión personal.

A pesar de realizarse de manera habitual en muchos países del mundo, el TR en aquellos pacientes que rechazan transfusiones continúa siendo una intervención quirúrgica que entraña riesgos añadidos.

Objetivo

La finalidad de nuestro estudio es analizar los resultados de nuestra serie histórica de TR en TJ, con el fin de conocer las complicaciones postquirúrgicas más frecuentes y el perfil de aceptación de alternativas a la transfusión de hemoderivados en nuestros pacientes.

Material y métodos

Se ha realizado un estudio descriptivo retrospectivo tras llevarse a cabo una revisión de las historias clínicas de los pacientes TJ intervenidos de un TR en un hospital de tercer nivel. El periodo de estudio fue entre marzo del año 2000 (fecha del primar TR en TJ en nuestro centro) y marzo del año 2022. Desde el año 2016, el manejo integral de estos pacientes se realiza según un protocolo intrahospitalario específico, avalado por la comisión de ética del centro.

Se han recopilado las siguientes variables tanto del receptor como del donante:

Variables del receptor:
- Datos demográficos: edad en el momento del TR, sexo, comunidad autónoma de procedencia.
- Comorbilidades y otras variables: hipertensión arterial, diabetes mellitus, aterosclerosis de arterias iliacas, cardiopatía isquémica, claudicación intermitente, clase según clasificación ASA, etiología de la insuficiencia renal, terapia sustitutiva renal previa al TR, cifra de hemoglobina prequirúrgica
- Tratamiento prequirúrgico: terapia anticoagulante y antiagregante.
- Aceptación y administración de componentes sanguíneos y otras estrategias de ahorro de hemoderivados: sangre alógenica, sangre autóloga, plasma fresco congelado, recuperador de sangre, hemodilución aguda normovolémica.
- Intervención quirúrgica: tiempo quirúrgico, características de las anastomosis vasculares y urinaria, uso de fármacos y materiales hemostáticos, tipo de abordaje, lateralidad de la incisión, volumen sanguíneo recuperado y transfundido.
- Seguimiento postoperatorio: cifra de hemoglobina a las 24h, terapia anticoagulante, complicaciones inmediatas y diferidas (incluyéndose tratamiento y grado según escala de Clavien-Dindo), necesidad de inotrópicos, tiempo de ingreso, estado actual del injerto, causa de pérdida del injerto, fallecimiento del paciente.

Variables del donante:
- Datos del paciente: edad, tipo de donante
- Datos del injerto: tiempo de isquemia fría, anomalías anatómicas, lateralidad.

Las variables cualitativas se expresaron como número total y porcentaje. Tras comprobar que las variables cuantitativas analizadas en el estudio seguían una distribución normal empleando el test de Shapiro-Wilk, estas se expresaron mediante la media, especificándose además los valores extremos de cada variable. El análisis estadístico se realizó a fecha de julio de 2022, empleando el programa estadístico SPSS 22.0 (IBM Cor., Armonk, NY, EE.UU.).

Resultados

Se han realizado un total de 15 TR en 13 pacientes TJ, los cuales representan el 1.4% de los trasplantes realizados en nuestro centro durante el periodo de estudio (1062). La distribución en cuanto al género fue semejante y la

edad media en el momento de la realización del TR fue de 57.2 años. En cuanto a la procedencia de los receptores, Cantabria fue la principal comunidad autónoma. Entre las causas de insuficiencia renal crónica de los pacientes, predominan la enfermedad poliquística y la nefropatía diabética. Los datos demográficos de los receptores se recogen en la **tabla I**.

En el momento de la intervención quirúrgica, el 93.2% de los pacientes recibían como terapia renal sustitutiva la hemodiálisis, frente al 6.7% que llevaban a cabo diálisis peritoneal.

La aceptación y empleo de las diferentes estrategias ahorradoras de sangre se describen en la **tabla II**. Únicamente 2 pacientes aceptaron transfusión de hemoderivados en caso de riesgo extremo, uno de los cuáles especificando que en caso de necesidad de dicha terapia no se informara a la familia. En los casos en los que se empleó el recuperador de sangre, el volumen medio recuperado e infundido fue de 1184cc y 434cc respectivamente.

En cuanto a los pacientes donantes de los injertos renales, la media de edad fue de 55.8 años, predominando los donantes en muerte encefálica (80%). No se ha llevado ningún trasplante de donante vivo. Las características de los donantes y de los injertos renales se describen más detalladamente en la **tabla III**. Ninguno de los injertos renales presentaba anomalías venosas ni urinarias, mientras que 2 de ellos presentaban variaciones anatómicas arteriales (1 de los injertos 1 arteria polar inferior seccionada y otro de ellos 2 arterias renales principales).

En 13 casos (86.7%) se trataba de un primer TR y en 2 (13.3%) de una segunda cirugía. La media del tiempo quirúrgico fue de 180.9 (120-284) minutos, siendo sometidos los injertos a un tiempo isquemia fría medio de 21.4 (14-29) horas. En la totalidad de los casos se abordó la fosa iliaca mediante una incisión de Gibson, 13 (6.7%) en el lado derecho y 2 (13.3%) en el izquierdo.

En 13 (86.7%) de los casos se realizaron las anastomosis vasculares en los vasos iliacos externos. Sólo en dos ocasiones (13.3%) se eligieron la arteria y la vena iliacas comunes. El reimplante ureteral se hizo en todos los casos con técnicas extravesicales.

En todos los casos se optó por la reversión de la heparinización con sulfato de protamina, realizándose a mitad de dosis en 6 casos (40%) y de manera completa en 9 (60%). En 3 casos (20%) se utilizó material hemostático.

La media de la cifra de hemoglobina preoperatoria fue de 12.7 (9.7-16) g/dl, mientras que a las 24 horas de la cirugía fue de 9.6 (5.5-13) g/dl. Únicamente en 1 caso (7.7%) se utilizó heparina de bajo peso molecular en el postoperatorio inmediato. 5 pacientes (33.3%) requirieron inotrópicos como tratamiento de soporte hemodinámico.

10 pacientes (66.7%) presentaron alguna complicación postquirúrgica inmediata. Estas se describen de manera detallada en la **tabla IV**.

De manera diferida, 4 pacientes (26.6%) presentaron complicaciones, las cuales fueron ordenadas según la clasificación de Clavien-Dindo:

- Grado II: 1 trombosis venosa profunda tratada con heparina de bajo peso molecular y 1 isquemia parcial del riñón con disfunción del injerto.
- Grado III: 1 linfocele persistente que requirió realización de una ventana peritoneal robótica y 1 infarto diferido masivo del injerto que requirió trasplantectomía.

Tabla I: Datos demográficos de los receptores.

Datos demográficos de los receptores (Total=13)	
Edad media (años)	57.2 (34-68)
Sexo, n (%)	
Varones	6 (46)
Mujeres	7 (54)
Procedencia del receptor, n (%)	
Cantabria	9 (60)
País Vasco	3 (20)
Murcia	2 (13.3)
Castilla y León	1 (6.7)
Hipertensión arterial, n (%)	10 (76.9)
Diabetes mellitus, n (%)	
Tipo I	2 (15.4)
Tipo II	3 (23.1)
Aterosclerosis de arterias iliacas, n (%)	3 (23.1)
Cardiopatía isquémica, n (%)	1 (7.7)
Claudicación intermitente, n (%)	2 (15.4)
Toma de antiagregantes, n (%)	2 (15.4)
Toma de anticoagulantes, n (%)	0 (0)
Riesgo ASA, %	
III	12 (92.3)
IV	1 (7.7)
Causa de insuficiencia renal, n (%)	
Enfermedad poliquística	6 (46.2)
Nefropatía diabética	4 (30.8)
Litiasis infecciosa	1 (7.7)
Nefropatía IgA	1 (7.7)
Desconocida	1 (7.7)

Tabla II: Estrategias ahorradoras de hemoderivados.

Método	Aceptación, n (%)	Empleo, n (%)
Concentrado de hematíes	2 (13,4)	1 (6.7)
Autotransfusión	2 (13.4)	0 (0)
Plasma fresco congelado	4 (26.7)	1 (6.7)
Hemodilución preanestésica	5 (33.3)	1 (6.7)
Recuperador de sangre	5 (33.3)	5 (33.3)

Tabla III: Datos de donantes e injertos renales.

Datos de donantes y de injertos renales (Total=15)	
Edad media	55.8 (25-78)
Clasificación de los donantes, n (%)	
Asistolia no controlada	1 (6.7)
Asistolia controlada	2 (13.3)
Muerte encefálica	12 (80)
Lateralidad del injerto, n (%)	
Derecha	9 (60)
Izquierda	6 (40)

Tabla IV: Complicaciones postquirúrgicas inmediatas.

Complicaciones postquirúrgicas inmediatas, n (%)			
		Frecuencia	**Tratamiento**
CLAVIEN I (40%)	Hematoma periinjerto	4	Conservador
CLAVIEN IIIb (20%)	Dehiscencia de la herida quirúrgica Trombosis del injerto	1 1	Reparación quirúrgica Trasplantectomía
CLAVIEN IVa (40%)	Estenosis de arteria renal Hematoma periinjerto Insuficiencia cardiaca por sobrecarga hídrica Sangrado posquirúrgico activo	1 1 1 1	Soporte hemodinámico +reanastomosis arterial Soporte hemodinámico+ reintervención quirúrgica Soporte hemodinámico Reintervención quirúrgica + soporte hemodinámico + transfusión sanguínea

La media de ingreso de los pacientes fue de 26 días (7-77) y en el momento del análisis estadístico, con un seguimiento medio de 94 meses (5.8-270), 10 injertos (66.7%) se encuentran funcionantes, siendo la duración media de estos de 61 meses (0-156). Se han perdido 6 injertos a lo largo del seguimiento: 2 (40%) por trombosis, 2 (40%) por rechazo crónico y 1 (20%) por toxicidad a anticalcineurínicos y problemas de flujo vascular. Ninguno de los pacientes ha fallecido como consecuencia directa del procedimiento quirúrgico o sus complicaciones inmediatas.

Discusión

Los TJ representan un grupo muy específico dentro de los pacientes subsidiarios de TR. Aunque dicho procedimiento quirúrgico se encuentra agrupado en hospitales de referencia, a menudo el número de pacientes por centro suele ser reducido y representa un pequeño porcentaje del total de TR, como se muestra en nuestra serie histórica y en la literatura publicada hasta el momento[7-11]. Del análisis de nuestros datos sacamos la conclusión de que el origen geográfico representa un factor determinante a la hora de elección de un centro hospitalario para llevar a cabo el TR, ya que un 86.7% de los pacientes proceden de Cantabria o comunidades autónomas limítrofes.

El TR en TJ conlleva un importante debate en el campo de la bioética al entrar en conflicto principios fundamentales como la autonomía (derecho a rechazar la administración de hemoderivados) y la beneficencia (derecho a recibir el mejor tratamiento renal sustitutivo disponible)[12], con la no maleficencia (realización de cirugía mayor sin posibilidad de transfusión en caso de una complicación hemorrágica) y la justicia (inclusión de pacientes TJ en lista de espera de TR cuando otros pacientes sí aceptan transfusión de hemoderivados para optimizar el éxito del procedimiento)[7]. Sin embargo, actualmente es generalmente aceptado por la comunidad médica que este tratamiento debe ser ofrecido a pacientes TJ que rechazan las transfusiones de sangre[13,14], siempre y cuando las instituciones receptoras cuenten con protocolos multidisciplinares que garanticen la seguridad del paciente, favorezcan la viabilidad del órgano trasplantado y respeten las creencias religiosas de los TJ[14,15].

Numerosos casos en la historia de la medicina legal han apoyado el derecho de los TJ a rechazar hemoderivados en situaciones de peligro vital, priorizando el principio de autonomía (16). Los datos de la literatura sugieren que la supervivencia del injerto y del paciente son semejantes en los TJ a las del resto de población, tratándose el TR en TJ de un procedimiento seguro[8,11]. Estos datos son concordantes con el elevado porcentaje de supervivencia del injerto y de los pacientes observado en nuestra serie. Kaufman et al. evidencian una mayor tasa de rechazo y un aumento de la mortalidad en aquellos casos que presentan rechazo agudo asociado a anemia en TJ[11]. En nuestro estudio, entre las causas de pérdida del injerto hemos observado que el rechazo supone un porcentaje sustancial (40%).

En nuestro hospital, todos los injertos renales procedían de donante fallecido. El trasplante renal de vivo en TJs continúa siendo un tema controvertido y raramente reportado debido al riesgo que supone para la supervivencia de los donantes. Además, como ya se ha mecionado previamente, la posibilidad de un aumento de rechazo en casos de anemia podría suponer un problema de mayor importancia en este tipo de trasplantes[17].

Dado que un cierto grado de anemia postoperatoria es frecuente tras el TR, es necesaria la optimización prequirúrgica del paciente mediante la administración de EPO y hierro en casos de deficiencia de este[5,18-20], estando todavía por determinar las concentraciones de hemoglobina preoperatorias mínimas necesarias para realizar cirugía mayor sin transfusión sanguínea en TJ con seguridad. En nuestro centro se ha conseguido una hemoglobina preoperatoria media de 12.7 ng/dl, lo cual permite asumir la reducción de 3.1 puntos de media observada a las 24 horas de la cirugía. A pesar de que nuestro protocolo intrahospitalario elaborado en 2016 establece el límite de hemoglobina mínima preoperatoria en 12 ng/dl, previamente a dicho año se han realizado TR en TJ con cifras menores.

Las alteraciones de la capacidad excretora y homeostática del riñón en pacientes con insuficiencia renal crónica justifican que el sangrado postoperatorio suponga la complicación temprana más frecuente del TR, variando su incidencia entre el 0.2 y 14%[3,21-24]. La incidencia de complicaciones inmediatas de nuestra serie fue elevada en comparación a la descrita en la

literatura, siendo también las de origen hemorrágico más frecuentes. Hay que tener en cuenta que únicamente dos de las seis complicaciones hemorrágicas fueron consideradas >1 según la escala de Clavien-Dindo. Las diferencias observadas podrían deberse a la variabilidad de la población de los diferentes estudios, el momento de diagnóstico de la complicación y la falta de consenso a la hora de clasificar y diagnosticar las hemorragias, teniendo además en cuenta el sesgo introducido por la realización en nuestros pacientes de una ecografía precoz a las 4 horas de la cirugía según nuestro protocolo intrahospitalario de TR en TJ.

La presencia de múltiples arterias en los injertos renales parece predisponer a un mayor riesgo sangrado (24). En nuestra serie se han empleado en dos ocasiones injertos renales con variantes anatómicas arteriales, sin presentar complicaciones hemorrágicas que precisasen tratamiento activo. En este contexto, cabría discutir si el principio de justicia estaría comprometido en caso de decidir priorizar la utilización de injertos renales de mejor calidad y con arteria única en TJ para tratar de disminuir el riesgo hemorrágico. Por otro lado, también existe la posibilidad de un sesgo en la selección de los propios receptores, excluyendo de la posibilidad del trasplante aquellos con condiciones de alto riesgo de complicaciones, sobre todo por patología vasculorrenal.

La aceptación de hemoderivados y alternativas ahorradoras de estos no se ha estudiado de manera específica en los pacientes TJ sometidos a TR. Entre aquellos pacientes subsidiarios de algún tratamiento invasivo a los que se le ofrece transfusión de hemoderivados, el porcentaje de aceptación es de aproximadamente 10%[25,26], muy semejante a nuestra cohorte. En lo referente a otras estrategias ahorradoras de sangre, Gyamfi y Berkowitz en un estudio en pacientes obstétricas describen un porcentaje de aceptación de 39% de productos derivados de la sangre, 55% de hemodilución aguda normovolémica y 46% de recuperador de sangre[26], datos que concuerdan con lo observado en nuestro estudio. En la única encuesta realizada en una congregación de TJ, el 100% de los participantes rechazaban el uso de hemoderivados[27]. Dada la variabilidad de estrategias y la heterogeneidad de aceptación de estas por los TJ, es necesario un modelo específico de consentimiento informado que contemple las diversas alternativas posibles y el grado de conformidad del paciente con estas[14].

Este estudio tiene limitaciones. En primer lugar, el bajo número de pacientes: nuestra cohorte es pequeña dado que se trata de un colectivo religioso concreto sometido a un tipo de cirugía específica exclusiva para el tratamiento de la insuficiencia renal, por lo que no es adecuada para ningún análisis estadístico avanzado. Además, el amplio marco temporal, la ausencia de un grupo control y el carácter retrospectivo del estudio son factores limitantes adicionales.

Conclusión

Nuestro trabajo se suma al conjunto de evidencias sobre el TR en TJ. Aunque los datos sugieren que se trata de un procedimiento que se puede realizar con seguridad, buenas cifras de supervivencia del injerto y una mortalidad procedimiento-dependiente reducida, no se encuentra exento de riesgos y complicaciones. Es por esta razón que es necesaria la centralización de este tipo de pacientes en hospitales de referencia que cuenten con un equipo multidisciplinar especializado. El conocimiento de ciertas consideraciones ético-legales específicas de este colectivo, sumado a un manejo perioperatorio basado en un protocolo específico de cirugía sin posibilidad de trasfusión de hemoderivados, constituyen los pilares fundamentales del TR en TJ.

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Bibliografía

1. Augustine J. Kidney transplant: New opportunities and challenges. Cleveland Clinic Journal of Medicine. 2018;85(2):138-44.

2. Axelrod DA, Schnitzler MA, Xiao H, Irish W, Tuttle-Newhall E, Chang S-H, et al. An economic assessment of contemporary kidney transplant practice. American Journal of Transplantation. 2018;18(5):1168-76.

3. Sitio Oficial de los Testigos de Jehová [Internet]. Washington; 2001 [actualizado 4 Feb 2023; consultado 15 Feb 2023]. Disponible en: https://www.jw.org/es/.

4. Ariga T. Refusal of blood by Jehovah's Witnesses and the patient's right to self-determination. Leg Med (Tokyo). 2009;11 Suppl 1:S138-40.

5. Goodnough LT, Maniatis A, Earnshaw P, Benoni G, Beris P, Bisbe E, et al. Detection, evaluation, and management of preoperative anaemia in the elective orthopaedic surgical patient: NATA guidelines. British Journal of Anaesthesia. 2011;106(1):13-22.

6. Crowe EP, DeSimone RA. Transfusion support and alternatives for Jehovah's Witness patients. Curr Opin Hematol. 2019;26(6):473-9.

7. Boggi U, Vistoli F, Del Chiaro M, Croce C, Signori S, Marchetti P, et al. Kidney and pancreas transplants in Jehovah's witnesses: ethical and practical implications. Transplant Proc. 2004;36(3):601-2.

8. Carvalho Fiel D, Nunes Ficher K, Bernardi Taddeo J, Linhares Silva K, Rosso Felipe C, Aguiar W, et al. Is There Sufficient Evidence Justifying Limited Access of Jehovah's Witness Patients to Kidney Transplantation? Transplantation. 2021;105(1):249-54.

9. Figueiro J, Vaidya A, Ciancio G, Olson L, Miller J, Burke GW. Simultaneous pancreas-kidney transplantation in Jehovah's Witness patients. Clin Transplant. 2003;17(2):140-3.

10. Hernández-Navarrete LS, Hernández-Jiménez JD, Jiménez-López LA, Budar-Fernández LF, Méndez-López MT, Martínez-Mier G. [Experience in kidney transplantation without blood transfusion: kidney transplantation transfusion-free in Jehovah's Witnesses. First communication in Mexico]. Cir Cir. 2013;81(5):450-3.

11. Kaufman DB, Sutherland DE, Fryd DS, Ascher NL, Simmons RL, Najarian JS. A single-center experience of renal transplantation in thirteen Jehovah's Witnesses. Transplantation. 1988;45(6):1045-9.

12. Marco Guerrero G. Enfrentamiento médico legal del paciente testigo de jehová. Revista Médica Clínica Las Condes. 2011;22(3):397-403.

13. Cummins PJ, Nicoli F. Justice and Respect for Autonomy: Jehovah's Witnesses and Kidney Transplant. J Clin Ethics. 2018;29(4):305-12.

14. Martorell MV, Sánchez Urrutia AV. Documento sobre el rechazo a las transfusiones de sangre por parte de los testigos de Jehová [Internet]. Barcelona: Observatori de Bioètica i Dret; 2005 [consultado 15 Feb 2023]. Disponible en http://hdl.handle.net/2445/11374.

15. Takaschima AK, Sakae TM, Takaschima AK, Takaschima RD, Lima BJ, Benedetti RH. Ethical and legal duty of anesthesiologists regarding Jehovah's Witness patient: care protocol. Braz J Anesthesiol. 2016;66(6):637-41.

16. Retamales P A. AUTONOMÍA DEL PACIENTE: LOS TESTIGOS DE JEHOVÁ Y LA ELECCIÓN DE ALTERNATIVAS A LA TRANSFUSIÓN. Revista chilena de obstetricia y ginecología. 2006;71(4).

17. Spasovski G, Stankov O, Masin-Spasovska J. Living-related donor kidney transplantation in Jehovah's Witness patient: the importance of EPO preconditioning. Int Urol Nephrol. 2014;46(3):669-70.

18. Rashid M, Kromah F, Cooper C. Blood transfusion and alternatives in Jehovah's Witness patients. Curr Opin Anaesthesiol. 2021;34(2):125-30.

19. Zurales KR, Janke M, Carver AR, Napolitano LM. When blood is not an option: Optimal bloodless management of severe anemia in pregnancy. J Obstet Gynaecol Res. 2022;48(11):2968-72.

20. Gohel MS, Bulbulia RA, Slim FJ, Poskitt KR, Whyman MR. How to approach major surgery where patients refuse blood transfusion (including Jehovah's Witnesses). Ann R Coll Surg Engl. 2005;87(1):3-14.

21. Hachem LD, Ghanekar A, Selzner M, Famure O, Li Y, Kim SJ. Postoperative surgical-site hemorrhage after kidney transplantation: incidence, risk factors, and outcomes. Transpl Int. 2017;30(5):474-83.

22. Hernandez D, Rufino M, Armas S, Gonzalez A, Gutierrez P, Barbero P, et al. Retrospective analysis of surgical complications following cadaveric kidney transplantation in the modern transplant era. Nephrol Dial Transplant. 2006;21(10):2908-15.

23. Osman Y, Shokeir A, Ali-el-Dein B, Tantawy M, Wafa EW, el-Dein AB, et al. Vascular complications after live donor renal transplantation: study of risk factors and effects on graft and patient survival. J Urol. 2003;169(3):859-62.

24. Salehipour M, Salahi H, Jalaeian H, Bahador A, Nikeghbalian S, Barzideh E, et al. Vascular complications following 1500 consecutive living and cadaveric donor renal transplantations: a single center study. Saudi J Kidney Dis Transpl. 2009;20(4):570-2.

25. Benson K. Management of the Jehovah's Witness Oncology Patient: Perspective of the Transfusion Service. Cancer Control. 1995;2(6):552-6.

26. Gyamfi C, Berkowitz RL. Responses by pregnant Jehovah's Witnesses on health care proxies. Obstet Gynecol. 2004;104(3):541-4.

27. Findley LJ, Redstone PM. Blood transfusion in adult Jehovah's Witnesses. A case study of one congregation. Arch Intern Med. 1982;142(3):606-7.

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ORIGINAL

Dental caries and stress in Kurdish adolescents

Caries dental y estrés en adolescentes kurdos

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Abstract

Introduction: Kurds, an ethnic group in Iraq, faced significant challenges after the ISIS invasion in 2014. Continuous conflicts exposed majority of inhabitants, including adolescents, to higher rates of psychological stress, which in turn trigger cortisol secretion. Previous studies suggested a two-way relationship between dental caries stress, creating a potential vicious cycle. However, this relationship hasn't been explored specifically in Kurdish adolescents.

Methods: This cross-sectional study explored the correlation between salivary cortisol levels and the severity of dental caries in Kurdish adolescents in Erbil city, Iraq. The following categories were considered to define dental caries severity: caries free, caries without consequences, and caries with consequences. The consequences of dental caries were evaluated using PUFA index, by recording the presence of visible Pulp, Ulceration, Fistula or Abscess.

Results: A significant positive correlation was found, suggesting that individuals had caries "with consequences" reported higher mean cortisol level (4.17ng/mL) compared to those who were caries-free (1.30ng/mL) or had caries "without consequences" (1.86ng/mL). Additionally, female participants were found to have higher cortisol levels compared to males, while age and socioeconomic status did not show significant correlations with cortisol levels.

Conclusions: The research highlights the value of salivary cortisol as a biomarker for evaluating stress levels concerning adolescents' oral health.

Key words: Dental caries, stress, salivary cortisol, adolescent, Kurds.

Resumen

Introducción: Los kurdos, un grupo étnico de Irak, se enfrentaron a importantes retos tras la invasión del ISIS en 2014. Los continuos conflictos expusieron a la mayoría de los habitantes, incluidos los adolescentes, a mayores índices de estrés psicológico, que a su vez desencadenan la secreción de cortisol. Estudios anteriores sugerían una relación bidireccional entre el estrés y la caries dental, creando un posible círculo vicioso. Sin embargo, esta relación no se ha explorado específicamente en adolescentes kurdos.

Material y métodos: Este estudio transversal exploró la correlación entre los niveles de cortisol salival y la gravedad de la caries dental en adolescentes kurdos de la ciudad de Erbil, Irak. Se consideraron las siguientes categorías para definir la gravedad de la caries dental: sin caries, caries sin consecuencias y caries con consecuencias. Las consecuencias de la caries dental se evaluaron mediante el índice PUFA, registrando la presencia de Pulpa visible, Ulceración, Fístula o Absceso.

Resultados: Se encontró una correlación positiva significativa, lo que sugiere que los individuos que tenían caries "con consecuencias" informaron de un nivel medio de cortisol más alto (4,17ng/mL) en comparación con los que no tenían caries (1,30ng/mL) o tenían caries "sin consecuencias" (1,86ng/mL). Además, se observó que los niveles de cortisol eran más elevados en las mujeres que en los hombres, mientras que la edad y el nivel socioeconómico no mostraron correlaciones significativas con los niveles de cortisol.

Conclusión: La investigación pone de relieve el valor del cortisol salival como biomarcador para evaluar los niveles de estrés en relación con la salud bucodental de los adolescentes.

Palabras clave: Caries dental, estrés, cortisol salival, adolescente, kurdos.

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Introduction

Kurds are an ancient ethnic group residing in the Middle East, predominantly in the region known as Kurdistan, which encompasses parts of Turkey, Iraq, Syria, and Iran[1]. Following the ISIS invasion of Iraq in 2014, Kurds have been significantly affected by various mortality-inducing factors, such as armed conflicts, displacements, floods, and the economic crisis in the region[2]. Continuous conflicts exposed the majority of inhabitants including adolescents' higher rates of psychological stress and trauma[3]. Moreover, ethnic minorities experience higher degrees of neglect, adding to the challenges they face in accessing mental health services and support, as a result of limited resources and infrastructure[4]. Stress is prevalent in early adolescence stage and linked to impaired social, emotional, academic, and family functioning[3]. Correlations have been identified between stress and various negative outcomes that may extend into adulthood including suboptimal academic achievements, compromised peer relationships, addiction, and suicide attempts[5]. The stage denoted as "Early Adolescence" spans the age range of 11 to 14 years, during which individuals undergo significant and concurrent changes in physical, biological, psychological, and social dimensions[6]. Those changes adversely affects oral health behavioral patterns including diet and oral hygiene practices[7,8]. High sugar consumption and improper oral hygiene practices during early adolescence stage disrupt the ecological equilibrium within the dental biofilm structure, thereby causing the onset of dental caries[9]. Unfortunately, those behavioral patterns acquired during this stage may potentially last throughout adulthood, leading to a long-lasting high susceptibility to dental caries and subsequently tooth loss[10,11]. Individuals with dental caries during adolescence reported various stress-inducing factors, encompassing repressed emotions, fears, dissatisfaction with achievement, feelings of inferiority, rebellion against familial circumstances, traumatic school experiences, continuous anxiety, emotional disturbances, and other factors correlated with socioeconomic status[12-14].

Stress can be defined as a perceived or actual threat to an individual's physical or psychological well-being, that triggers a series of physiological and behavioral responses aimed at maintaining balance, known as homeostasis[15]. The concept of allostatic load explains how chronic stress leads to "wear and tear" on body systems, including central nervous system, autonomic nervous system (ANS), and the hypothalamic-pituitary-adrenal (HPA), when the body experiences chronic stress, it activates the HPA axis[16]. This activation leads to the secretion of cortisol, a hormone often referred to as the "stress biomarker"[17,18]. Evidence based literature considered salivary cortisol levels as a reliable, accurate, and non-invasive method for assessing stress[19], thereby mitigating variability associated with blood sampling[20].

Research suggests a connection between dental caries and salivary cortisol levels in children. Studies have found positive correlations between dental caries and salivary cortisol levels[21,22]. Further research even showed that children with rampant caries had elevated cortisol levels, and subsequent declination noted 3 months post dental treatment[14]. Conversely, saliva plays a crucial role in maintaining oral health by ensuring the balance and stability of the oral environment. Its functions include protection, lubrication, buffering, and antimicrobial activity. Salivary proteins and peptides also contribute significantly to controlling the ecological balance within dental biofilm and regulating the balance between processes of remineralization and demineralization[23]. The ANS governs the innervation and secretion of salivary glands, thereby influencing salivary protein concentration and flow rate[24,25]. Chronic stress can disrupt ANS function, leading to alterations in salivary gland activity that may increase the risk of dental caries[26].

These findings suggest a two-way relationship: dental problems can contribute to stress in children, and conversely, stress can also worsen oral health, creating a potential vicious cycle between elevated cortisol levels and dental caries. However, this relationship hasn't been explored in the Kurdish adolescent population specifically. As we know, early adolescence is a crucial developmental stage marked by significant changes[27]. Identifying potential sources of stress for adolescents living in conflict zones is particularly important during this period. This study hypothesizes that the presence of dental caries and its consequences caused by its high severity may trigger a stress response in early adolescence. Therefore, the present study aims to evaluate the association of salivary cortisol levels "as a stress biomarker" with the severity of dental caries, along with factors like age, gender, and socioeconomic status, in a sample of Kurdish early adolescents residing in Erbil city, the capital of the Kurdistan Region of Iraq (KRI).

Methodology

Study setting and participants

A school-based cross-sectional study, conducted from September 2021 to May 2023, investigated the association between the severity of dental health and stress in Kurdish adolescents residing in Erbil City, Kurdistan Region of Iraq. The study focused on public secondary school students aged 12-14 years at permanent dentition stage. To ensure data integrity and isolate the stress response related to dental caries, students with retained deciduous teeth, diagnosed psychiatric conditions, any type of facial trauma, dental prostheses, previous or current orthodontic treatment, or using any medications affecting the central nervous system were excluded.

Sample size and sampling technique

In 2021, the Ministry of Education of KRI reported a total student population of 27,283 aged 12-14 years residing in the Erbil city center, distributed across 275 public schools. To determine the sample size for this study, EpiInfo software was used, assuming a 95% confidence level and a 5% margin of error. The Decayed, Missing, and Filled Teeth (DMFT) index was chosen as the primary measure of dental caries severity. This index considers both past and present dental caries experience, with the total score reflecting the number of Decayed, Missing due to caries, and Filled permeant teeth[28]. No prior knowledge was available about the prevalence of dental caries while overcoming the cumulative effect of DMFT index in 12-14 years old population in Erbil city nor in Iraq, therefore a conservative prevalence of 50% was assumed, which can result in the largest sample size, which was estimated as 379 for a given level of confidence and precision[29]. Assumed prevalence of dental caries may affect the precision of the calculated sample size, but this was overcome by recruiting 480. A systematic sampling method was used to sample participants amongst all students attending public schools. A random starting point was selected from the list of all public schools in Erbil City, thirty schools were selected using systematic random sampling technique. The sample size was allocated proportionally based on the number of 12-14 years old students in each selected school. Participants were selected randomly based on their name lists taken from the school database.

Data collection

A questionnaire sent to parents asking about medical history and oral health problems, to assess the eligibility of the student for the study. Written informed consent was obtained from parents/guardians of participants who met the inclusion criteria after a thorough explanation of the study procedures. These parents then completed a structured questionnaire to gather information on the following sociodemographic characteristics: age, gender, father and mother's level of education and occupation, monthly income, house and car ownership.

A twenty-one unit scoring system was used to define the socioeconomic status (SES) adopted from Shabu and Al-Tawil[30]. A total score of >8, 8-14, and 15-21 translated as low, medium, and high SES group respectively. The scoring system incorporates variables with predetermined weights: mother's education, father's education, mother's occupation, and father's occupation (4 scores for each), house ownership and monthly income (2 scores for each), and 1 score for car ownership.

Exposure: Severity of dental caries

Dental examination was carried out for all participants by a specialist pediatric dentist using the criteria established by the International Caries Detection and Assessment System (ICDAS II) and the World Health Organization (WHO) criteria under natural daylight using disposable dental mirrors and probes. Calculation was based on D component of DMFT index[31]. The consequences of dental caries were evaluated using PUFA index, an index used to assess the presence of oral conditions resulting from untreated caries by recording the "presence of either a visible Pulp, Ulceration of the oral mucosa due to root fragments, a Fistula or an Abscess" (32). Lesions in surrounding tissues that were not related to a tooth with visible pulpal involvement as a result of caries were not recorded.

Then a combination of D component of DMFT index and PUFA index was used to assess the severity of dental caries. The following categories were considered to define the severity of dental caries: caries free (D=0), caries without consequences (D ≥1, PUFA=0), and caries with consequences (D ≥1, PUFA≥1).

Outcome: Salivary cortisol

To assess basal cortisol levels, reflecting the body's response to daily routines[33], unstimulated saliva samples were collected between 11:00 AM and noon to minimize the effect of circadian rhythm[34,35]. In order to reduce potential confounding effects from daily stressors, participants were scheduled for sample collection on days without exams or physical education and instructed to avoid brushing teeth, drinking, or eating for 30 minutes beforehand.

Salivary cortisol enzyme linked immunosorbent assay (ELISA) kit manufactured by DRG in Germany was used for sample collection and cortisol level estimation. Upon arrival, participants were asked to relax, remain calm, and minimize facial expressions, swallowing, and speaking. They then sat comfortably, leaned their heads forward, and drooled saliva using special saliva sampling devices, vial and straw, (DRG Salivary Cortisol ELISA) for five minutes. Collected samples were immediately stored at 2 °C to 8°C in an icebox and transported to a laboratory within 20 minutes for storage at -20°C. Prior to analysis, samples were thawed, and centrifuged for 5-10 minutes (at 3000 - 2000 x g) to separate the mucins. Then samples were assayed, and salivary cortisol levels were measured in nanograms per milliliter (ng/ml) following the manufacturer's instructions for the laboratory kit used.

Data analyses

All the information was analyzed using IBM SPSS Statistics 29.0 software (IBM Corp. Released 2023. IBM SPSS Statistics for Windows, Version 29.0. Armonk, NY: IBM Corp). To describe the characteristics of the data, frequencies and percentages were used to describe categorical variables, while means and standard deviations summarized continuous variables. Relationships between categorical variables using chi-square tests. For continuous variables, independent t-tests and ANOVA tests were used. To identify factors independently associated with the outcome while accounting for other variables, we performed a

multivariate logistic regression analysis, including factors with p-values less than or equal to 0.2. Throughout the analysis, a p-value of less than 0.05 was considered statistically significant.

Ethical considerations

The study was carried out in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki) after obtaining ethical clearance on (15-1-2021), from the Ethical Review Committee of College of Dentistry at Hawler Medical University (reference number: 28/2021). Written consent was obtained from adolescents' parents before the data collection and dental examination. All participants were given oral hygiene instruction and motivation, while cases of dental caries were advised to seek dental care.

Results

A total of 480 participants aged 12-14 years were initially recruited from public secondary schools within Erbil city center. All participants provided complete demographic data were included in the analysis, while those did not match the inclusion criteria and those who failed to collect saliva or submit insufficient samples were excluded. During the course of the study, 12 participants dropped out due to non-compliance with study procedures. An additional 46 participants were excluded. Among those excluded, 23 participants were excluded because they did not match the inclusion criteria, 16 participants failed to provide saliva samples, and 7 participants were excluded because their saliva samples were contaminated with blood.

The final sample size included in the analysis was 422 participants with a mean age of 12.94 years (SD = 0.73). The sample exhibited near-equal gender distribution, with 52.6% being male and 47.4% being female. The distribution of socioeconomic status (SES) demonstrated the medium group having the highest percentage (47.4%), followed by the high group (28.9%) and the low group (23.7%) as shown in (**Table I**).

The number of decayed teeth ranged from 0 to 12 teeth within the sample population with a mean range 3.52 teeth (SD=2.43), and PUFA index varied between 0 to 8 with a mean range of 0.81 (SD=1.43). Meanwhile, cortisol level in the sample ranged from 0.08 to 6.414 ng/mL with a mean range 2.65 ng/mL (SD=1.76) (**Table II**).

While distribution of dental caries within the sample (**Figure 1**) demonstrated the caries free group having the lowest percentage, followed by caries with consequences, then caries without consequences groups (10.9%, 36.79%, and 52.13% respectively).

Figure 1: Distribution of dental caries.

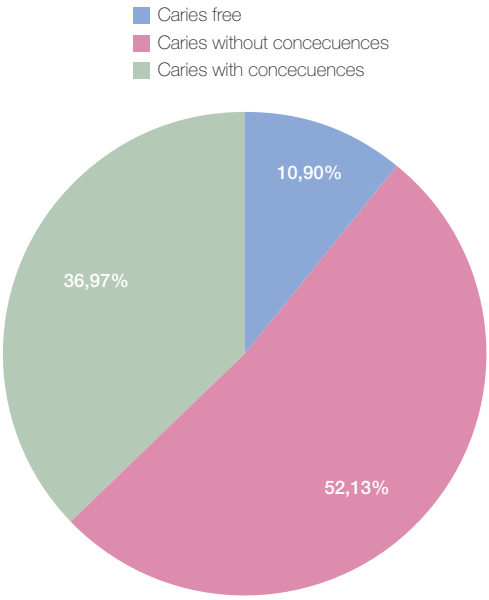

Table I: Distribution of demographic characteristics.

Variables	N	Mean (SD) / (%)
Age	422	12.94±0.73
12	125	29%
13	197	46.7%
14	100	23.7%
Gender		
Male	222	52.6%
Female	200	47.4%
SES		
Low	100	23.7%
Medium	200	47.4%
High	122	28.9%

Table II: Descriptive statistics of exposure and outcome.

Variables	N	Minimum	Maximum	Mean (SD)
Number of Decayed teeth	422	0	12	3.52±2.43
PUFA	422	0	8	.81±1.43
Cortisol Level	422	.080	6.414	2.65±1.76

A statistically significant association emerged between gender and cortisol level (**Table III**). Females exhibited a higher mean cortisol level (2.86ng/mL) compared to males (2.47ng/mL) (p value= 0.01). Conversely, age, and SES did not display significant correlations with cortisol levels. Therefore, only gender was included as covariate in subsequent analysis.

Individuals with dental caries "with consequences" showed a significantly higher mean cortisol level (4.17ng/mL) compared to those who were caries-free (1.30ng/mL) or had caries "without consequences" (1.86ng/mL) ($p < 0.001$). This result shows the more the severity of dental caries the higher the cortisol level. This finding suggests a potential link between the dental caries and stress levels, as indicated by cortisol.

A generalized linear model (**Table IV**) was employed to further investigate the factors influencing cortisol levels while controlling for potential confounding variables. The model confirmed the significant association between gender and cortisol level. Males were found to have 0.38 units lower cortisol levels, on average, compared to females. Additionally, the model revealed that having dental caries "with consequences" was a significant predictor of higher cortisol levels, with an estimated increase of 2.88 units in cortisol levels compared to being caries-free, and the model showed an increase of 0.53 units in cortisol levels in individuals having dental caries "without consequences" compared with caries free individuals. Notably, age did not significantly contribute to explaining the variation in cortisol levels in this model.

Discussion

This cross-sectional investigation explored the associations between salivary cortisol levels, a biomarker of stress response, and dental caries in early adolescence. The study assessed the relationship between cortisol levels and severity of dental caries, categorized as caries-free, caries without consequences, and caries with consequences. Results show a significant positive association, suggesting that individuals with more severe dental caries (caries with consequences) exhibited elevated cortisol levels compared to those who were caries-free or had caries without consequences. These findings suggest a potential link between dental caries and the physiological stress response as measured by salivary cortisol.

This finding agrees with Padmanabhan et al who explored the interplay of caries and saliva in 2023, indicating that elevated cortisol levels are linked with active carious lesions[16], and with a systematic review in 2018, as the authors concluded a "possible positive association between salivary cortisol level as indicator of stress and dental caries"[24], as well as with a cross-sectional study conducted in Brazil by Barbosa et al in 2012[14], where diurnal cortisol level decreased less in 8-14 years old participants who experienced more dental caries than those with low caries experience.

On the other hand, Vacaru et al found no correlations between salivary cortisol levels and caries experience indices or untreated dental caries in 5-13 years old participants[36], contradicting our finding. This can be

Table III: Association between demographics, dental caries, and cortisol level.

Variables	N	Mean±SD / Spearman's rho	p-Value*
Gender			
Male	222	2.47±1.75	0.010
Female	200	2.86±1.75	
Age	422	-0.082	0.094
SES			
Low	100	2.62±1.66	0.300
Medium	200	2.79±1.82	
High	122	2.46±1.73	
Dental caries			
Caries free	46	1.30±1.31	<0.001
Caries without consequences	220	1.86±1.55	
Caries with consequences	156	4.17±0.87	

*Non-parametric approach

Table IV: Generalized Linear Model .

Variables	Beta	Std. Error	p-Value
Gender			
Male	-0.380	0.127	0.003
Female			
Dental caries			
Caries free			
Caries without consequences	0.531	0.209	<0.011
Caries with consequences	2.878	0.218	<0.001
Age	0.090	0.09	0.305

explained by sample variability in terms of wider range of age group and different context when compared with our study sample.

The elevation observed in adaptive salivary cortisol levels concurrent with presence of dental caries or its consequences can be related to various factors. First, the association between dental caries and discomfort, often characterized by pain, prompts a physiological stress response within affected individuals. This response initiates the activation of the HPA axis, culminating in the secretion of cortisol[16]. Second, the persistent inflammatory state and microbial infection inherent in dental caries pathology can induce systemic inflammation and perturbations in the HPA axis regulation, thereby elevating cortisol concentrations[37]. Third, the psychological manifestation of dental caries, including anxiety and fear associated with dental treatments, may contribute to increase cortisol secretion as well[23]. Based on our findings, untreated dental caries is a source of stress, highlighting the need for seeking dental care in early adolescence stage to overcome the psychological effect of dental caries and its consequences.

While literature on adolescents suggests that females and males typically exhibit comparable patterns of cortisol secretion in response to stress, with certain investigations indicating a marginally higher reactivity among males compared to females[38]. The present study found higher levels in females. This finding can be attributed to various factors including biological, psychological, and social.

Biological Factors, hormonal changes during adolescence, particularly in females, lead to heightened emotional sensitivity and susceptibility to stress[39]. Besides, fluctuations in estrogen and progesterone hormones levels can affect mood regulation and stress response[40]. Moreover, gender differences in physical resilience, and overall health influence the ability to cope with and respond to stressors[16]. In terms of social factors, social expectations and gender roles often place different pressures on females and males, as female tends to be a competitive student, and loving daughter as a part of her perfection seeking challenge[41]. At the present time, It is also observed that females often contend with the expectation to navigate between contemporary societal norms and enduring cultural traditions[32]. The competitive nature of the contemporary world introduces internal dilemmas that may induce stress, manifested in the internalized pressure to excel by exerting maximal effort, occasionally beyond their capacities[41]. These expectations may lead to higher levels of perceived stress among females compared to males. Moreover, females tend to prioritize social relationships and seek emotional support more than male[42]. While socialization can be beneficial in stress coping, but it may expose females to interpersonal stressors and relational conflicts[43], which can contribute to overall stress levels. On top of that, Females may be subjected to unique stressors related to gender discrimination, sexism, and societal pressures to adapt to certain standards of behavior and appearance[44]. Regarding Psychological Factors, gender differences in personality traits, temperament, and cognitive appraisal processes can influence susceptibility to stress[38]. Literature suggests that females may be more prone to rumination and negative self-evaluation, which can exacerbate stress levels[42].

The absence of a statistically significant relationship between salivary cortisol levels and age, as well as SES, in this study may be attributed to several factors inherent to the study design, measurement techniques, and the complex interplay of biological and psychosocial determinants of cortisol secretion. In terms of age, Cross-Sectional Design limits the ability to capture dynamic changes in cortisol levels over time and age-related variations in cortisol secretion. Moreover, our target population restricted to early adolescence stage that is characterized by significant hormonal and physiological changes[14], the relationship between age and cortisol levels may exhibit non-linear patterns influenced by pubertal development and individual maturation trajectories.

Regarding the SES, the sociocultural context and economic conditions of the study setting may influence the manifestation and perception of stressors[22], thereby attenuating the association between SES and cortisol levels. Besides, the association can be influenced by multifaceted psychosocial factors, including chronic stress exposure, social support networks, and coping mechanisms[15].

Strengths of this study appears in addressing a significant gap in the literature by investigating the association between salivary cortisol levels and the severity of dental caries in early adolescence, a stage that has received limited attention in previous research. Moreover, employing comprehensive methodology including study design, standardized data collection procedures, and the use of validated assessment tools for dental caries severity utilizing well-established indices, providing standardized measures for comparison with existing research. In addition to standardized approach to measure salivary cortisol levels, considering factors such as circadian rhythm, participants' activities, and instructions for saliva collection, contributing to the validity and reliability of data. Besides, recruiting a substantial sample size ensures a representative sample from the targeted population, enhancing the generalizability of the findings to similar populations within the KRI, while implementing strict inclusion criteria that contributed to a more homogenous study population and enhanced the internal validity of the study. Finally, collecting comprehensive data on sociodemographic characteristics and the use of multifaceted SES scoring system incorporating various

factors, offers a nuanced understanding of participants' socioeconomic backgrounds while enabling a thorough analysis of potential factors influencing the association investigated.

Limitations of this Study can be due to some reasons. First, the nature of the study limits the establishment of causality or temporal relationships. Longitudinal studies would provide more robust evidence regarding the directionality of the observed associations[45]. Second, parental reporting for medical history and oral health problems introduces the potential for recall bias[46]. Third, while the study measured unchallenged salivary cortisol levels as a proxy for stress, other physiological and psychological factors contributing to cortisol secretion were not accounted for, such as anxiety, and depression. Despite these limitations, the study's strengths, including its innovative focus, rigorous methodology, and comprehensive approach, contribute valuable insights to the existing literature on stress, cortisol, and dental caries during early adolescence.

Conclusions

In conclusion, the results of the present study highlight a relationship between salivary cortisol levels and severity of dental caries in individuals in early adolescence. This study suggests that there is a link between cortisol levels, stress, and dental caries in the adolescent population. Besides, it underscores the potential of salivary cortisol as a biomarker for stress assessment within the realm of adolescents' oral health. Dental practitioners may find value in its integration as a tool for identifying oral health concerns associated with stress. While the study provides valuable insights into the studied association, future research should address the identified limitations to enhance the validity and generalizability of the findings.

Acknowledgement

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Conflict of interest

The authors declare that they have no competing interests.

References

1. Kirmanj S. Kurdistan region: A country profile. Journal of International Studies (JIS). 2013;9:1-14.

2. Kulaksiz S. Kurdistan regional government: economic and social impact assessment of the Syrian conflict and ISIS insurgency. 2015.

3. de Castro F, Cappa C, Madans J. Anxiety and depression signs among adolescents in 26 low-and Middle-Income Countries: prevalence and association with functional difficulties. Journal of Adolescent Health. 2023;72(1):S79-S87.

4. Dimitry L. A systematic review on the mental health of children and adolescents in areas of armed conflict in the Middle East. Child: care, health and development. 2012;38(2):153-61.

5. Kupferberg A, Hasler G. The social cost of depression: Investigating the impact of impaired social emotion regulation, social cognition, and interpersonal behavior on social functioning. Journal of Affective Disorders Reports. 2023:100631.

6. Board T. National Academies of Sciences E and Medicine. Environmental engineering for the 21st century: Addressing grand challenges. 2019.

7. Petersen PE, Bourgeois D, Ogawa H, Estupinan-Day S, Ndiaye C. The global burden of oral diseases and risks to oral health. Bulletin of the world health organization. 2005;83:661-9.

8. Silk H, Kwok A. Addressing adolescent oral health: a review. Pediatrics in Review. 2017;38(2):61-8.

9. Sá-Pinto A, Rego T, Marques L, Martins C, Ramos-Jorge M, Ramos-Jorge J. Association between malocclusion and dental caries in adolescents: a systematic review and meta-analysis. European Archives of Paediatric Dentistry. 2018;19(2):73-82.

10. Collins WA, Steinberg L. Adolescent development in interpersonal context. 2006. doi.org/10.1002/9780470147658.chpsy0316

11. Zhu L, Petersen PE, Wang H-Y, Bian J-Y, Zhang B-X. Oral health knowledge, attitudes and behaviour of children and adolescents in China. International dental journal. 2003;53(5):289-98.

12. Morse DR, Schacterle GR, Furst ML, Esposito J, Zaydenburg M. Stress, relaxation and saliva: relationship to dental caries and its prevention, with a literature review. Annals of dentistry. 1983;42(2):47-54.

13. Klages U, Weber AG, Wehrbein H. Approximal plaque and gingival sulcus bleeding in routine dental care patients: relations to life stress, somatization and depression. Journal of clinical periodontology. 2005;32(6):575-82.

14. Barbosa T, Castelo P, Leme M, Gavião M. Associations between oral health-related quality of life and emotional statuses in children and preadolescents. Oral diseases. 2012;18(7):639-47.

15. Schneiderman N, Ironson G, Siegel SD. Stress and health: psychological, behavioral, and biological determinants. Annu Rev Clin Psychol. 2005;1:607-28.

16. Padmanabhan V, Islam MS, Habib M, Abdulaziz Z, Goud M, Chaitanya NC, et al. Association between Salivary Cortisol Levels, Dental Anxiety, and Dental Caries in Children: A Cross-Sectional Study. Dentistry Journal. 2023;11(9):205.

17. Hellhammer DH, Wüst S, Kudielka BM. Salivary cortisol as a biomarker in stress research. Psychoneuroendocrinology. 2009;34(2):163-71.

18. Bozovic D, Racic M, Ivkovic N. Salivary cortisol levels as a biological marker of stress reaction. Med Arch. 2013;67(5):374-7.

19. Jessop DS, Turner-Cobb JM. Measurement and meaning of salivary cortisol: a focus on health and disease in children. Stress. 2008;11(1):1-14.

20. Gozansky W, Lynn J, Laudenslager M, Kohrt W. Salivary cortisol determined by enzyme immunoassay is preferable to serum total cortisol for assessment of dynamic hypothalamic–pituitary–adrenal axis activity. Clinical endocrinology. 2005;63(3):336-41.

21. Rai K, Hegde A, Shetty S, Shetty S. Estimation of salivary cortisol in children with rampant caries. Journal of Clinical Pediatric Dentistry. 2010;34(3):249-52.

22. Boyce WT, Den Besten PK, Stamperdahl J, Zhan L, Jiang Y, Adler NE, et al. Social inequalities in childhood dental caries: the convergent roles of stress, bacteria and disadvantage. Social science & medicine. 2010;71(9):1644-52.

23. González-Aragón Pineda A, García Pérez A, García-Godoy F. Salivary parameters and oral health status amongst adolescents in Mexico. BMC Oral Health. 2020;20(1):1-7.

24. Tikhonova S, Booij L, D'Souza V, Crosara KT, Siqueira WL, Emami E. Investigating the association between stress, saliva and dental caries: a scoping. 2018.

25. Khairani A, Budiardjo SB, Fauziah E. Correlation between Oral-Health-Related Quality of Life and Salivary Cortisol Level in Children Ages 8–10 Years. Journal of International Dental and Medical Research. 2018;11(1):149-52.

26. Caruso S, Gatto R, Cinque B, Cifone M, Mattei A. Association between salivary cortisol level and caries in early childhood. Eur J Paediatr Dent. 2018;19(1):10-5.

27. Fuhrmann D, Knoll LJ, Blakemore S-J. Adolescence as a sensitive period of brain development. Trends in cognitive sciences. 2015;19(10):558-66.

28. Quah S. International encyclopedia of public health: Academic Press; 2016.

29. Kirkwood BR, Sterne JA. Essential medical statistics: John Wiley & Sons; 2010.

30. Shabu SA, Al-Tawil NG. Prevalence of childhood obesity among a sample of basic education school children in Erbil city. Prevalence of Childhood Obesity Among a Sample of Basic Education School Children in Erbil City page 4. 2012;7(10):4.

31. Klein H, Palmer CE, Knutson JW. Studies on dental caries: I. Dental status and dental needs of elementary school children. Public Health Reports (1896-1970). 1938:751-65.

32. Jazrawi KH. Evaluation of the sequelae of Untreated Dental Caries using PUFA Index. Al-Rafidain Dental Journal. 2014;14(1):101-10.

33. Nicolson NA. Stress, coping and cortisol dynamics in daily life. The experience of psychopathology: Investigating mental disorders in their natural settings. 1992:219-32.
34. Navazesh M. Methods for collecting saliva. Annals of the New York Academy of Sciences. 1993;694(1):72-7.

35. Guyton AC. Text book of medical physiology: China; 2006.

36. Vacaru R-P, Didilescu AC, Sfeatcu R, Tănase M, Munteanu A, Miricescu D, et al. The Effect of Dental Treatments in Caries Management on Stress and Salivary Protein Levels. Journal of Clinical Medicine. 2022;11(15):4350.

37. Panda S, Quadri MFA, Hadi IH, Jably RM, Hamzi AM, Jafer MA. Does dental fear in children predict untreated dental caries? An analytical cross-sectional study. Children. 2021;8(5):382.

38. Daughters SB, Gorka SM, Matusiewicz A, Anderson K. Gender specific effect of psychological stress and cortisol reactivity on adolescent risk taking. Journal of abnormal child psychology. 2013;41:749-58.

39. Stroud LR, Salovey P, Epel ES. Sex differences in stress responses: social rejection versus achievement stress. Biological psychiatry. 2002;52(4):318-27.

40. Kundakovic M, Rocks D. Sex hormone fluctuation and increased female risk for depression and anxiety disorders: from clinical evidence to molecular mechanisms. Frontiers in neuroendocrinology. 2022;66:101010.

41. Berger RP, Grob A, Flammer A. Gender-role orientation and social expectations regarding female adolescents' coping with developmental tasks. Swiss Journal of Psychology/Schweizerische Zeitschrift für Psychologie/Revue Suisse de Psychologie. 1999;58(4):273.

42. Barbee AP, Cunningham MR, Winstead BA, Derlega VJ, Gulley MR, Yankeelov PA, et al. Effects of gender role expectations on the social support process. Journal of Social Issues. 1993;49(3):175-90.

43. Belle D. Gender differences in the social moderators of stress. Stress and coping: An anthology: Columbia University Press; 1991. p. 258-74.

44. Garner DM, Garfinkel PE, Schwartz D, Thompson M. Cultural expectations of thinness in women. Psychological reports. 1980;47(2):483-91.

45. Wang X, Cheng Z. Cross-sectional studies: strengths, weaknesses, and recommendations. Chest. 2020;158(1):S65-S71.

46. Infante-Rivard C, Jacques L. Empirical study of parental recall bias. American journal of epidemiology. 2000;152(5):480-6.

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ORIGINAL

Influence of sociodemographic variables and healthy habits on the values of cardiometabolic risk scales in 386.924 spanish workers

Influencia de variables sociodemográficas y hábitos saludables en los valores de escalas de riesgo cardiometabólico en 386.294 trabajadores españoles

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Summary

Introduction: Cardiometabolic diseases are highly prevalent pathologies throughout the world and cause great morbidity and mortality. Their genesis is influenced by different factors. The aim of this study was to determine the influence of sociodemographic variables and healthy habits on different cardiometabolic risk scales.
Material and methods: A descriptive, cross-sectional study was carried out in 386924 Spanish workers. Cardiometabolic risk was assessed on the basis of metabolic syndrome, atherogenic risk determined by atherogenic indices and atherogenic dyslipidemia, heart age, and diabesity. The sociodemographic variables analyzed were age, gender, social class, and educational level. Physical activity, Mediterranean diet and tobacco consumption were assessed as healthy habits.
Results: The mean values and the prevalence of elevated values of the different cardiometabolic risk scales were influenced by all the sociodemographic variables (especially age) and healthy habits studied (especially physical activity and Mediterranean diet).
Conclusions: The risk profile of presenting cardiometabolic alterations would be an elderly male, low socioeconomic level, sedentary, with low adherence to the Mediterranean diet and smoker.

Key words: Cardiometabolic risk, metabolic syndrome, atherogenic risk, atherogenic dyslipidemia, heart age, diabesity.

Resumen

Introducción: Las enfermedades cardiometabólicas son patologías altamente prevalentes en todo el mundo ocasionando una gran morbimortalidad. En su génesis influyen diferentes factores. El objetivo de este estudio fue conocer la influencia de variables sociodemográficas y hábitos saludables en diferentes escalas de riesgo cardiometabólico.
Material y métodos: Estudio descriptivo y transversal realizado en 386.924 trabajadores españoles. El riesgo cardiometabólico se valora a partir del síndrome metabólico, riesgo de aterogénesis determinada por los índices aterogénicos y la dislipemia aterogénica, edad del corazón y diabesidad. Las variables sociodemográficas analizadas fueron edad, género, clase social y nivel educativo. Como hábitos saludables se valoraron actividad física, dieta mediterránea y consumo de tabaco.
Resultados: Los valores medios y la prevalencia de valores elevados de las diferentes escalas de riesgo cardiometabólico se vieron influenciadas por todas las variables sociodemográficas (especialmente edad) y hábitos saludables estudiado (especialmente actividad física y dieta mediterránea).
Conclusiones: El perfil de riesgo de presentar alteraciones cardiometabólicas sería un varón de edad avanzada, nivel socioeconómico bajo, sedentario, con baja adherencia a la dieta mediterránea y fumador.

Palabras clave: Riesgo cardiometabólico, síndrome metabólico, riesgo aterogénico, dislipemia aterogénica, edad del corazón, diabesidad.

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Introduction

Cardiometabolic risk, encompassing factors predisposing individuals to cardiovascular and metabolic diseases, is a critical public health concern[1]. In this introduction, we delve into how socio-demographic variables and lifestyle habits intersect to impact this risk.

Age plays a pivotal role[2,3]. As individuals age, the likelihood of developing cardiovascular and metabolic conditions increases[4-6], Physiological changes and cumulative risk factors contribute to this association[7].

Gender differences significantly influence cardiometabolic risk8. For instance, women tend to exhibit more favorable lipid profiles before menopause[9], but afterward, their risk escalates[10,11]. Sex hormones impact fat distribution[12] and insulin resistance[13].

Socioeconomic status matters. Individuals with lower socioeconomic standing often have a higher prevalence of risk factors such as obesity[14,15], smoking[16,17] and unhealthy diets[18,19]. Access to resources and opportunities shapes lifestyle choices[20].

Diet is fundamental. Adopting a balanced eating pattern, like the Mediterranean diet rich in fruits, vegetables, fish, and olive oil, can mitigate cardiometabolic risk[21,22]. Conversely, excessive saturated fats[23], sugars[24], and ultra-processed foods[25] elevate risk.

Regular exercise is essential for preventing cardiovascular and metabolic diseases. Sedentary behavior correlates with higher risk[26]. Tailoring age-appropriate physical activity recommendations is crucial.

Smoking remains a major modifiable risk factor[27]. It raises blood pressure[28], damages blood vessels[29], and adversely affects lipid profiles[30]. Smoking cessation is vital for risk reduction[31].

In summary, the interplay of these variables significantly influences cardiometabolic risk. Understanding their impact allows us to design personalized preventive strategies and enhance cardiovascular and metabolic health in the population.

Methods

We conducted a survey involving 386,924 people who operate in several autonomous communities in Spain and come from diverse work sectors. The information was taken from the occupational health examinations that these workers attend. The time frame for gathering data was January 2019 to June 2020.

Age between 18 and 69 years old was one of the inclusion criteria used to choose the sample.
- An employment contract being in place at one of the study's participating companies.
- Marking a consent form in order to take part in the research.
- Give permission for the data to be used for epidemiological research.

The flowchart of the study participants is presented in **figure 1**.

Identifying the variables

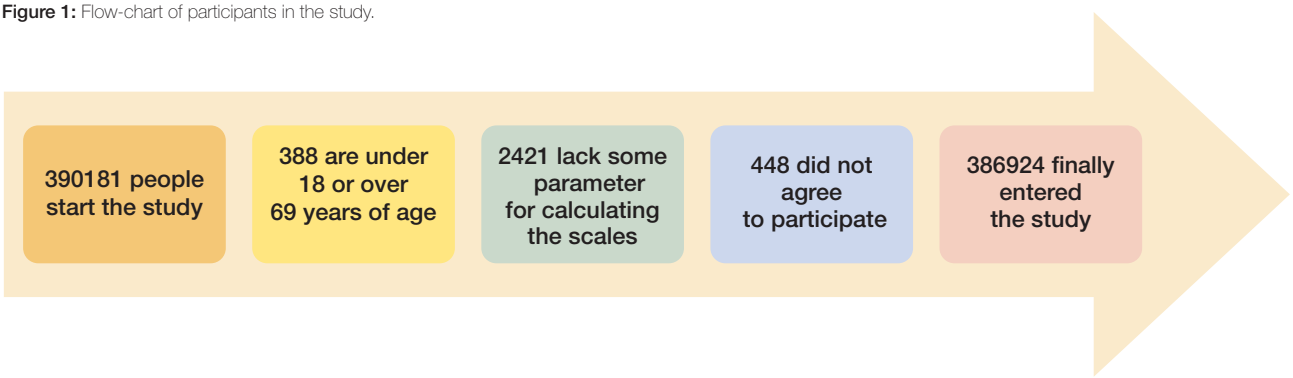
It was the responsibility of each health professional in the participating companies to gather the data needed to compute the various scales examined in this research. These methods were used to gather the data:

- Medical background. It comprises healthy behaviors (tobacco, alcohol, Mediterranean diet, and physical activity) as well as sociodemographic factors (age, sex, socioeconomic class, and degree of education).
- Clinical and anthropometric computations. includes systolic and diastolic blood pressure, height, weight, and the size of the hips and waist.
- Tests on the blood. glycemia and lipid profile included.

Standardized measurements were made for each variable to reduce the appearance of bias.

The worker is measured for height and weight while standing straight and only wearing underpants. The head needs to be facing forward, and the arms should be parallel to the thorax. A SECA model scale-measuring apparatus is used to collect measurements, and the results are reported in kilograms and millimeters.

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



A SECA model measuring tape, parallel to the floor and positioned at the level of the last floating rib, is used to measure the circumference of the abdominal waist. The employee has a relaxed abdomen and is standing erect. By holding the tape measure parallel to the floor at the level of the gluteal area's widest point, one can acquire the hip perimeter in the same manner.

Blood pressure is measured with the OMROM-M3 blood pressure monitor. For an accurate evaluation, the subject needs to be seated and at rest for a minimum of 10 minutes. Because they should be worn around the arm without being too tight, cuffs come in a variety of sizes. We run three different tests lasting one minute each. The average of the three statistics serves as the basis for the evaluation.

Venous punctures are used to take blood samples following a 12-hour fast. For optimal preservation, samples undergo processing and are chilled for a maximum of 48 to 72 hours. Analyzing the samples is done by reference laboratories using comparable techniques. While HDL cholesterol is measured using precipitation techniques, blood glucose, total cholesterol, and triglycerides are determined by enzymatic methods. The indirect estimation of LDL cholesterol is done using the Friedewald formula32, which is valid as long as the triglycerides do not exceed 400 mg/dL. LDL is calculated immediately if the reading is greater than 400 mg/dL. The milligrams per deciliter are used to display all analytical variables.

Three criteria were used to define metabolic syndrome: the Joint Interim Statement (JIS), the International Diabetes Federation (IDF) update, and the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP-III)[33,34].

The new Heart Age (HA) scale is derived from the traditional Framingham Scale[35-36]. The HA measures how our heart has aged, as opposed to the conventional cardiovascular risk scales, which calculate the likelihood that a cardiovascular event will occur within the next ten years. A number of factors are needed to calculate it, including gender, age, height, weight, and circumference around the waist, as well as the presence of cardiovascular disease in the family, diabetes, smoking, lipid profile, systolic blood pressure, and antihypertensive medication[37]. You can use all of these details to get to the calculator at www.heartage.me. The period between 20 and 80 years can be used to calculate HA.

A new notion known as ALLY (avoidable years of life lost)[38] is derived from the subtraction of chronological age from cardiac age. The age thresholds for high ALLY (17 years) and moderate ALLY (11 years)[39].

Atherogenic dyslipidemia can occur when there is a combination of high triglyceride, low HDL cholesterol (less than 50 mg/dL in women and less than 40 mg/dL in men), and normal LDL cholesterol levels[40].

The total cholesterol/HDL (high values > 5 in males and > 4,5 in women) is one of the atherogenic indexes[41-43].

- High values (>3) for LDL-c/HDL-c and triglycerides/ HDL-c

The American Diabetes Association's guidelines44 were followed for classifying blood glucose levels, with 125 mg/ dL or more being deemed hyperglycemia. Individuals who had previously been diagnosed with diabetes were included in the classification, as were those on hypoglycemic medication and those whose glycated hemoglobin (HbA1c) was ≥ 6.5% following a glycemia reading more than 125 mg/dL. Patients with diabetes were classified as diabetics if their body mass index was 30 kg/m^2 or higher.

Male and female are the established genders.

By deducting the date of birth from the date of the medical examination, the age is determined.

The highest educational level out of all those taken is the one being considered. Studying at the primary, secondary, and university levels are the three recognized levels.

The Spanish Society of Epidemiology's criteria, which are based on the kinds of jobs covered by the 2011 national classification of occupations (CNO-11)[45], were applied to determine social class. There were three tiers established: - Social class I. This include university-trained professionals, artists, professional athletes, and managers. - Social class II. This covers competent independent contractors as well as intermediate-level professions. - Social class III. This also applies to unskilled laborers.

If someone has smoked for at least one day in the last thirty days or has quit smoking less than a year ago, we classify them as smokers.

A fourteen-question survey with a 0 or 1 point system is used to assess adherence to the Mediterranean diet. Nines represent high adherence[46,47].

To ascertain an individual's level of physical activity, the International Physical Activity Questionnaire (IPAQ)[48] is utilized. This self-administered questionnaire's goal is to determine how much physical activity was done during the previous seven days.

Ethical aspects

The 2013 Helsinki Declaration[50] and all other ethical guidelines governing research have been followed. Participants' privacy and anonymity have always been guaranteed. The study was approved by the Balearic Islands Research Ethics Committee (CEI-IB), which issued consent under number IB 483/20.

Since all of the data are coded, only the lead investigator is aware of the identities of the participants. The Organic Law 3/2018, which was passed on December 5, 2018, stipulates that study participants will always be able to access, correct, cancel, and object to the use of the data that has been gathered. It also safeguards digital rights.

Statistical analysis.

The Student's t test was used to examine quantitative data and determine means and standard deviations. For quantitative variables, the chi2 test was used to evaluate prevalence. The multinomial logistic regression analysis was performed and odds ratios with 95% confidence intervals were computed. The statistical analysis was carried out using the SPSS 28.0 software. For this investigation, the accepted threshold of statistical significance was $p<0.05$.

Results

The study's 386924 workers' anthropometric, clinical, analytical, sociodemographic, and healthy habit data are displayed in **table I**. The participants' average age was somewhat above 39. The other variables, with the exception of LDL cholesterol, have lower values in the female group. Men made up 60.2% of the participants, while women made up 39.8%. The population's mean age falls between 30 and 49 years old. The majority of them are from socioeconomic class III and just have an elementary education. A Mediterranean diet is followed by 41% of men and 51.4% of women, and 45.5% of men and 52.2% of women frequently exercise. Men smoked in proportions of 37% and women in percentages of 33%.

The mean values of the various cardiometabolic risk measures included in this study rise with age and as one moves down the socioeconomic or educational scale, as seen in **tables IIa** and **IIb**. Additionally, the levels are greater in smokers, inactive individuals, and people who follow the Mediterranean diet less closely.

The prevalence of elevated values of the cardiometabolic risk scales follows the same pattern as we have seen with the mean values, that is, they are more prevalent with increasing age and with decreasing socioeconomic level. Similarly, the prevalences are higher in people who do not engage in regular physical activity, in those who do not eat a Mediterranean diet, and in smokers. All the data can be consulted in **tables IIIa** and **IIIb**.

The multivariate analysis findings using multinomial logistic regression are shown in **table IV**. A consistent trend is observed across all the scales; high values on these cardiometabolic risk scales are influenced by all the variables, including sociodemographic and healthy behavior factors. This risk rises with age, falls with social status, in individuals who follow the Mediterranean diet but don't exercise regularly, and in nonsmokers. Physical activity had the highest odds ratios, followed by age and a Mediterranean diet.

Table I: Characteristics of the population.

	Men n=232.814	Women n=154.110	
	Mean (SD)	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	
Elementary school	61.2	51.8	<0.001
High 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 Mediterranean diet	59.0	48.6	<0.001
Yes Mediterranean diet	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 IIa: Mean values of the different cardiometabolic risk scales according to sociodemographic variables and healthy habits in men.

		nº factors MS ATPIII	nº factors MS JIS	ALLY HA	TC/HDL-c	LDL-c/HDL-c	TG/HDL-c
Men	**n**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
20-29 years	41742	0.5 (0.8)	0.7 (0.9)	1.2 (4.9)	3.2 (0.8)	1.8 (0.7)	1.8 (1.4)
30-39 years	76960	0.8 (0.9)	0.9 (1.0)	4.1 (6.7)	3.8 (1.0)	2.3 (0.9)	2.4 (2.1)
40-49 years	69068	1.1 (1.1)	1.3 (1.2)	7.6 (8.0)	4.2 (1.1)	2.7 (0.9)	2.9 (2.5)
50-59 years	38028	1.3 (1.2)	1.5 (1.2)	11.3 (7.9)	4.6 (1.2)	2.9 (1.0)	3.1 (2.4)
60-69 years	7016	1.5 (1.1)	1.7 (1.2)	11.5 (7.5)	4.7 (1.2)	3.0 (1.0)	3.1 (2.0)
Elementary school	142494	1.0 (1.1)	1.1 (1.1)	6.5 (7.9)	4.0 (1.2)	2.5 (0.9)	2.6 (2.3)
High school	79226	0.9 (1.0)	1.0 (1.1)	5.3 (7.8)	3.9 (1.1)	2.4 (1.0)	2.5 (2.1)
University	11094	0.8 (1.0)	0.9 (1.1)	4.7 (7.6)	3.9 (1.1)	2.4 (1.0)	2.5 (2.3)
Social class I	12262	0.8 (1.0)	0.9 (1.1)	4.7 (7.6)	3.9 (1.1)	2.4 (1.0)	2.5 (2.2)
Social class II	40650	0.9 (1.0)	1.0 (1.1)	4.9 (7.3)	3.9 (1.1)	2.4 (0.9)	2.5 (2.1)
Social class III	179902	1.0 (1.1)	1.1 (1.1)	6.3 (7.9)	4.0 (1.2)	2.5 (0.9)	2.6 (2.2)
Non physical activity	126808	1.4 (1.1)	1.6 (1.1)	8.6 (7.7)	4.4 (1.3)	2.8 (1.1)	3.4 (2.7)
Yes physical activity	106006	0.4 (0.6)	0.4 (0.6)	2.9 (6.8)	3.4 (0.7)	2.1 (0.7)	1.6 (0.6)
Non Mediterranean diet	137464	1.3 (1.1)	1.5 (1.2)	8.3 (7.8)	4.4 (1.2)	2.7 (1.1)	3.3 (2.6)
Yes Mediterranean diet	95350	0.4 (0.6)	0.5 (0.6)	2.7 (6.7)	3.3 (0.7)	2.0 (0.6)	1.6 (0.6)
Non smokers	146480	0.9 (1.0)	1.1 (1.1)	3.1 (6.7)	3.9 (1.1)	2.4 (0.9)	2.4 (1.8)
Smokers	86334	1.0 (1.1)	1.2 (1.2)	10.9 (7.1)	4.0 (1.3)	2.5 (1.1)	2.9 (2.7)

HDL-c High density lipoprotein cholesterol. LDL Low density lipoprotein cholesterol. TC Total cholesterol. TG Triglycerides. MS Metabolic syndrome. NCEP ATP III National cholesterol Education Program Adult Treatment Panel III. JIS Joint Interim Statement. ALLY Avoidable lost life years. HA Heart age

Table IIb: Mean values of the different cardiometabolic risk scales according to sociodemographic variables and healthy habits in women.

		nº factors MS ATPIII	nº factors MS JIS	ALLY HA	TC/HDL-c	LDL-c/HDL-c	TG/HDL-c
Women	**n**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
20-29 years	29978	0.3 (0.6)	0.4 (0.7)	-2.0 (5.0)	3.2 (0.8)	1.9 (0.7)	1.4 (0.8)
30-39 years	51392	0.4 (0.7)	0.6 (0.8)	-2.0 (7.7)	3.5 (0.9)	2.2 (0.9)	1.5 (0.9)
40-49 years	45296	0.7 (0.9)	0.9 (1.0)	2.5 (10.1)	3.9 (1.0)	2.5 (0.9)	1.8 (1.0)
50-59 years	23516	1.1 (1.0)	1.3 (1.1)	7.9 (10.4)	4.4 (1.1)	3.0 (1.0)	2.1 (1.3)
60-69 years	3928	1.4 (1.1)	1.5 (1.1)	9.1 (9.7)	4.5 (1.0)	3.1 (0.9)	2.2 (1.1)
Elementary school	79810	0.7 (0.9)	0.9 (1.0)	2.7 (9.6)	3.8 (1.1)	2.4 (1.0)	1.7 (1.0)
High school	62690	0.5 (0.8)	0.7 (0.9)	-0.3 (8.8)	3.6 (1.0)	2.3 (0.9)	1.6 (1.0)
University	11610	0.4 (0.7)	0.6 (0.8)	-1.9 (8.3)	3.6 (1.0)	2.3 (0.9)	1.6 (0.8)
Social class I	10744	0.4 (0.8)	0.5 (0.8)	-2.0 (8.3)	3.6 (0.9)	2.3 (0.9)	1.6 (0.8)
Social class II	51230	0.5 (0.8)	0.7 (0.9)	-0.5 (8.7)	3.7 (1.0)	2.3 (0.9)	1.6 (1.0)
Social class III	92136	0.7 (0.9)	0.9 (1.0)	2.4 (9.6)	3.8 (1.1)	2.4 (1.0)	1.7 (1.0)
Non physical activity	73684	1.0 (1.0)	1.3 (1.0)	4.8 (9.5)	4.2 (1.1)	2.8 (1.1)	2.2 (1.2)
Yes physical activity	80426	0.3 (0.5)	0.3 (0.6)	-2.3 (7.8)	3.2 (0.7)	2.0 (0.6)	1.3 (0.4)
Non Mediterranean diet	74828	1.0 (1.0)	1.2 (1.0)	4.5 (9.6)	4.2 (1.1)	2.8 (1.0)	2.1 (1.2)
Yes Mediterranean diet	79282	0.3 (0.5)	0.3 (0.6)	-2.2 (7.9)	3.3 (0.7)	2.0 (0.7)	1.3 (0.5)
Non smokers	103300	0.6 (0.9)	0.7 (0.9)	-1.3 (8.6)	3.7 (1.1)	2.3 (0.9)	1.7 (1.0)
Smokers	50810	0.6 (0.8)	0.7 (1.0)	6.0 (8.9)	3.7 (1.0)	2.4 (1.0)	1.8 (1.1)

HDL-c High density lipoprotein cholesterol. LDL Low density lipoprotein cholesterol. TC Total cholesterol. TG Triglycerides. MS Metabolic syndrome. NCEP ATP III National cholesterol Education Program Adult Treatment Panel III. JIS Joint Interim Statement. ALLY Avoidable lost life years. HA Heart age

Table IIIa: Prevalence of high values of the different cardiometabolic risk scales according to sociodemographic variables and healthy habits in men.

		MS ATPIII	MS IDF	MS JIS	ALLY HA high	AD	TC/HDL -c high	LDL-c/HDL -c high	TG/HDL -c high	diabesity
Men	**n**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**
20-29 years	41742	2.8	4.1	3.8	4.2	1.6	0.1	5.2	10.4	1.3
30-39 years	76960	6.3	8.3	8.2	17.6	3.5	0.2	16.2	20.0	2.8
40-49 years	69068	11.5	14.7	14.9	36.4	5.9	0.3	30.8	30.3	6.0
50-59 years	38028	14.7	19.0	20.2	55.3	8.2	0.4	44.0	36.1	8.9
60-69 years	7016	14.5	21.4	24.1	56.0	9.1	0.5	46.8	36.3	11.4
Elementary school	142494	9.4	12.2	12.5	30.4	5.1	0.3	24.0	25.0	5.0
High school	79226	8.1	10.9	10.9	24.7	4.4	0.2	23.5	23.8	4.4
University	11094	6.9	9.0	9.8	22.1	4.1	0.1	23.0	21.5	2.9
Social class I	12262	6.9	9.1	9.7	22.5	4.2	0.1	22.5	21.4	3.0
Social class II	40650	8.0	10.9	10.8	23.0	4.4	0.2	23.4	23.8	4.4
Social class III	179902	9.2	11.9	12.2	29.6	5.0	0.3	23.9	24.8	4.9
Non physical activity	126808	16.2	20.7	21.4	39.6	8.9	0.5	37.4	43.8	8.7
Yes physical activity	106006	0.5	0.7	0.3	23.5	1.3	0.1	8.0	1.3	0.6
Non Mediterranean diet	137464	14.9	19.1	19.7	38.2	8.2	0.4	35.7	40.0	8.9
Yes Mediterranean diet	95350	0.7	0.8	0.5	13.4	1.9	0.1	7.1	2.0	1.2
Non smokers	146480	7.3	10.7	10.2	13.8	2.1	0.7	23.6	22.4	5.2
Smokers	86334	11.4	13.0	14.6	52.3	9.4	4.1	24.7	27.9	5.8

HDL-c High density lipoprotein cholesterol. LDL Low density lipoprotein cholesterol. TC Total cholesterol. TG Triglycerides. MS Metabolic syndrome. NCEP ATP III National cholesterol Education Program Adult Treatment Panel III. IDF International Diabetes Federation. JIS Joint Interim Statement. ALLY Avoidable lost life years. HA Heart age. AD Atherogenic dyslipidemia.

Table IIIb: Prevalence of high values of the different cardiometabolic risk scales according to sociodemographic variables and healthy habits in women.

		MS ATPIII	MS IDF	MS JIS	ALLY HA high	AD	TC/HDL -c high	LDL-c/HDL -c high	TG/HDL -c high	diabesity
Women	**n**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**
20-29 years	29978	0.9	1.4	1.8	2.1	0.9	0.4	7.5	4.7	0.6
30-39 years	51392	2.0	2.7	3.1	6.8	1.5	0.6	15.1	5.7	1.4
40-49 years	45296	4.2	5.4	7.0	23.7	2.4	1.3	25.9	8.8	2.6
50-59 years	23516	9.2	7.9	13.1	43.8	5.7	3.7	45.6	15.8	4.8
60-69 years	3928	12.6	10.0	18.3	49.5	8.2	4.3	48.9	18.9	7.7
Elementary school	79810	4.6	5.2	7.4	22.6	2.8	1.6	24.8	9.2	3.0
High school	62690	3.0	3.4	4.6	12.8	2.0	1.1	19.8	7.5	1.5
University	11610	2.3	2.3	3.1	9.1	1.9	1.0	18.7	5.9	1.2
Social class I	10744	2.5	2.4	3.2	9.0	1.9	0.9	18.1	6.0	1.5
Social class II	51230	3.0	3.4	4.6	12.3	2.0	1.1	20.6	7.4	1.6
Social class III	92136	4.4	4.9	7.0	21.5	2.7	1.5	23.8	9.0	2.8
Non physical activity	73684	7.7	8.5	12.0	29.2	5.0	2.8	39.4	17.2	4.7
Yes physical activity	80426	0.2	0.2	0.4	7.0	0.2	0.3	6.7	1.3	0.2
Non Mediterranean diet	74828	7.2	8.5	11.8	28.4	5.0	2.7	37.8	16.4	4.7
Yes Mediterranean diet	79282	0.2	0.2	0.4	7.4	0.3	0.4	7.7	1.6	0.2
Non smokers	103300	3.7	4.1	5.8	10.9	2.5	1.3	23.5	7.9	1.6
Smokers	50810	3.8	4.4	6.2	31.2	2.6	1.4	19.8	9.1	2.1

HDL-c High density lipoprotein cholesterol. LDL Low density lipoprotein cholesterol. TC Total cholesterol. TG Triglycerides. MS Metabolic syndrome. NCEP ATP III National cholesterol Education Program Adult Treatment Panel III. IDF International Diabetes Federation. JIS Joint Interim Statement. ALLY Avoidable lost life years. HA Heart age. AD Atherogenic dyslipidemia.

Table IV: Multinomial logistic regression.

	MS NCEP ATPIII	MS IDF	MS JIS	ALLY HA high	AD	TC/HDL -c high	LDL-c/HDL -c high	TG/HDL -c high	Diabesity
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Female	1	1	1	1	1	1	1	1	1
Male	2.08 (2.01-2.14)	2.63 (2.55-2.71)	1.83 (1.78-1.88)	1.98 (1.70-3.27)	1.11 (1.07-1.15)	0.89 (0.80-0.98)	0.90 (0.81-0.97)	2.21 (2.07-2.35)	2.19 (2.01-2.38)
20-29 years	1	1	1	1	1	1	1	1	1
30-39 years	1.11 (1.04-1.18)	1.18 (1.11-1.25)	1.34 (1.27-1.41)	3.12 (2.80-3.44)	1.06 (1.03-1.10)	1.16 (1.11-1.21)	1.15 (1.07-1.23)	1.20 (1.13-1.28)	1.22 (1.15-1.29)
40-49 years	1.43 (1.35-1.52)	1.38 (1.31-1.46)	1.80 (1.71-1.90)	6.10 (5.30-6.90)	1.09 (1.05-1.13)	1.30 (1.20-1.41)	1.30 (1.21-1.39)	1.59 (1.41-1.77)	1.40 (1.30-1.51)
50-59 years	2.13 (2.00-2.27)	2.03 (1.92-2.15)	2.82 (2.68-2.98)	8.15 (7.05-9.25)	1.21 (1.16-1.26)	1.79 (1.65-1.93)	1.80 (1.59-2.01)	1.99 (1.70-2.29)	1.89 (1.65-2.13)
60-69 years	3.50 (3.24-3.79)	3.00 (2.80-3.22)	4.32 (4.04-4.62)	11.33 (10.01-12.65)	1.30 (1.16-1.45)	2.45 (2.20-2.7.)	2.10 (1.98-2.23)	2.75 (2.41-3.09)	2.31 (2.05-2.57)
Social class I	1	1	1	1	1	1	1	1	1
Social class II	1.07 (1.02-1.11)	1.08 (1.04-1.11)	1.07 (1.04-1.11)	1.15 (1.10-1.21)	1.12 (1.05-1.19)	1.36 (1.23-1.40)	1.18 (1.12-1.24)	1.23 (1.18-1.28)	1.33 (1.21-1.45)
Social class III	1.18 (1.10-1.26)	1.26 (1.19-1.34)	1.20 (1.13-1.27)	1.45 (1.37-1.54)	1.28 (1.21-1.36)	1.88 (1.71-2.05)	1.39 (1.27-1.51)	1.56 (1.40-1.72)	1.57 (1.40-1.74)
Yes physical activity	1	1	1	1	1	1	1	1	1
Non physical activity	46.37 (38.58-55.74)	13.81 (12.58-15.15)	18.43 (16.69-20.34)	4.12 (3.50-4.75)	1.89 (1.75-2.03)	8.13 (7.83-8.44)	6.38 (5.98-6.79)	8.52 (8.13-8.91)	6.25 (6.01-6.49)
Yes Mediterranean diet	1	1	1	1	1	1	1	1	1
Non Mediterranean diet	5.38 (4.66-6.21)	3.26 (2.97-3.57)	3.73 (3.40-4.09)	2.28 (1.70-2.86)	1.71 (1.60-1.82)	5.25 (4.95-5.56)	5.29 (4.99-5.60)	5.32 (4.97-5.67)	5.03 (4.74-5.32)
Non smokers	1	1	1	1	1	1	1	1	1
Smokers	1.73 (1.69-1.78)	1.39 (1.36-1.43)	1.69 (1.65-1.73)	4.29 (3.80-4.79)	1.19 (1.11-1.27)	1.21 (1.13-1.29)	1.19 (1.08-1.30)	1.28 (1.21-1.36)	1.23 (1.08-1.39)

HDL-c High density lipoprotein cholesterol. LDL Low density lipoprotein cholesterol. TC Total cholesterol. TG Triglycerides. MS Metabolic syndrome. NCEP ATP III National cholesterol Education Program Adult Treatment Panel III. IDF International Diabetes Federation. JIS Joint Interim Statement. ALLY Avoidable lost life years. HA Heart age. AD Atherogenic dyslipidemia.

Discussion

All sociodemographic variables (age, sex, social class and educational level) and all health habits (physical activity, Mediterranean diet and smoking) influence the values of all the cardiometabolic risk scales analyzed, whether metabolic syndrome, atherogenic risk, diabesity or heart age.

Understanding the intricate relationship between age, gender, socioeconomic status (SES), education level, physical activity, adherence to the Mediterranean diet, and tobacco use is essential for comprehensively addressing various metabolic disorders. This discussion

aims to delve into the multifaceted influences of these factors on conditions such as metabolic syndrome, atherogenesis, diabesity, and heart age, to provide a holistic understanding.

Age plays a pivotal role in the onset and progression of metabolic disorders. Advancing age is associated with an increased risk of developing metabolic syndrome, atherogenesis, and diabesity, as physiological changes occur, leading to alterations in lipid metabolism, insulin sensitivity, and cardiovascular function[51]. Gender differences also influence the prevalence and presentation of these disorders, with men generally exhibiting higher rates of metabolic syndrome and atherogenesis, while women may experience increased risks post-menopause due to hormonal changes[52].

SES and education level significantly impact the development and management of metabolic disorders. Individuals from lower SES backgrounds often face barriers to accessing healthcare, nutritious foods, and opportunities for physical activity, leading to a higher prevalence of metabolic syndrome, atherogenesis, and diabesity[53]. Additionally, lower educational attainment is associated with poorer health outcomes and limited health literacy, contributing to disparities in disease prevalence and management[54].

Regular physical activity is a cornerstone in the prevention and management of metabolic disorders. Engaging in exercise improves insulin sensitivity, lipid profiles, and cardiovascular health, thereby reducing the risk of metabolic syndrome, atherogenesis, and diabesity[55]. Conversely, sedentary behavior exacerbates these conditions, leading to metabolic dysfunction and increased cardiovascular risk.

Adherence to the Mediterranean diet has been consistently associated with a reduced risk of metabolic disorders. This dietary pattern, rich in fruits, vegetables, whole grains, fish, and olive oil, exerts cardioprotective effects, improving lipid profiles, insulin sensitivity, and endothelial function[56]. Furthermore, the Mediterranean diet may mitigate the progression of atherogenesis and diabesity, thereby promoting overall cardiovascular health.

Tobacco use is a modifiable risk factor that significantly influences the development and progression of metabolic disorders. Smoking is associated with insulin resistance, dyslipidemia, and systemic inflammation, contributing to the pathogenesis of metabolic syndrome, atherogenesis, and diabesity[57]. Smoking cessation interventions are crucial for reducing the burden of these conditions and improving overall health outcomes.

Metabolic syndrome, characterized by a cluster of metabolic abnormalities including central obesity, hypertension, dyslipidemia, and insulin resistance, is influenced by various demographic and lifestyle factors. Age, gender, SES, education level, physical activity, adherence to a healthy diet, and tobacco use collectively contribute to the development and progression of metabolic syndrome[58].

Atherogenesis, the process of plaque formation in arterial walls, is closely linked to metabolic syndrome and its associated risk factors. Age, gender, SES, education level, physical inactivity, poor dietary habits, and tobacco use promote atherogenesis by exacerbating inflammation, oxidative stress, and endothelial dysfunction[59]. Lifestyle modifications targeting these factors are essential for preventing this process.

Diabesity, the intertwined occurrence of diabetes and obesity, represents a major public health challenge. Age, gender, SES, education level, physical inactivity, unhealthy dietary patterns, and tobacco use contribute to the rising prevalence of diabesity[60,61]. Addressing these factors through lifestyle interventions and population-level strategies is critical for stemming the diabesity epidemic and reducing its associated.

Heart age, an estimate of cardiovascular risk based on multiple risk factors, is influenced by age, gender, socioeconomic factors, lifestyle behaviors, and comorbidities. Age, gender, SES, education level, physical inactivity, poor diet quality, and tobacco use contribute to accelerated aging of the heart, increasing the risk of cardiovascular events and mortality[62]. Strategies aimed at optimizing cardiovascular health across the lifespan are essential for reducing heart age and improving overall cardiovascular outcomes.

As strengths we can highlight the enormous size of the sample, which exceeds 132,000 people, and the wide variety of cardiometabolic risk scales analyzed.

The main limitation is that the study was carried out in the working population (aged 18 to 69 years), so it is not possible to extrapolate our results to those of the general population.

Conclusion

The relationship between age, gender, SES, education level, physical activity, adherence to a Mediterranean diet, tobacco use, and various metabolic disorders including metabolic syndrome, atherogenesis, diabesity, and heart age is complex and multifaceted. Addressing these factors through targeted interventions and population-level strategies is paramount for reducing the burden of these disorders and improving overall cardiovascular health outcomes

Conflict of interest

The authors declare that they have no competing interests.

References

1. Lancellotti P. Focus on cardiometabolic risk factors. Acta Cardiol. 2023 Jul;78(5):515-518. doi: 10.1080/00015385.2023.2231702.

2. O'Hearn M, Lauren BN, Wong JB, Kim DD, Mozaffarian D. Trends and Disparities in Cardiometabolic Health Among U.S. Adults, 1999-2018. J Am Coll Cardiol. 2022 Jul 12;80(2):138-151. doi: 10.1016/j.jacc.2022.04.046.

3. Brown AF, Liang LJ, Vassar SD, Escarce JJ, Merkin SS, Cheng E, et al. Trends in Racial/Ethnic and Nativity Disparities in Cardiovascular Health Among Adults Without Prevalent Cardiovascular Disease in the United States, 1988 to 2014. Ann Intern Med. 2018 Apr 17;168(8):541-549. doi: 10.7326/M17-0996.

4. El Khoudary SR, Aggarwal B, Beckie TM, Hodis HN, Johnson AE, Langer RD, et al. Menopause Transition and Cardiovascular Disease Risk: Implications for Timing of Early Prevention: A Scientific Statement From the American Heart Association. Circulation. 2020 Dec 22;142(25):e506-e532. doi: 10.1161/CIR.0000000000000912.

5. Wakabayashi I. Age-dependent influence of gender on the association between obesity and a cluster of cardiometabolic risk factors. Gend Med. 2012 Aug;9(4):267-77. doi: 10.1016/j.genm.2012.05.004.

6. Chang CY, Chu NF, Lin MH, Wang SC, Wu DM, Tsai MK, et al. Association between Grip Strength, Obesity, and Cardiometabolic Risk Factors among the Community-Dwelling Elderly Population in Taiwan. Int J Environ Res Public Health. 2022 Sep 9;19(18):11359. doi: 10.3390/ijerph191811359.

7. Ruiz LD, Zuelch ML, Dimitratos SM, Scherr RE. Adolescent Obesity: Diet Quality, Psychosocial Health, and Cardiometabolic Risk Factors. Nutrients. 2019 Dec 23;12(1):43. doi: 10.3390/nu12010043.

8. Strack C, Behrens G, Sag S, Mohr M, Zeller J, Lahmann C, et al. Gender differences in cardiometabolic health and disease in a cross-sectional observational obesity study. Biol Sex Differ. 2022 Mar 4;13(1):8. doi: 10.1186/s13293-022-00416-4.

9. Mehta LS, Velarde GP, Lewey J, Sharma G, Bond RM, Navas-Acien A, et al. Cardiovascular Disease Risk Factors in Women: The Impact of Race and Ethnicity: A Scientific Statement From the American Heart Association. Circulation. 2023 May 9;147(19):1471-1487. doi: 10.1161/CIR.0000000000001139.

10. Marlatt KL, Pitynski-Miller DR, Gavin KM, Moreau KL, Melanson EL, Santoro N, et al. Body composition and cardiometabolic health across the menopause transition. Obesity (Silver Spring). 2022 Jan;30(1):14-27. doi: 10.1002/oby.23289.

11. Abdulnour J, Doucet E, Brochu M, Lavoie JM, Strychar I, Rabasa-Lhoret R, et al. The effect of the menopausal transition on body composition and cardiometabolic risk factors: a Montreal-Ottawa New Emerging Team group study. Menopause. 2012 Jul;19(7):760-7. doi: 10.1097/gme.0b013e318240f6f3.

12. Greendale GA, Han W, Finkelstein JS, Burnett-Bowie SM, Huang M, Martin D, et al. Changes in Regional Fat Distribution and Anthropometric Measures Across the Menopause Transition. J Clin Endocrinol Metab. 2021 Aug 18;106(9):2520-2534. doi: 10.1210/clinem/dgab389.

13. De Paoli M, Zakharia A, Werstuck GH. The Role of Estrogen in Insulin Resistance: A Review of Clinical and Preclinical Data. Am J Pathol. 2021 Sep;191(9):1490-1498. doi: 10.1016/j.ajpath.2021.05.011.

14. Daran B, Levasseur P, Clément M. Updating the association between socioeconomic status and obesity in low-income and lower-middle-income sub-Saharan African countries: A literature review. Obes Rev. 2023 Oct;24(10):e13601. doi: 10.1111/obr.13601.

15. Li Y, Li J, Nima Q. Associations of socioeconomic status and obesity with hypertension in tibetan adults in a Chinese plateau area. BMC Public Health. 2023 Sep 21;23(1):1840. doi: 10.1186/s12889-023-15864-9.

16. Pelekanakis A, O'Loughlin JL, Maximova K, Montreuil A, Kalubi J, Dugas EN, et al. Associations of Quantity Smoked and Socioeconomic Status With Smoke-Free Homes and Cars Among Daily Smokers. Health Educ Behav. 2022 Jun;49(3):488-496. doi: 10.1177/10901981211010437.

17. Ayo-Yusuf OA, Omole OB. Nicotine dependence, socioeconomic status, lifestyle behaviours and lifetime quit attempts among adult smokers in South Africa. S Afr Med J. 2020 Jul 29;110(8):796-801. doi: 10.7196/SAMJ.2020.v110i8.13466.

18. Li R, Li R, Xie J, Chen J, Liu S, Pan A, et al. Associations of socioeconomic status and healthy lifestyle with incident early-onset and late-onset dementia: a prospective cohort study. Lancet Healthy Longev. 2023 Dec;4(12):e693-e702. doi: 10.1016/S2666-7568(23)00211-8.

19. Merhout F, Doyle J. Socioeconomic Status and Diet Quality in College Students. J Nutr Educ Behav. 2019 Oct;51(9):1107-1112. doi: 10.1016/j.jneb.2019.06.021.

20. Silva FACCD, Bragança MLBM, Bettiol H, Cardoso VC, Barbieri MA, Silva AAMD. Socioeconomic status and cardiovascular risk factors in young adults: a cross-sectional analysis of a Brazilian birth cohort. Rev Bras Epidemiol. 2020 Feb 21;23:e200001. doi: 10.1590/1980-549720200001.

21. Barnard ND, Alwarith J, Rembert E, Brandon L, Nguyen M, Goergen A, et al. A Mediterranean Diet and Low-Fat Vegan Diet to Improve Body Weight and Cardiometabolic Risk Factors: A Randomized, Cross-over Trial. J Am Nutr Assoc. 2022 Feb;41(2):127-139. doi: 10.1080/07315724.2020.1869625.

22. Estruch R, Ros E. The role of the Mediterranean diet on weight loss and obesity-related diseases. Rev Endocr Metab Disord. 2020 Sep;21(3):315-327. doi: 10.1007/s11154-020-09579-0.

23. Astrup A, Magkos F, Bier DM, Brenna JT, de Oliveira Otto MC, Hill JO, et al. Saturated Fats and Health: A Reassessment and Proposal for Food-Based Recommendations: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020 Aug 18;76(7):844-857. doi: 10.1016/j.jacc.2020.05.077.

24. Huang Y, Chen Z, Chen B, Li J, Yuan X, Li J, et al. Dietary sugar consumption and health: umbrella review. BMJ. 2023 Apr 5;381:e071609. doi: 10.1136/bmj-2022-071609.

25. Madalosso MM, Martins NNF, Medeiros BM, Rocha LL, Mendes LL, Schaan BD, et al. Consumption of ultra-processed foods and cardiometabolic risk factors in Brazilian adolescents: results from ERICA. Eur J Clin Nutr. 2023 Nov;77(11):1084-1092. doi: 10.1038/s41430-023-01329-0.

26. Park W, Jung WS, Hong K, Kim YY, Kim SW, Park HY. Effects of Moderate Combined Resistance- and Aerobic-Exercise for 12 Weeks on Body Composition, Cardiometabolic Risk Factors, Blood Pressure, Arterial Stiffness, and Physical Functions, among Obese Older Men: A Pilot Study. Int J Environ Res Public Health. 2020 Oct 3;17(19):7233. doi: 10.3390/ijerph17197233.

27. Rosoff DB, Davey Smith G, Mehta N, Clarke TK, Lohoff FW. Evaluating the relationship between alcohol consumption, tobacco use, and cardiovascular disease: A multivariable Mendelian randomization study. PLoS Med. 2020 Dec 4;17(12):e1003410. doi: 10.1371/journal.pmed.1003410.

28. Vallée A. Association between tobacco smoking and alcohol consumption with arterial stiffness. J Clin Hypertens (Greenwich). 2023 Aug;25(8):757-767. doi: 10.1111/jch.14669.

29. Ishida M, Sakai C, Kobayashi Y, Ishida T. Cigarette Smoking and Atherosclerotic Cardiovascular Disease. J Atheroscler Thromb. 2024 Mar 1;31(3):189-200. doi: 10.5551/jat.RV22015.

30. Chavan RP, Ingole SM, Jagtap VR, Desai WV, Kanchewad GS. Comparative Study of Serum Lipid Profile in Tobacco Addicts, Tobacco Non-addicts and Head-Neck Malignancy. Indian J Otolaryngol Head Neck Surg. 2022 Oct;74(Suppl 2):1803-1808. doi: 10.1007/s12070-020-01812-1.

31. Kos K. Cardiometabolic Morbidity and Mortality with Smoking Cessation, Review of Recommendations for People with Diabetes and Obesity. Curr Diab Rep. 2020 Dec 8;20(12):82. doi: 10.1007/s11892-020-01352-6.

32. Romaszko J, Gromadziński L, Buciński A. Friedewald formula may be used to calculate non-HDL-C from LDL-C and TG. Front Med (Lausanne). 2023 Sep 14;10:1247126. doi: 10.3389/fmed.2023.1247126.

33. Riutord Sbert P, Riutord Fe B, Riutord Fe N, Arroyo Bote S, López-González AA, Ramírez Manent JI. Relationship between physical activity and adherence to the mediterranean diet with metabolic syndrome, hypertriglyceridemic waist phenotype and hypertensive waist. Academic Journal of Health Sciences 2022;37(6):33-8 doi: 10.3306/AJHS.2022.37.06.33

34. Martínez Jover A, López-González AA, Tomás Gil P, Coll Villalonga JL, Martí Lliteras P, Ramírez Manent JI. Association between different cardiometabolic risk scales and metabolic syndrome scales in 418.343 Spanish workers. Academic Journal of Health Sciences 2022;38(4):152-7 doi: 10.3306/AJHS.2023.38.04.152

35. Sastre-Alzamora T, Tomás-Gil P, Paublini H, Pallarés L, Ramírez-Manent JI, López-González AA. Relationship between heart age and cardiometabolic risk scales in 139634 Spanish workers. Academic Journal of Health Sciences 2024; 39 (1):141- 148 doi: 10.3306/AJHS.2024.39.01.141

36. Sastre-Alzamora T, Tomás-Gil P, Paublini H, Pallarés L, Ramírez-Manent JI, López-González AA. Relationship between heart age and insulin resistance risk scales in 139634 Spanish workers. Academic Journal of Health Sciences 2024; 39 (1):16-22 doi: 10.3306/AJHS.2024.39.01.16

37. Sastre-Alzamora T, Tomás-Gil P, Paublini H, Pallarés L, Ramírez-Manent JI, López-González AA. Relationship between heart age and insulin resistance risk scales in 139634 Spanish workers. Academic Journal of Health Sciences 2024; 39 (1):16-22 doi: 10.3306/AJHS.2024.39.01.16

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

39. Sastre-Alzamora T, Tomás-Gil P, Martí Lliteras P, Pallarés L, Ramírez-Manent JI, López-González AA. Estimation of heart age in 139.634 spanish workers: influence of sociodemographic variables and healthy habits and determination of cut-off points. Academic Journal of Health Sciences 2023; 38 (2): 24-30 doi: 10.3306/AJHS.2023.38.02.24

40. Ramírez-Manent JI, Tomás-Gil P , Coll-Villalonga JL , Marti-Lliteras P, López-González AA, Paublini H. Influence of sociodemographic variables and tobacco consumption on the prevalence of atherogenic dyslipidemia and lipid triad in 418.343 spanish workers. Academic Journal of Health Sciences 2023; 38 (6):84-9 doi: 10.3306/AJHS.2023.38.06.84

41. Alifu J, Xiang L, Zhang W, Qi P, Chen H, Liu L, et al. Association between the atherogenic index of plasma and adverse long-term prognosis in patients diagnosed with chronic coronary syndrome. Cardiovasc Diabetol. 2023 Sep 21;22(1):255. doi: 10.1186/s12933-023-01989-z.

42. Qin Z, Zhou K, Li Y, Cheng W, Wang Z, Wang Jet al. The atherogenic index of plasma plays an important role in predicting the prognosis of type 2 diabetic subjects undergoing percutaneous coronary intervention: results from an observational cohort study in China. Cardiovasc Diabetol. 2020 Feb 21;19(1):23. doi: 10.1186/s12933-020-0989-8.

43. López González ÁA, Rivero Ledo YI, Vicente Herrero MT, Gil Llinás M, Tomás Salvá M, Riutord Fe B. Índices aterogénicos en trabajadores de diferentes sectores laborales del área Mediterránea Española [Atherogenic indices in workers of different occupational sectors of the Spanish Mediterranean area]. Clin Investig Arterioscler. 2015 May-Jun;27(3):118-28. Spanish. doi: 10.1016/j.arteri.2014.10.004.

44. Li Y, Teng D, Shi X, Qin G, Qin Y, Quan H, et al. Prevalence of diabetes recorded in mainland China using 2018 diagnostic criteria from the American Diabetes Association: national cross sectional study. BMJ. 2020 Apr 28;369:m997. doi: 10.1136/bmj.m997.

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

46. Hosking DE, Eramudugolla R, Cherbuin N, Anstey KJ. MIND not Mediterranean diet related to 12-year incidence of cognitive impairment in an Australian longitudinal cohort study. Alzheimers Dement. 2019 Apr;15(4):581-589. doi: 10.1016/j.jalz.2018.12.011.

47. Vieira LM, Gottschall CBA, Vinholes DB, Martinez-Gonzalez MA, Marcadenti A. Translation and cross-cultural adaptation of 14-item Mediterranean Diet Adherence Screener and low-fat diet adherence questionnaire. Clin Nutr ESPEN. 2020 Oct;39:180-189. doi: 10.1016/j.clnesp.2020.06.018.

48. Cleland C, Ferguson S, Ellis G, Hunter RF. Validity of the International Physical Activity Questionnaire (IPAQ) for assessing moderate-to-vigorous physical activity and sedentary behaviour of older adults in the United Kingdom. BMC Med Res Methodol. 2018 Dec 22;18(1):176. doi: 10.1186/s12874-018-0642-3.

49. Montero-Sandiego E, Ruiz-Robledillo N, Ferrer-Cascales R, Clement-Carbonell V, Alcocer-Bruno C, Albaladejo-Blázquez N. Spanish validation of the simple lifestyle indicator questionnaire: validity and reliability analysis. Front Public Health. 2024 Jan 9;11:1146010. doi: 10.3389/fpubh.2023.1146010.

50. Ashall V, Morton D, Clutton E. A Declaration of Helsinki for animals. Vet Anaesth Analg. 2023 Jul;50(4):309-314. doi: 10.1016/j.vaa.2023.03.005.

51. Kim MK, Han K, Park YM, et al. Associations of variability in blood pressure, glucose and cholesterol concentrations, and body mass index with mortality and cardiovascular outcomes in the general population. Circulation. 2020;141(9):782-793.

52. Bowen ME, Xuan L, Lingvay I, Halm EA. Association between sex and clinical outcomes in patients with type 2 diabetes and cardiovascular disease: A report from TECOS. Diabetes, Obesity and Metabolism. 2019;21(9):2125-2134.

53. Gnavi R, Karaghiosoff L, Costa G, Merletti F, Bruno G. Socioeconomic differentials in mortality and disease occurrence among people with diabetes mellitus: a population-based study in Turin, Italy. Soc Sci Med. 2014;101:36-45.

54. Chen X, Kwan S, Wang S, et al. The association between education level and obesity among adults aged 50 years and older in six middle-income countries. PLOS ONE. 2021;16(5):e0251972.

55. Colberg SR, Sigal RJ, Yardley JE, et al. Physical activity/exercise and diabetes: A position statement of the American Diabetes Association. Diabetes Care. 2021;44(1):S83-S99.

56. Estruch R, Ros E, Salas-Salvadó J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. New England Journal of Medicine. 2018;378(25):e34.

57. Rønn PF, Andersen GS, Lauritzen T, et al. Tobacco smoking and risk of type 2 diabetes: A systematic review and dose-response meta-analysis. Diabetologia. 2020;63(2):107-114.

58. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009 Oct 20;120(16):1640-5. doi: 10.1161/CIRCULATIONAHA.109.192644.

59. Libby P, Pasterkamp G, Crea F, Jang IK. Reassessing the Mechanisms of Acute Coronary Syndromes. Circ Res. 2019 Jan 4;124(1):150-160. doi: 10.1161/CIRCRESAHA.118.311098.

60. Michaelidou M, Pappachan JM, Jeeyavudeen MS. Management of diabesity: Current concepts. World J Diabetes. 2023 Apr 15;14(4):396-411. doi: 10.4239/wjd.v14.i4.396.

61. Pappachan JM, Fernandez CJ, Chacko EC. Diabesity and antidiabetic drugs. Mol Aspects Med. 2019 Apr;66:3-12. doi: 10.1016/j.mam.2018.10.004.

62. Arai H, Kawakubo M, Kadokami T. Editorial for "Image-Based Biological Heart Age Estimation Reveals Differential Aging Patterns Across Cardiac Chambers". J Magn Reson Imaging. 2023 Dec;58(6):1813-1814. doi: 10.1002/jmri.28687.

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ORIGINAL

MutS Homolog 2 and MutS Homolog 3 genes are equivocal in prostate disease diagnosis: A study from Niger Delta University Teaching Hospital (NDUTH) in Okolobiri, Bayelsa State, Nigeria

Los genes MutS Homolog 2 y MutS Homolog 3 son equívocos en el diagnóstico de la enfermedad prostática: Un estudio del Hospital Universitario del Delta del Níger (NDUTH) en Okolobiri, Estado de Bayelsa, Nigeria.

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Abstract

Introduction: The most prevalent cancer among men worldwide is prostate cancer. It is the third most prevalent disease in America and the sixth most common cause of cancer-related death for males globally. For advanced prostate cancer, immunotherapy and other treatments are guided only by microsatellite instability (MSI) as a biomarker. This study was aimed at evaluating the expression of MutS Homolog 2 (MSH2) and MutS Homolog 3 (MSH3) genes in prostate disease patients attending Niger Delta University Teaching Hospital (NDUTH) Okolobiri Bayelsa State, Nigeria.
Methods: A total of 113 formalin-fixed paraffin embedded (FFPE) archived prostate tissue blocks from 2010 to 2020 were used for the study, with a mean age of 63.3years. Haematoxylin and eosin and avidin-biotin methods were adopted for histomorphology and immunohistochemistry evaluations, respectively.
Results: Malignant samples were 48 (42.5%), non-malignant samples 59 (52.2%), and inadequate samples of 06 (5.3%). Less than 4% of the participants were below 50 years old, and 96.5% were above 50 years old. 75.0% of those above 50 years showed positive expression for the MSH2 and MSH3 genes. Adenocarcinoma accounted for 48 (42.5%), benign prostatic hyperplasia 45 (39.8%), hypertrophy and prostatitis 6 (0.05%), prostatitis 3 (0.03%), and PIN 4 (0.04%). The expression of MSH2 and MSH3 was highest in adenocarcinoma of the prostate (98% and 98%), followed by benign prostatic hyperplasia (97.8% and 95.6%), and hypertrophy and prostatitis (83.3% and 100%), respectively.
Conclusions: The expression of MSH2 and MSH3 is equivocal in prostrate pathology in the present study and therefore lacks merit as prostate cancer biomarkers among the indigenous black population.

Key words: Prostate cancer, MSH2, MSH3, Microsatellite, immunohistochemistry.

Resumen

Introducción: El cáncer de próstata es la neoplasia maligna masculina más frecuente. Es el segundo más frecuente de todos los cánceres diagnosticados y representa la sexta causa de muerte por cáncer en hombres en todo el mundo y la tercera en América. La inestabilidad de microsatélites (MSI) es el único biomarcador que guía la inmunoterapia y el tratamiento del cáncer de próstata avanzado. El objetivo de este estudio era evaluar la expresión de los genes MutS Homolog 2 (MSH2) y MutS Homolog 3 (MSH3) en la enfermedad de próstata en pacientes que acudían al Niger Delta University Teaching Hospital (NDUTH) del estado de Okolobiri Bayelsa, Nigeria.
Material y métodos: Un total de 113 bloques de tejido de próstata fijados en formol e incluidos en parafina (FFPE) archivados de 2010 a 2020 sirvieron como muestras de estudio, con una edad media de 63,3 años. Se adoptaron los métodos de hematoxilina y eosina y avidina-biotina para las evaluaciones histomorfológicas e inmunohistoquímicas, respectivamente.
Resultados: Las muestras malignas fueron 48 (42,5%), las no malignas 59 (52,2%) y las inadecuadas 06 (5,3%). Menos del 4% de los participantes tenían menos de 50 años, y el 96,5% tenían más de 50 años. El 75,0% de los mayores de 50 años mostraban una expresión positiva para los genes MSH2 y MSH3. El adenocarcinoma representaba 48 (42,5%), la hiperplasia benigna de próstata 45 (39,8%), la hipertrofia y la prostatitis 6 (0,05%), la prostatitis 3 (0,03%) y el PIN 4 (0,04%). La expresión de MSH2 y MSH3 fue mayor en el adenocarcinoma de próstata (98% y 98%), seguido de la hiperplasia prostática benigna (97,8% y 95,6%), y la hipertrofia y prostatitis (83,3% y 100%), respectivamente.
Conclusiones: La expresión de MSH2 y MSH3 es equívoca en el diagnóstico de la próstata en el presente estudio y, por lo tanto, carece de mérito como biomarcadores del cáncer de próstata entre la población negra indígena.

Palabras clave: Cáncer de próstata, MSH2, MSH3, Microsatélite, inmunohistoquímica.

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Introduction

The growth of cancer in the prostate, a gland in the male reproductive system, is known as prostate cancer or carcinoma of the prostate[1]. Prostate cancer accounted for 15% of all male cancers in 2018 and was the sixth most common cause of cancer-related deaths in men globally, making it the second most commonly diagnosed cancer[2]. For American males, prostate cancer ranks as the third leading cause of cancer-related death. Prostate tumours that spread to metastatic castration-resistant illness typically have poor survival rates[3]. Metastatic castration-resistant prostate cancer (mCRPCa) has several therapy options and recent advancements, but results vary and clinicians are unable to anticipate how patients will respond to these treatments[4].

A set of intriguing markers for the assessment of prostate cancer is microsatellite instability (MSI), with strong responses to pemubrolizumab observed in MSI-advanced mCRPCa[5]. The Bethesda panel, a 5-marker microsatellite panel, was suggested by the National Cancer Institute (NCI). The panel was created in 2004 to check for Lynch syndrome, a genetic non-polyposis colorectal cancer that affects people[6,7,8]. It is explicitly stated in the original NCI study[9] that the Bethesda reference panel should only be used for characterising MSI in colorectal cancer. Research has demonstrated the effectiveness of utilising the Bethesda panel for MSI testing in many cancer types, including as endometrial malignancies[10]. According to other research, there can be significant differences in the instability of microsatellite loci between various cancer types[11].

Microsatellite instability (MSI) is defined as the recurrent mutation of DNA sequence tracts due to the inability of the DNA mismatch repair system to rectify these errors. Deficient DNA mismatch repair (dMMR) is the outcome of bi-allelic mutational inactivation or epigenetic silencing of any of the genes in the MMR pathway (most commonly MSH2, MSH3, or MSH6, MLH1, and PMS2)[12]. The most extensively researched application of MSI has been in colorectal cancers, where expression is observed in up to 15-20% of cases[13].

A wide range of cancer types have been linked to MSI, including gastric cancer (8-22%), ovarian cancer (10%), cervical cancer (8%), and endometrial cancer (26-33%)[11,14,15]. A minority of tumours, ranging from approximately 1% in primary malignancies to up to 12% in metastatic cancers, have been reported to have MSI[15,16]. However, there has been limited research on the role of MutS homolog 2 (MSH 2) and MutS homolog 3 (MSH 3) in the detection of prostate cancer. A powerful auxiliary method such as immunohistochemistry (IHC) uses the specific binding between an antibody and antigen to identify and locate certain antigens in cells and tissue, as well as to see the reaction under a light microscope[17]. IHC has become a crucial supplementary method for clinical anatomic pathology diagnosis[18] and a standard tool in medical research settings. The study identifies the gap in MSI applications and is therefore aimed at evaluating the expression patterns of MSH 2 and MSH3 genes in prostate disease diagnosis.

Methodology

Study Area

The study was conducted in Histopathology Department, Niger Delta University Teaching Hospital (NDUTH), Okolobiri, Bayelsa State. The location is a suburban community in Yenagoa Local Government Area of Bayelsa State in the Niger Delta region of Nigeria. NDUTH is a tertiary hospital that serves the entire Bayelsa State and neighboring communities in Delta and Rivers states of Nigeria. Bayelsa State is located within latitude 4.15N and lat. 5.23S and longitude 5.21 and 6.51E of the equator, bounded by the Atlantic Ocean to the south of Nigeria. The state is the second largest producer of crude oil in Nigeria and has the largest gas reserve and oil well.

Consent and Ethical Approval

Informed consent was obtained from some respondents through their phone numbers, and all information was kept confidential in accordance with the Helsinki Declaration of 1975, as revised in 1983. The approval was obtained from the ethical and research committees at the Niger Delta University Teaching Hospital in Okolobiri. The ethical approval number for the study is NDUTH/REC/0028/2021.

Study concept

The design used was a cross-sectional and retrospective study design. A retrospective assessment of all previously reported formalin-fixed paraffin embedded (FFPE) archived prostate tissue blocks from the year 2010 to 2020 was reviewed. A total of one hundred and thirteen (113) prostate tissue blocks were retrieved from the histopathology laboratory of the Niger Delta University Teaching Hospital (NDUTH), Okolobiri, within the stipulated period. Clinical details such as the age of the patient, clinical details, and available tissue blocks, was selected, and all samples with insufficient tissue blocks and clinical details were classified or regarded as inadequate for histological and immunohistochemical diagnosis. A convenience non-probability sampling method was used to select the formalin-fixed paraffin-embedded prostate tissue blocks from the histopathology laboratory.

Histological studies and Avidin biotin complex immunohistochemistry staining

The method of[19] was adopted in preparing the prostate tissues. The tissue blocks selected were sectioned into four (4) microns using a rotatory microtome. Serial sections were floated in a water bath at a temperature of 55ºC for 2 minutes. The floated sections were picked

using labeled grease-free frosted ends slides. Some slides were used for immunohistochemistry procedures and Erhlich's hematoxylin and eosin staining. The methods of[20,21] and[17] were adopted. The Avidin Biotin Complex (ABC) method, also known as the Avidin Biotin Immunoperoxidase method, was applied to the formalin-fixed paraffin-embedded sections (FFPE). The data generated was analyzed using the statistical software package for science (SPSS) version 23.0. (Graphed Software Inc., 2014).

Results

A total of one hundred and thirteen (113) prostate tissue blocks were retrieved from the histopathology archives of the Niger Delta University Teaching Hospital (NDUTH). The mean age at presentation was 63.3 years. The results are presented in photomicrographs and tables. **Table IV-1** presents the pathology of prostate disease using the haematoxylin and eosin methods. The method describes the morphology of the tissue into malignant (cancerous) and non-malignant (pre-cancerous) lesions. Of the one hundred and thirteen samples, 48 (42.5%) showed evidence of malignancy, and 59 (52.2%) were non-malignant samples. Samples without complete clinical information and tissue blocks were 6 (5.3%).

Table IV-2 presents the distribution of prostate disorders and gene expression based on age of individual. The observation shows that 3.5% of the participants were below 50 years of age, while 96.5 percent of the participants were more than 50 years of age. Seventy-five percent (75.0%) of those above 50 years of age showed positive expression for the MSH2 and MSH3 genes.

Table IV-3 presents the distribution of prostate pathology in the population studied. Adenocarcinoma constituted 48 (42.5%) as the highest, followed by Benign prostatic hyperplasia 45 (39.8%), hypertrophy and prostatitis accounted for 6 (0.05%), prostatitis 3 (0.03%), and intraepithelial neoplasia 4 (0.04%). The expression of MSH2 and MSH3 was high in adenocarcinoma of the prostate (98%, 98%), benign prostatic hyperplasia (97.8%, 95.6%), and hypertrophy and prostatitis (83.3%, 100%), respectively.

Table IV-1: Histopathological distribution of prostate disorders.

Diagnosis	% frequency
Malignant	48(42.5)
Non-malignant	59(52.2)
Inadequate sample (poor documentation)	06(5.3)

Table IV-2: Frequency Distribution of prostate disorders and genes expression based on Age.

Age (yrs)	% frequency	Gene Expression	
		Positive	Negative
Less than 50 years	04 (3.5)	0.0	100.0
Greater than 50 years	109 (96.5)	75.0	25.0

Table IV-3: MSH 2 and MSH3 expression based on disease conditions.

Diagnosis	No examined	% MSH3 expression		% MSH2 expression	
		Positive	Negative	Positive	Negative
Adenocarcinoma	48 (42.5)	98.0	2.0	98.0	2.0
Benign prostatic hyperplasia	45 (39.8)	97.82.2		95.64.4	
Hypertrophy	1 (0.0)	0.00.0		100.0	0.0
Prostatitis	3 (0.03)	0.00.0		100.0	0.0
Hypertrophy and prostatitis	6 (0.05)	83.3	16.7	100.00.0	
Intraepithelial neoplasia	4 (0.04)	0.00.0	100.0	0.0	
Inadequate sampling	6 (0.05)	0.00.0		100.0	0.0

Plate 4.1: Transverse section of prostate tissue showing negative for malignancy. Histological grading of the tissue shows numerous dilated glands lined by double rows of cuboidal and basal epithelial cells. The stroma is fibromuscular and positive for MSH2 with moderate cytoplasmic staining (x400).

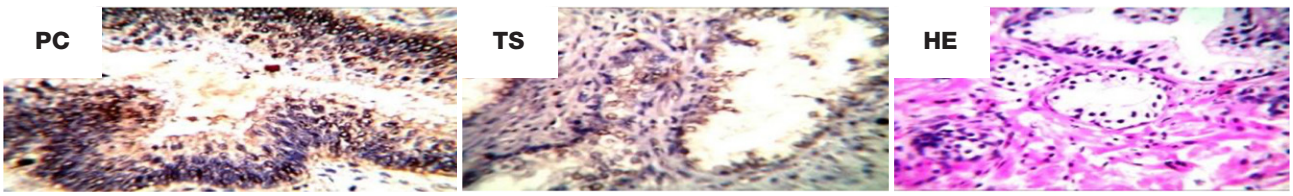


Plate 4.2: A transverse section of prostate tissue shows benign nodular hyperplasia. Histologically displaying numerous dilated glands, lined by benign epithelial cells. The stroma is hyperplastic. Immunoreactivity for MSH2 is positive with moderate to high cytoplasmic staining. (x400).

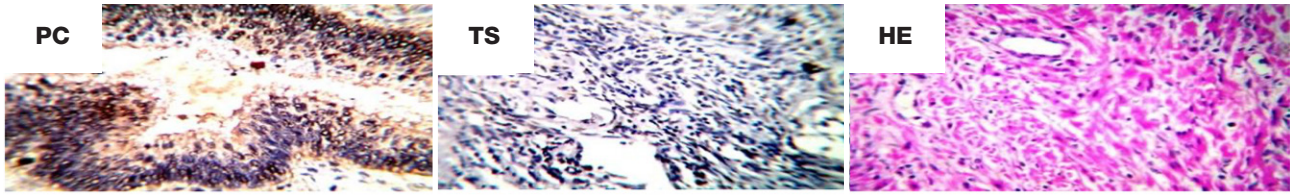


Plate 4.3: A transverse section of prostate tissue shows an Adenocarcinoma Gleason score of 5+ 2 = 7/10. Histologically, they show effaced architecture by proliferating small glands that are compact and have a back-to-back appearance with little intervening stroma. The lining cells are cosmophilic with granular cytoplasm. Positive for MSH2 immunoreactivity with moderate cytoplasmic staining (x400).

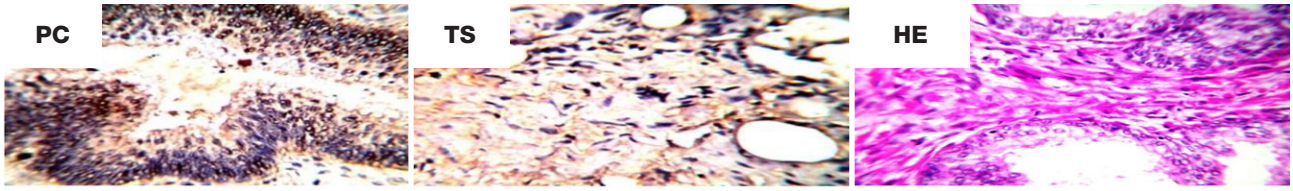


Plate 4.4: A transverse section of prostate tissue shows an atrophic prostate with prostatitis. Histology shows predominantly hyperplastic fibromuscular stroma, within which are embedded occasional clusters of cystically enlarged acini lined by multilayered epithelium. Positive for MSH2 immunoreactivity with moderate to weak cytoplasmic staining (x400).

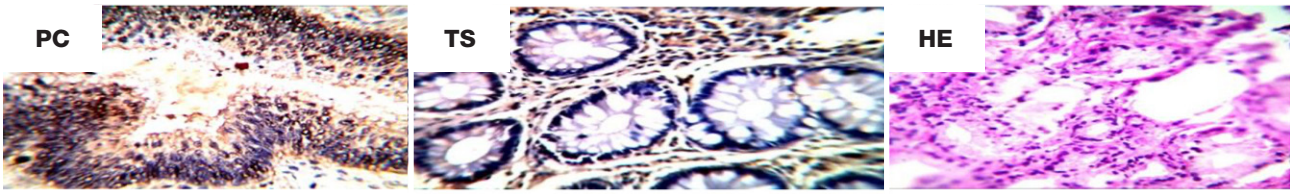


Plate 4.5: A transverse section of prostate tissue shows nodular hyperplasia with prostatitis. Histology show Glands of different sizes, most of which are dilated and lined by benign columnar cells thrown into papillary infoldings, The glands are lined by hyperplastic epithelium. The stroma is fibromuscular, enlarged, and focally infiltrated by chronic inflammatory cells. Positive for MSH2 immunoreactivity with moderate to strong cytoplasmic staining. (x400).

Plate 4.6: A transverse section of prostate tissue shows poorly differentiated adenocarcinoma of the prostate. Histology shows massive infiltration of the stroma by a sheet of malignant columnar cells in all the fragments. There is infiltration of the nerve bundle. Negative for MSH2 immunoreactivity with absence of weak cytoplasmic staining (x400).

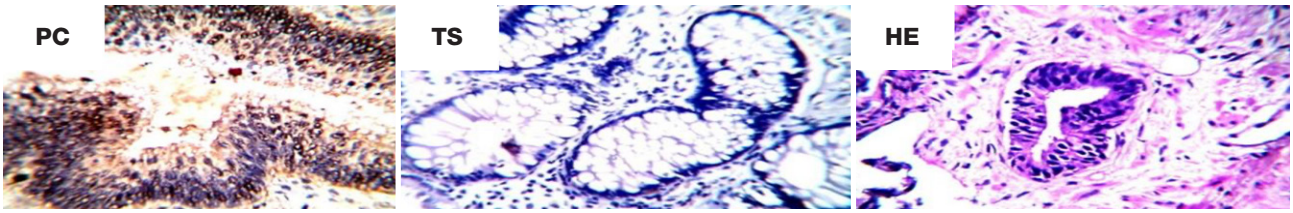


Plate 4.7: A transverse section of prostate tissue showing adenocarcinoma of the prostate Gleason score: 3+ 3 = 6/10. Histology shows a cluster of irregularly shaped glands lined by a single layer of atypical epithelium. Negative for MSH2 immunoreactivity with absence of weak cytoplasmic staining (x400).

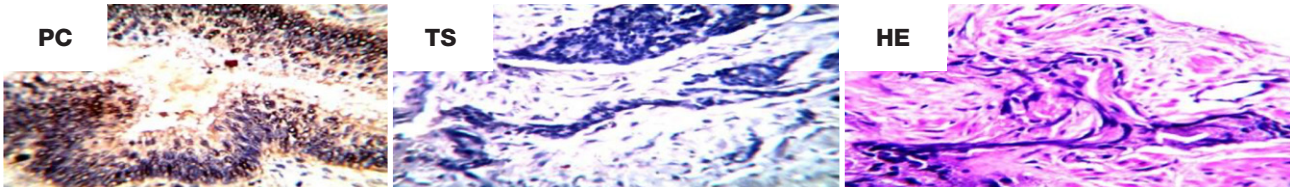


Plate 4.2.1: Transverse section of prostate tissue showing benign nodular hyperplasia. Histology shows an increased number of glands of different sizes per unit space. Some of the glands are lined by hyperplastic epithelial cells, and some dilated glands contain prostatic concretions. The stroma is fibromuscular and enlarged. Positive for MSH3 immunoreactivity with moderate to strong cytoplasmic staining (x400).

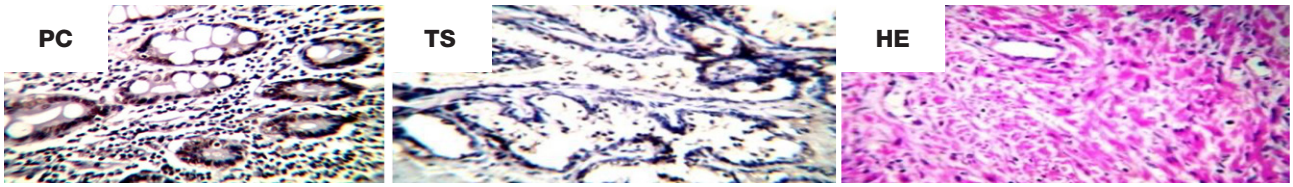


Plate 4.2.2: Transverse section of prostate tissue showing Adenocarcinoma Gleason score 5+ 2=7/10. Histology shows enfaced architecture with proliferating small glands that are compact with little intervening stroma. The lining cells are cosmophilic with granular cytoplasm. Positive for MSH3 immunoreactivity with moderate cytoplasmic staining (x400).

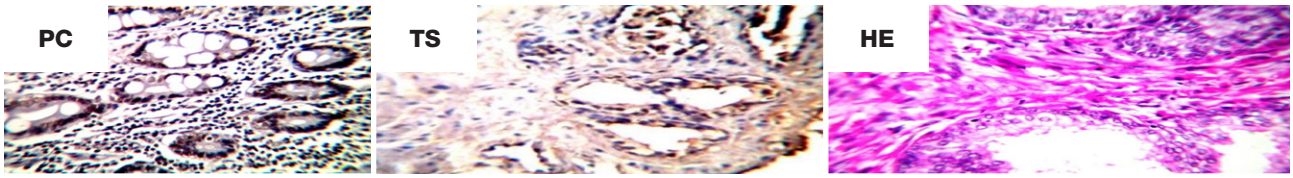


Plate 4.2.3: A transverse section of prostate tissue shows poorly differentiated adenocarcinoma of the prostate. Histology Shows diffuse infiltration of the fibromuscular stroma by sheets of malignant columnar cells. Positive for MSH3 immunoreactivity with moderate to strong cytoplasmic staining (x400).

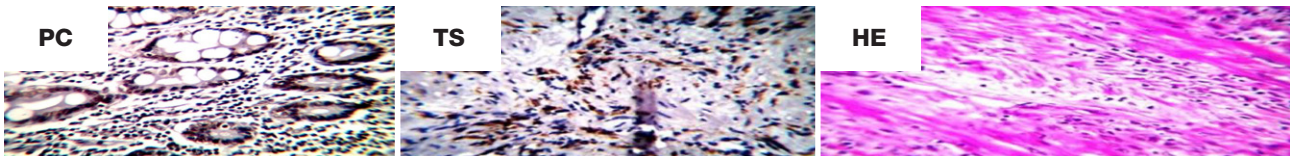


Plate 4.2.4: Transverse section of prostate tissue showing invasive, poorly differentiated adenocarcinoma. Histology Show massive infiltration of the stroma by a sheet of malignant columnar cells in all the fragments. There is infiltration of the nerve bundles. Positive for MSH3 immunoreactivity with weak to moderate cytoplasmic staining (x400).

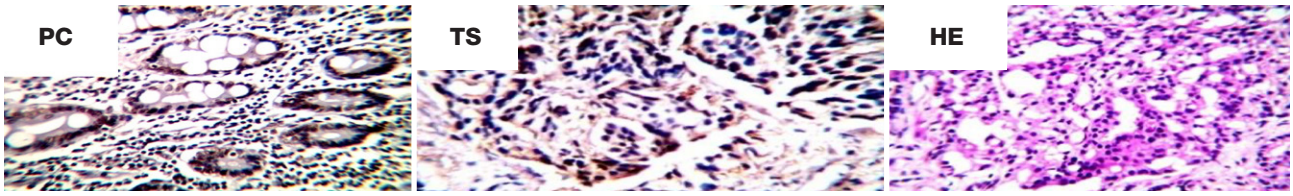


Plate 4.2.5: A transverse section of prostate tissue shows nodular hyperplasia with prostatitis. Histology shows glands of different sizes, most of which are dilated and lined by benign columnar cells thrown into the papillary in folding. Glands are lined by hyperplastic epithelial cells. Positive for MSH3 immunoreactivity with moderate to strong cytoplasmic staining (x400)

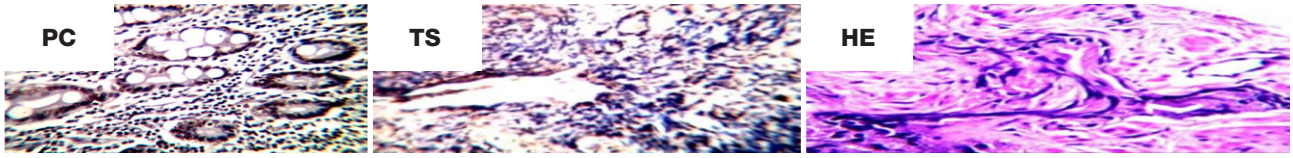


Plate 4.2.6: A transverse section of prostate tissue shows low-grade prostate intraepithelial neoplasia. Histology Show tiny fragments of fibromuscular stroma tissue with a paucity of glands. A fragment has a focal peripheral tuft of glands lined by columnar epithelial cells with a loss of basement membranes focally. Positive for MSH3 immunoreactivity with weak to moderate cytoplasmic staining (x400).

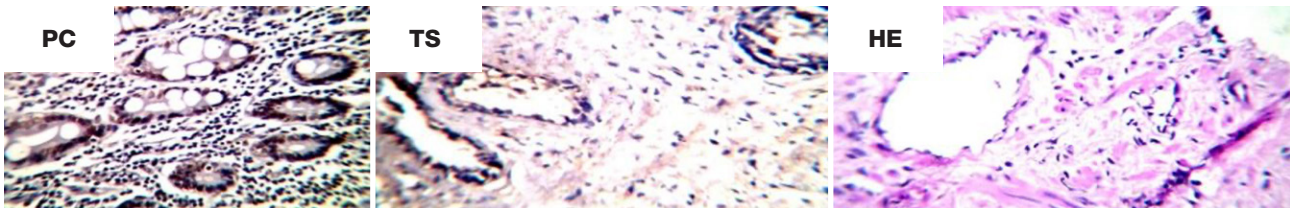


Plate 4.2.7: A transverse section of prostate tissue showing adenocarcinoma of the prostate Gleason score: 5+ 5 = 10/10. Histology shows diffuse loose sheets of malignant epithelial cells that are forming glands in places. The individual cells have large, round, and hyperchromatic nuclei, with some prominent nucleoli. The stroma is scanty and fibromuscular. There are some spindle-shaped cells scattered in the background. Positive for MSH3 immunoreactivity with moderate cytoplasmic staining (x400).

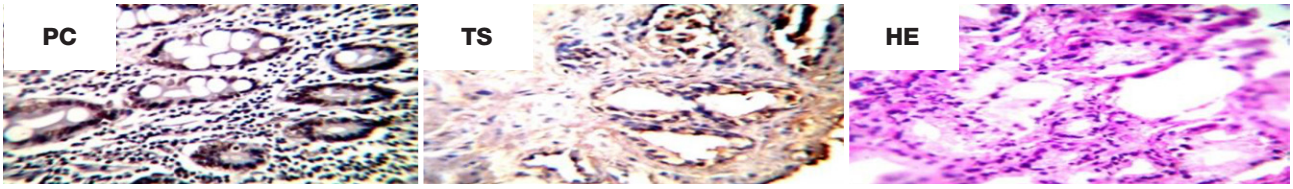
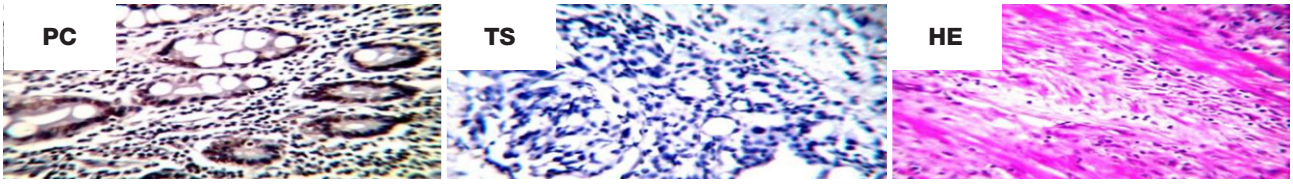


Plate 4.2.8: Transverse section of prostate tissue showing poorly differentiated adenocarcinoma of the prostate. Histology shows diffuse infiltration of the fibromuscular stroma by sheets of malignant columnar cells. Negative for MSH3 immunoreactivity with absence of weak cytoplasmic staining (x400).



Discussion

The second most common cause of cancer-related male fatalities in the United States and the most common cancer diagnosed in men globally is prostate cancer[2]. In clinical settings, prostate cancer is typically referred to as an old age disease due to its causative factors, which include increased tissue sensitivity to carcinogenic agents, age-related accumulation of mutations and carcinogenesis, and decreased ability to repair genetic damage[22].The mean age at presentation among participants was 63.3 years, meaning prostate-related disorder is a disease of the elderly in our study center, in agreement with[23], who stated that 68.3 years is the average age of Nigerian prostate cancer patients at the time of diagnosis.Histopathological assessment showed that malignant cases were 42.5% and non-malignant cases were 52%. Adenocarcinoma was the predominant cancer type, and this is in agreement with[24], which documented that ductal adenocarcinoma is the vast majority of prostate cancer pathology.

Prostate cancer with deficiency in mismatch repair (dMMR) is uncommon and poorly researched. These MMR genes include MLHI, MLH3, MSH2, MSH3, MSH6, and others[25]. The present study evaluates MSH2 and MSH3 among prostate disease patients in the Niger Delta University Teaching Hospital in Okolobiri. The study observed MSH2 and MSH3 loss in both malignant and pre-cancerous prostate tissue. This observation is in agreement with[26], which reported that microsatellite mismatch caused by defects in DNA mismatch repair proteins (MSH2, MSH3, MSH6, PMSI, PMS2, and MLH1) is widely used as a marker of cancer in the prostate among western clinicians. The majority of MSH2 and MSH3 losses occur in adenocarcinoma with a high Gleason score. This study is also in line with[26], who reported that the majority of prostate cancer associations with mutations in MSH2, MLH1, and MSH6 and the loss of respective mismatch repair proteins were expressed in 69% of the study population. Considering the percentage prevalence[26], the report is lower compared to the present report of 98.0%.

Additionally, follow-up research has demonstrated the effectiveness of the Bethesda panel for MSI testing in various cancer types, particularly endometrial malignancies[10]. According to other research, there can be significant differences in the instability of microsatellite loci between various forms of cancer [11], as documented in the present study[16,15]. also reported MSI and dMMR in several tumors ranging from ~1% in primary to up to 12% in metastatic cancers. Finally, the age of higher MSH2 and MSH3 expression was 63.3 years in our present study. This is in agreement with[26] and several other studies.

Conclusion

The expression of MSH2 and MSH3 is not specific to prostate cancer in our study, and it is expressed in both cancerous and precancerous samples. Adenocarcinoma of the prostate was the vast majority in the present study, while benign prostatic hyperplasia (BPH) was the most common benign lesion among participants. The mean age at presentation of the disease was 63 years.

Conflict of interest

The authors declare that they have no competing interests.

References

1. Hawk ET, Habermann EB, Ford JG, Wenzel JA, Brahmer JR, Chen MS Jr, et al. Five National Cancer Institute-designated cancer centers' data collection on racial/ethnic minority participation in therapeutic trials: a current view and opportunities for improvement. Cancer. 2014 Apr 1;120 Suppl 7(0 7):1113-21. doi: 10.1002/cncr.28571.

2. Prashanth R. Epidemiology of Prostate Cancer. World Journal of Oncology 2019;10(2)63-89.

3. Kirby M, Hirst C, Crawford ED. Characterizing the castration-resistant prostate cancer population: a systematic review. International Journal Clinical Practice 2011; 65:1180-92.

4. Van Soest RJ, Efstathiou JA, Sternberg CN, Tombal B. The natural history and outcome predictors of metastatic castration-resistant prostate Cancer. European Urology Focus 2016; 2:480-7.

5. Graff RE, Pettersson A, Lis RT, Ahearn TU, Markt SC, Wilson KM, et al. Dietary lycopene intake and risk of prostate cancer defined by ERG protein expression. Am J Clin Nutr 2016 Mar;103(3):851-60. doi:10.3945/ajcn.115.118703.

6. Bacher JW, Flanagan LA, Smalley RL, Nassif NA, Burgart LJ, Halberg RB, Megid WM, Thibodeau SN. Development of a fluorescent multiplex assay for detection of MSI-High tumors. Dis Markers. 2004;20(4-5):237-50. doi: 10.1155/2004/136734.

7. Bauer C, Ray A, Halstead-Nussloch B, Dekker R, Raymond V, Gruber S, et al. Hereditary prostate cancer as a feature of Lynch Syndrome. Fam Cancer 2011;10:37-42.

8. Vasen HF, Blanco I, Aktan-Collan K, Gopie JP, Alonso A, Aretz S, et al. Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. Gut 2013;62:812–23.

9. Boland CR, Thibodeau SN, Hamilton SR, Sidransky D, Eshleman JR, Burt RW, Meltzer SJ, Rodriguez-Bigas MA, Fodde R, Ranzani GN, Srivastava S. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer Res. 1998 Nov 15;58(22):5248-57.

10. Goodfellow PJ, Billingsley CC, Lankes HA, Ali S, Cohn DE, Broaddus RJ, et al. Combined Microsatellite Instability, MLH1 Methylation Analysis, and Immunohistochemistry for Lynch Syndrome Screening in Endometrial Cancers From GOG210: An NRG Oncology and Gynecologic Oncology Group Study. J Clin Oncol. 2015 Dec 20;33(36):4301-8. doi: 10.1200/JCO.2015.63.9518.

11. Hause RJ, Pritchard CC, Shendure J, Salipante SJ. Classification and Characterization of Microsatellite Instability across 18 Cancer Types. National Medical Journal 2016; 22(11), 1342-50.

12. Ryan S, Jenkins MA, Win AK. Risk of prostate cancer in Lynch syndrome: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2014 Mar;23(3):437-49. doi: 10.1158/1055-9965. EPI-13-1165.

13. Chappell WH, Candido S, Abrams SL, Russo S, Ove R, Martelli AM, et al. Roles of p53, NF-κB and the androgen receptor in controlling NGAL expression in prostate cancer cell lines. Adv Biol Regul. 2018 Aug;69:43-62. doi: 10.1016/j.jbior.2018.05.002.

14. Burger M, Denzinger S, Hammerschmied CG, Tannapfel A, Obermann EC, Wieland WF, et al. Elevated microsatellite alterations at selected tetranucleotides (EMAST) and mismatch repair gene expression in prostate cancer. J Mol Med (Berl). 2006 Oct;84(10):833-41. doi: 10.1007/s00109-006-0074-0.

15. Beltran H. DNA mismatch repair in prostate cancer. Journal Clinical Oncology 2013; 31:1782-4.

16. Oboma YI, Susan BE, Elesha SO, Jonathan M. Breast cancer biomarkers at Niger delta university hospital: Comparisons with national and international trends and clinical significance. Pathophysiology. 2017 Sep;24(3):191-196. doi: 10.1016/j.pathophys.2017.05.002.

17. Lin SL. microRNAs and Fragile X Syndrome. Advances in Experimental Medicine and Biology 2015;888, 107-21.

18. Bancroft JD, Gamble M. Theory and Practice of Histological Techniques. 6th Edition, Churchill Livingstone 2008 Elsevier China. 12(5), 725.

19. Nielsen HB, Almeida M, Juncker AS, Rasmussen S, Li J, Sunagawa S, et al. Identification and Assembly of Genomes and Genetic elements in Complex Metagenomic samples without using Reference Genomes. Nature Biotechnology 2014; 32, 822-8.

20. Aunan JR, Cho WC, Søreide K. The Biology of Aging and Cancer: A Brief Overview of Shared and Divergent Molecular Hallmarks. Aging Dis. 2017 Oct 1;8(5):628-642. doi: 10.14336/AD.2017.0103.

21. Yibala Ibor Oboma and Okutu Jackson Borobuebi. Combined aqueous extracts of garlic and ginger reduces neuronal damage by gfap and p53 protein alterations in rats exposed to lead acetate . journal of Medicine and Medical Sciences 2019, Vol.10(1)79-85, DOI:http:/dx.doi.org/10.14303/jmms.2019.1 http://www.interesjournals.org/JMMS

22. Osegbe DN. Prostate Cancer in Nigerians: facts and nonfacts. Journal of Urology 2003; 157(4), 1340-1341.

23. Lavery A, Kirby RS. Prostate Cancer. Journal of Postgraduate Medicine 2016; 44(1), 47-51.

24. Ye S, Wang H, He K, Peng M, Wang Y, Li Y, et al. Clinical Characterization of Mismatch Repair Gene-Deficient Metastatic Castration-Resistant Prostate Cancer. Front Oncol. 2020 Oct 7;10:533282. doi: 10.3389/fonc.2020.533282.

25. Caja F, Vodickova L, Kral J, Vymetalkova V, Naccarati A, Vodicka P. DNA Mismatch Repair Gene Variants in Sporadic Solid Cancers. Int J Mol Sci. 2020 Aug 3;21(15):5561. doi: 10.3390/ijms21155561.

26. Dominguez-Valentin M, Joost P, Therkildsen C, Jonsson M, Rambech E, Nilbert M. Frequent mismatch-repair defects link prostate cancer to Lynch syndrome. BMC Urol. 2016 Mar 24;16:15. doi: 10.1186/s12894-016-0130-1

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ORIGINAL

A Comparative Analysis of Radiofrequency Ablation with Contact Force Sensing and Second-Generation Cryoballoon Catheter Ablation for Paroxysmal Atrial Fibrillation: A Study at the Najaf Cardiac Center

Un análisis comparativo de la ablación por radiofrecuencia con detección de fuerza de contacto y la ablación con catéter criobalón de segunda generación para la fibrilación auricular paroxística: Un estudio en el Centro Cardiológico de Nayaf

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Summary

Introduction: Atrial fibrillation (AF) is a highly prevalent cardiac arrhythmia with substantial implications for the health of affected individuals. In light of its significant impact, current guidelines propose pulmonary vein isolation through catheter ablation as the recommended therapeutic approach for drug-refractory paroxysmal AF. Radiofrequency ablation is the predominant technique in this context, with cryoballoon ablation representing the second most frequently employed technology.
Objective: This study aimed to evaluate and compare the effectiveness and safety of radiofrequency ablation (RFA) with contact force sensing and second-generation cryoballoon ablation, specifically in treating paroxysmal AF.
Methods: The study enrolled 60 patients with paroxysmal AF at Najaf Cardiac Center, with 25 in the RFA group and 35 in the CBA group. This prospective study aimed to assess if cryoballoon ablation was non-inferior to radiofrequency ablation for drug-refractory paroxysmal atrial fibrillation. The primary efficacy endpoint, analyzed using time-to-event methods, was the first documented clinical failure (atrial fibrillation recurrence, atrial flutter/tachycardia, antiarrhythmic drug use, or repeat ablation) within 90 days post-index ablation. The primary safety endpoint was a composite of death, cerebrovascular events, or treatment-related severe adverse events.
Results: The study demonstrated that cryoballoon ablation was non-inferior to radiofrequency ablation in efficacy, showing comparable acute success and total complication rates. Both short- and long-term assessments supported the promising effectiveness and safety of cryoballoon ablation. Among 60 patients undergoing AF ablation, 35 received cryoballoon and 25 radiofrequency over a 6-month follow-up; radiofrequency procedures were lengthier without significant differences in success or complication rates.
Conclusion: The study affirms cryoballoon ablation as a viable alternative to radiofrequency ablation for drug-refractory paroxysmal atrial fibrillation. Both methods demonstrated comparable efficacy and safety, underscoring the need for personalized treatment selection.

Key words: Ablation, Atrial fibrillation, Cryoballoon, Radiofrequency.

Resumen

Introducción: La fibrilación auricular (FA) es una arritmia cardiaca muy prevalente con implicaciones sustanciales para la salud de los individuos afectados. A la luz de su importante impacto, las guías actuales proponen el aislamiento de la vena pulmonar mediante ablación con catéter como el abordaje terapéutico recomendado para la FA paroxística refractaria a fármacos. La ablación por radiofrecuencia es la técnica predominante en este contexto, y la ablación con criobalón representa la segunda tecnología más frecuentemente empleada.
Objetivo: Este estudio tiene como objetivo evaluar y comparar la eficacia y seguridad de la ablación por radiofrecuencia (ARF) con detección de fuerza de contacto y la ablación con criobalón de segunda generación, específicamente en el tratamiento de la FA paroxística.
Métodos: El estudio reclutó a 60 pacientes con FA paroxística en el Centro Cardiaco de Nayaf, con 25 en el grupo de ARF y 35 en el grupo de ACB. El objetivo de este estudio prospectivo era evaluar si la ablación con criobalón no era inferior a la ablación por radiofrecuencia en el tratamiento de la fibrilación auricular paroxística refractaria a fármacos. El criterio principal de valoración de la eficacia, analizado mediante métodos de tiempo transcurrido hasta el acontecimiento, fue el primer fracaso clínico documentado (recurrencia de la fibrilación auricular, aleteo auricular/taquicardia, uso de fármacos antiarrítmicos o repetición de la ablación) en los 90 días posteriores a la ablación de índice. El criterio de valoración primario de seguridad fue una combinación de muerte, acontecimientos cerebrovasculares o acontecimientos adversos graves relacionados con el tratamiento.
Resultados: El estudio demostró que la ablación con criobalón no era inferior a la ablación por radiofrecuencia en cuanto a eficacia, mostrando tasas comparables de éxito agudo y de complicaciones totales. Las evaluaciones a corto y largo plazo corroboraron la prometedora eficacia y seguridad de la ablación con criobalón. De los 60 pacientes sometidos a ablación de FA, 35 recibieron criobalón y 25 radiofrecuencia durante un seguimiento de 6 meses; los procedimientos con radiofrecuencia fueron más largos sin diferencias significativas en las tasas de éxito o complicaciones.
Conclusiones: El estudio afirma la ablación con criobalón como una alternativa viable a la ablación con radiofrecuencia para la fibrilación auricular paroxística refractaria a fármacos. Ambos métodos demostraron una eficacia y seguridad comparables, lo que subraya la necesidad de una selección personalizada del tratamiento.

Palabras clave: Ablación, Fibrilación auricular, Criobalón, Radiofrecuencia.

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Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting millions of individuals worldwide. Paroxysmal atrial fibrillation (PAF), characterized by recurrent episodes of AF that self-terminate within seven days, represents a significant clinical challenge due to its potential to progress to persistent or permanent forms of AF. Various treatment modalities have been developed to manage PAF, including antiarrhythmic drugs, electrical cardioversion, and catheter ablation. Catheter ablation has emerged as a practical therapeutic approach for PAF, offering the potential for long-term rhythm control and improvement in quality of life. Among the different catheter ablation techniques, radiofrequency ablation (RFA) with contact force sensing and second-generation cryoballoon catheter ablation have gained considerable attention due to their efficacy and safety profiles[1,2].

RFA with contact force sensing enables real-time assessment of catheter-tissue contact during ablation, aiming to optimize lesion formation and reduce complications. On the other hand, second-generation cryoballoon catheter ablation employs geothermal energy to create circumferential lesions around the pulmonary veins, targeting the triggers of AF. Although both techniques have demonstrated promising outcomes in treating PAF, limited studies have directly compared their efficacy and safety profiles. Therefore, this study aims to compare RFA with contact force sensing and second-generation cryoballoon catheter ablation for PAF, explicitly focusing on the outcomes achieved at the renowned Najaf Cardiac Center[3-5].

By evaluating the procedural success rates, freedom from AF recurrence, complications, and patient-reported outcomes, this study intends to shed light on the relative merits and limitations of these two ablation techniques. The findings may provide valuable insights for clinicians and guide the selection of the optimal approach for PAF ablation, ultimately improving patient outcomes and enhancing the management of this challenging arrhythmia. AF may be classified based on etiology, depending on whether it occurs without identifiable etiology in patients with a structurally normal heart (lone AF) or whether it complicates hypertensive, valvar, or other structural heart disease[6,7]. A classification system based on the temporal pattern of the arrhythmia has been recently recommended[1]. Patients presenting to medical attention may have a first detected episode of AF or, if previous episodes have been documented, recurrent arrhythmia. Episodes themselves may be paroxysmal if they terminate spontaneously, usually within seven days, or persistent if the arrhythmia continues, requiring electrical or pharmacological cardioversion for termination. AF that cannot be successfully terminated by cardioversion and longstanding (> 1 year) AF, where cardioversion is not indicated or has not been attempted, is termed permanent (**Table I**)[8,9].

In particular, treating paroxysmal AF (px AF) with pulmonary vein isolation (PVI) alone has become increasingly common. Radiofrequency (RF) technology, following the pioneering work of Hassaquere et al., has been the standard approach for RF ablation. However, with advancements in ablation tactics, novel technologies like cryoballoon ablation have emerged as alternative options. Published outcome statistics demonstrate variable results depending on the chosen ablation method, patient selection, and follow-up duration[10-12]. RF ablation has shown high success rates in treating paroxysmal and permanent AF. Nevertheless, RF ablation remains technically challenging and is associated with complications such as tamponades, atrial-esophageal fistula, thromboembolic strokes, and left atrial flutter. Cryoballoon ablation, utilizing cryothermal energy, has been introduced for pulmonary vein (PV) ablation. The cryoballoon technology, available in two sizes (23 mm and 28 mm), has shown promising efficacy and safety outcomes in short and long-term follow-ups[13,14]. However, most current evidence regarding cryoballoon treatment is based on feasibility and non-randomized clinical studies.

The primary objective in managing atrial fibrillation (AF) is to identify and address its root causes, alleviate symptoms, enhance quality of life, and prevent associated cardiovascular complications. Treatment of AF involves addressing four key aspects: preventing systemic embolization, controlling ventricular rate, restoring and maintaining normal sinus rhythm (NSR), and managing risk factors[15]. Factors such as patient preference, underlying heart conditions, symptom severity, and AF type influence medication choices. Catheter ablation is recommended for drug-resistant paroxysmal AF as a

Table I: Classification of AF ESC 2020.

AF pattern	Definition
First diagnosed	AF was not diagnosed before, irrespective of its duration or the presence/severity of AF-related symptoms.
Paroxysmal AF	That terminates spontaneously or with intervention within seven days of onset.
Persistent after >_7 days	AF that is continuously sustained beyond seven days, including episodes terminated by cardioversion (drugs or electrical cardioversion)
Long-standing persistent	Continuous AF of >12 months' duration when decided to adopt a rhythm control strategy.
Permanent	AF that the patient and physician accept, no further attempts to restore/maintain sinus rhythm will be undertaken.

first-line treatment, with pulmonary vein isolation being the standard technique. Standard methods include radiofrequency ablation, utilizing point-by-point heating to induce tissue necrosis, cryoablation, and freezing with a balloon catheter. While radiofrequency ablation minimizes fluoroscopy use due to electroanatomical mapping, cryoablation necessitates more fluoroscopic guidance. The cryoballoon technique simplifies the creation of lesions around pulmonary veins during cryoablation procedures[16-21]. The primary objective of this research is to assess the effectiveness and safety characteristics of radiofrequency ablation with contact force sensing compared to second-generation cryoballoon catheter ablation for treating paroxysmal atrial fibrillation at the Najaf Cardiac Center.

Methods

Study Population

Between December 2018 and February 2023, sixty patients with paroxysmal atrial fibrillation (AF) who underwent catheter ablation were included in this study. Patients were enrolled if they had paroxysmal AF and were unresponsive to one or more antiarrhythmic medications. Based on their characteristics, the patients were assigned to radiofrequency (RF) or cryoballoon (CB) ablation.

Preoperative Preparation

Antiarrhythmic medications were discontinued before the ablation procedure, except for amiodarone, which was stopped at least 14 days before the procedure. The CHA2DS2-VASc score was calculated for all patients, and anticoagulant medication was prescribed accordingly. Anticoagulation therapy was initiated at least four weeks before the ablation, with the international normalized ratio (INR) adjusted for warfarin-treated patients. Transthoracic and transesophageal echocardiography and CT scans were performed to assess cardiac structure and function and rule out left atrial thrombosis.

Radiofrequency Ablation (RFA) Strategy

Local anesthesia with 2% lidocaine was administered in the groin, and vital signs were monitored. A decapolar catheter was placed in the coronary sinus. Transseptal access to the left atrium was obtained using SL0 and Agills sheaths from the right femoral vein. Heparin was administered intravenously, and the active clotting time (ACT) was maintained above 300 seconds. Open irrigation ablation and Lasso catheters were inserted into the left atrium for three-dimensional reconstruction. Broad antral pulmonary vein ablation was performed to eliminate pulmonary vein potential (PVP) and achieve a bi-directional block. Electrical cardioversion was used if atrial arrhythmia persisted. Ablation energy settings were a posterior wall ablation index of 400 and an anterior wall ablation value of 500.

Cryoballoon Ablation (CBA) Strategy

Similar to RFA, patients received local anesthesia with 2% lidocaine and were monitored for vital signs. A decapolar catheter was placed in the coronary sinus. A steerable sheath and cryoballoon catheter were advanced to the left atrium through the right femoral vein. Heparin was administered, and ACT was maintained above 300 seconds. Pulmonary vein isolation (PVI) was achieved by cryoablation of each pulmonary vein for 180 seconds. Additional cryoablation was performed if necessary. Phrenic nerve stimulation was used to monitor phrenic nerve function. Cryoablation was terminated if diaphragmatic weakness or palsy occurred or the balloon temperature fell below -55 °C. A bidirectional conduction block confirmed PVI.

Post Ablation Management and Follow-Up

Patients were monitored with continuous ECG for 72 hours following the ablation. Oral anticoagulation therapy was continued for at least eight weeks, and the use of antiarrhythmic drugs was allowed during the blanking period. Follow-up visits were scheduled every three months, during which patients underwent 24-hour Holter ECG monitoring. Acute early recurrence (AER), non-acute early recurrence (NAER), and late recurrence (LR) were defined based on the occurrence of AF, atrial flutter, or atrial tachycardia within specific time intervals after the ablation procedure. Statistical analysis was performed using the SPSS program, with a p-value less than 0.05 considered significant.

Ethics approval and consent to participate

Ethical Approval was taken in Ministry of Higher Education and Scientific Research, Iraqi Board of Medical Specializations (6/2018-234).

Results

The present study involved 60 patients with an average age of 53.33; 56.7% were men. Men constituted 33.3% of the RF group and 23.3% of the cryoballoon group. Both groups had similar comorbidities and heart disease rates. 91.2% of cryoballoon patients and 92.0% of RF patients had normal LVEF, with a small percentage having lower LVEF (8.8% vs 8%) (**Table II**).

At Najaf Cardiac Center, RF ablation is performed on 41.7% of patients annually, while cryoablation is done on 58.3%. RF ablation uses a 3.5 mm irrigated tip electrode, with an arterial sheath more commonly used. In cryoablation, a median of 10 cryoballoon applications is made, with conventional mapping preferred (**Figure 1**).

The average total procedural duration in the RF cohort exceeded that of the cryoablation group by 355.8 minutes (141.156 minutes) ($P < 0.001$), with fluoroscopy time notably higher in the RF group (68.88 minutes) compared to the cryoablation group (39.78 minutes) ($P < 0.001$) as indicated in **Table III**.

Table II: Baseline Characteristics Comparison between RF Ablation and Cryoballoon Groups.

Variable	RF Ablation N=25	Cryoballoon N=35	P Value
Male gender (%)	33.3%	23.3%	0.002
Age (years) (mean)	42±.49	58±.48	<0.001
Diabetes mellitus (%)	6.7±4.5	8.3±4	1.00
Hypertension (%)	30.0±18	36.7±18.9	0.5
Coronary artery disease (%)	4±1.3	3±1.3	0.8
Cardiomyopathy (%)	12	5.7	0.4
Valve disease (%)	0.0	0.0	
Ejection fraction before ablation (>50%) (%)	92±.49	91.2±.27	0.9
Ejection fraction before ablation (≤40%) (%)	8±.5	8.8±.53	0.9
LA size dilatation before ablation %	23.3	23.3	0.2
LA size dilatation after ablation %	20.0	21.7	0.4

Figure 1: Comparison of RF Ablation and Cryoablation Techniques.

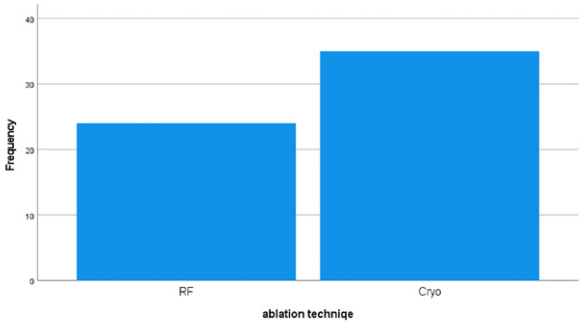

Table III: Comparison of Ablation Techniques and Procedural Times.

Variable	RF Ablation N=25	Cryoballoon N=35	P Value
Mean Procedure duration (minutes)	355.8 min	141.156 min	<0.001
Mean Fluoroscopy time (minutes)	68.88±20.01	39.78±11.0	<0.001

Table IV: Medication Usage Post-Ablation.

Variable	RF Ablation (N=25)	Cryoballoon (N=35)	P Value
Antiarrhythmic drug (%)			
Class III antiarrhythmics (%)	18.7	20	0.1
Class I antiarrhythmics (%)	23.3	20	0.1
Class II antiarrhythmics (%)	40.0	45.3	0.4

Table V: Efficacy Comparison and AF Recurrence Rates.

Variable	RF Ablation (N=25)	Cryoballoon (N=35)	P Value
Recurrence AF %	4	7	0.06

Table VI: Safety Profile and Complications.

		Type of procedure		Total	P value
		RF	CR		
3-month recurrence	no recurrence	19	26	45	0.07
	recurrence	6	9	15	
Total		25	35	60	

Upon discharge, nearly all patients post-cryoablation and RF ablation received antiarrhythmic medications. Class I antiarrhythmics were slightly more prevalent in cryoablation (20%) than RF ablation (23.3%), while Class III antiarrhythmics were used in 20% of cryoablation and 18.7% of RF ablation cases. Both groups received anticoagulants concurrently until the blanking phase, as seen in **table IV**.

The acute success rates were equivalent between the cryoballoon and RF groups, achieving 100% success (P = 0.9). Patients undergoing cryoballoon ablation had a briefer hospital stay. Until discharge, AF recurrence rates were similar and 0% in both groups. Over the initial three months, recurrence rates were 4% in the RF group compared to 7% in the cryo group (**Table V**).

All participants successfully concluded the follow-up. Following the 3-month blanking period, atrial fibrillation (AF) was identified in 15% of recordings in the cryoballoon group and 10% in the RF group. The 6-month success rate mirrored the 3-month phase, showing no statistical significance. Subsequently, three individuals in the cryoballoon group and one in the RF group required ablation procedures between the three and 6-month assessments (**Table VI**). Following AF ablation, no procedure-related complications were observed upon discharge. Minor bleedings, more prevalent in RF ablation (4%) than cryoablation (0.0%), did not require intervention. Neither group experienced PV stenosis, cerebrovascular accidents, gastroesophageal fistula, or severe groin hematoma. Groin-site issues were more common in the RF group (4%) than in the cryoballoon group (0%).

Discussion

The study conducted at Najaf Cardiac Center from December 2018 to February 2023 compared cryoballoon ablation with RF ablation in patients with persistent atrial fibrillation (px AF). Despite variations in ablation techniques among EP centers, both groups had similar structural heart dysfunction. Cryoballoon ablation patients exhibited a higher prevalence of lower ejection fraction (40%) than RF ablation patients. In our examination of patients with atrial fibrillation (AF), we found that the average duration of the entire procedure was significantly longer for RF ablation than for cryo ablation (355.8 minutes versus 141.156 minutes). Furthermore, fluoroscopy during RF ablation resulted in a considerably lengthier period (68.88 minutes) than cryoablation (39.78 minutes). In four similar clinical trials examining the comparison between RF and cryoballoon pulmonary vein isolation (PVI) in patients with atrial fibrillation (AF), cryoablation demonstrated shorter durations for both the procedure and fluoroscopy[22-25]. In our analysis of cryoablation, it was observed that the mean procedure and fluoroscopy times were notably shorter than those in RF ablation. Recent research involving 23 cryoballoon studies indicated a higher average total procedure time (206.3 minutes) and fluoroscopy duration (46 minutes) than our findings[26]. Various procedural aspects have been documented in RF ablation: a meta-analysis of RF ablation investigations reported a mean total procedure duration spanning from 81 ± 31 minutes to 357.4 ± 47.6 minutes, with a mean fluoroscopy time of 64 ± 48 minutes[27]. Consequently, the procedural times observed in our study align with those reported in prior research. The introduction of RF ablation as a new approach for treating atrial fibrillation (AF) at Najaf Cardiac Centre has led to extended procedure and fluoroscopy times. This can be attributed to the initial learning curve of the newly implemented treatment. Using contrast injection for angiography of the pulmonary vein and subsequent fluoroscopic examination may also contribute to the increased fluoroscopy duration.

In our research, cryoballoon ablation demonstrated non-inferiority to radiofrequency ablation concerning the primary efficacy endpoint, with neither method proving superior. Acute success rates in both RF and cryoablation were similar to findings in previous meta-analyses[28,29]. A study in 2011 reported a high acute success rate of 98.81% of patients and 98.47% of targeted PVs in their study on cryoballoon procedures. In 1.7% of cryoballoon patients, a treatment-related adverse event involving atrial arrhythmia was observed (P=0.09). These newly occurring arrhythmias could potentially be linked to inadequate pulmonary vein isolation. Previous studies, more extensive or nonrandomized, compared radiofrequency ablation to cryoballoon ablation in six trials[30-34], exceeding the scope of the current study.

Regarding effectiveness, four trials reported comparable results for both methods[4,5,8,9], while two studies indicated that cryoballoon ablation exhibited greater efficacy. Concerning safety, five investigations concluded that both technologies had similar levels of protection[35]. Pulmonary vein isolation is a fundamental ablation strategy for managing individuals with paroxysmal atrial fibrillation. However, it is essential to note that achieving acute pulmonary vein isolation does not guarantee sustained long-term electrical isolation of the pulmonary veins[36]. Advanced radiofrequency catheters equipped with contact-force sensors have enhanced long-term pulmonary vein isolation. Similarly, the second-generation cryoballoon catheter has shown improvements, likely attributed to its ability to perform significant wide-area circumferential ablation. This approach offers benefits beyond pulmonary vein isolation, potentially impacting ganglionated plexus activity[36-41].

The primary safety outcome showed no significant difference between the radiofrequency and cryoballoon groups, with comparable rates of procedural complications (0.0% in both groups). Phrenic nerve injury (PNP) was the most common safety event in the cryoballoon group, with reported rates of up to 10%[10-12,24]. This aligns with findings

from the STOP AF trial, which reported a 13.5% incidence rate[42]. The cryoballoon's reduced convective warming by atrial blood flow enhances freezing penetration into deeper tissues, potentially increasing the risk of phrenic nerve palsy (PNP) when using smaller balloons in right-sided pulmonary veins[43]. The FreezeAF study indicated a higher safety profile for radiofrequency ablation than cryoballoon ablation, mainly due to phrenic nerve injuries associated with cryoablation. Despite phrenic nerve damage occurrences in the FreezeAF trial, these issues were resolved before discharge, with a focus on first-generation catheters[30]. During our investigation, we did not observe any cases of PNP in either group of patients. This could be attributed to the continuous pacing of the phrenic nerve during the isolation procedure from the right superior pulmonary vein (RSPV) and right inferior pulmonary vein (RIPV), as well as the utilization of an enormous balloon (28 mm) in our facility.

The most frequently encountered safety issue in the radiofrequency group was related to complications at the groin site, albeit its occurrence was rare in this study (1.7%). In their analysis, Andrade et al. observed that the utilization of a smaller cryoballoon size (23 mm) resulted in nearly two-thirds (64.7%) of cases experiencing PNP[26]. Therefore, examining the cryoballoon sizes related to pulmonary vein diameter and the occurrence of PNP would have been of significant interest in this registry's analysis. It is worth noting that the two-sheath method, often employed using a radiofrequency catheter and a separate circular mapping catheter, may contribute to specific groin injuries[19,44].

Vascular issues (4% in RF; 0.0% in cryo), significant bleedings (0.0% in both RF and cryo), and tamponades (0.0% in both RF and cryo) were the primary complications associated with RF ablation. Neither group experienced pulmonary vein stenosis or left atrial-esophageal fistula cases. Cappato et al.[27] documented a complication rate of 4.5% in a global survey, while Calkins et al. reported a 4.9% complication rate in their meta-analysis of RF ablation studies[29]. Notably, Leipzig's most extensive single-centre study reported a 3.9% incidence of significant complications in over 1,000 RF ablation procedures for atrial fibrillation[42]. We observed that pulmonary vein isolation through cryoballoon ablation was comparable to radiofrequency ablation in efficacy and safety for patients with drug-resistant paroxysmal atrial fibrillation. The incidence of procedural complications in our cryoballoon ablation cohort was lower than that reported in a recent meta-analysis of cryoballoon ablation trials, potentially influenced by our attentive patient care and the limited number of participants. Andrade et al., in their meta-analysis involving 1,349 patients, documented a complication rate of 3.99%[26].

During the 3-month and 6-month assessments, 74.3% of patients undergoing cryoablation and 76% undergoing radiofrequency (RF) achieved freedom from atrial fibrillation (AF). The success rates did not exhibit statistically significant differences; however, in an initial study involving 57 patients treated with cryoballoon pulmonary vein isolation, 60% attained AF freedom after three months[43]. Similarly, it has been reported that 74% of patients with paroxysmal AF and 42% with chronic AF maintained sinus rhythm without antiarrhythmic medications after cryoballoon ablation. The higher success rate may be linked to the more frequent follow-up appointments involving daily event recordings, contrasting with their less frequent quarterly follow-up visits relying on 7-day Holter ECG recordings[45].

Conclusion

This document compares radiofrequency with contact force sensing and second-generation cryoballoon catheter ablation for paroxysmal atrial fibrillation. The study included sixty patients with paroxysmal AF who underwent catheter ablation—the research aimed to evaluate these two methods' efficacy and safety profiles at Najaf Cardiac Center. The study found that cryoballoon ablation was non-inferior to radiofrequency ablation in terms of effectiveness and safety for treating drug-refractory paroxysmal atrial fibrillation. Both methods showed comparable acute success rates, with no significant difference in overall safety outcomes. Cryoballoon ablation demonstrated similar AF freedom rates at 3-month and 6-month follow-ups compared to radiofrequency ablation. The study concluded that cryoballoon ablation is a viable alternative to radiofrequency ablation for treating paroxysmal atrial fibrillation.

Conflict of interest

The authors declare that they have no competing interests.

References

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. Arch Intern Med. 1987;147(9):1561-4. [PubMed ID: 3632164].

2. Haïssaguerre M, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. The New England journal of medicine. 1998;339(10):659-66. doi.org/10.1056/nejm199809033391003

3. Raviele A, Natale A, Calkins H, Camm JA, Cappato R, Ann Chen S, et al. Venice Chart international consensus document on atrial fibrillation ablation: 2011 update. Journal of cardiovascular electrophysiology. 2012;23(8):890-923. doi.org/10.1111/j.1540-8167.2012.02381.x

4. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, et al. Worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circulation. 2005;111(9):1100-5. doi.org/10.1161/01.cir.0000157153.30978.67

5. Dewire J, Calkins H. State-of-the-art and emerging technologies for atrial fibrillation ablation. Nature reviews Cardiology. 2010;7(3):129-38. doi.org/10.1038/nrcardio.2009.232

6. Marrouche NF, Dresing T, Cole C, Bash D, Saad E, Balaban K, et al. Circular mapping and ablation of the pulmonary vein for treatment of atrial fibrillation: impact of different catheter technologies. Journal of the American College of Cardiology. 2002;40(3):464-74. doi.org/10.1016/s0735-1097(02)01972-1

7. Pappone C, Oreto G, Rosanio S, Vicedomini G, Tocchi M, Gugliotta F, et al. Atrial electroanatomic remodeling after circumferential radiofrequency pulmonary vein ablation: efficacy of an anatomic approach in a large cohort of patients with atrial fibrillation. Circulation. 2001;104(21):2539-44. doi.org/10.1161/hc4601.098517

8. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, et al. Prevalence and causes of fatal outcome in catheter ablation of atrial fibrillation. Journal of the American College of Cardiology. 2009;53(19):1798-803. doi.org/10.1016/j.jacc.2009.02.022

9. Jaïs P, Sanders P, Hsu LF, Hocini M, Sacher F, Takahashi Y, et al. Flutter localized to the anterior left atrium after catheter ablation of atrial fibrillation. Journal of cardiovascular electrophysiology. 2006;17(3):279-85. doi.org/10.1111/j.1540-8167.2005.00292.x

10. Van Belle Y, Janse P, Rivero-Ayerza MJ, Thornton AS, Jessurun ER, Theuns D, et al. Pulmonary vein isolation using an occluding cryoballoon for circumferential ablation: feasibility, complications, and short-term outcome. European heart journal. 2007;28(18):2231-7. doi.org/10.1093/eurheartj/ehm227

11. Choi JH, Park SJ, Park KM, Kim JS, On YK. Efficacy and safety of cryoballoon pulmonary vein isolation for paroxysmal and persistent atrial fibrillation: A comparison with radiofrequency ablation. PloS one. 2022;17(7):e0265482. doi.org/10.1371/journal.pone.0265482

12. Neumann T, Vogt J, Schumacher B, Dorszewski A, Kuniss M, Neuser H, et al. Circumferential pulmonary vein isolation with the cryoballoon technique results from a prospective 3-center study. Journal of the American College of Cardiology. 2008;52(4):273-8. doi.org/10.1016/j.jacc.2008.04.021

13. Chun KR, Schmidt B, Metzner A, Tilz R, Zerm T, Köster I, et al. The 'single big cryoballoon' technique for acute pulmonary vein isolation in patients with paroxysmal atrial fibrillation: a prospective observational single centre study. European heart journal. 2009;30(6):699-709. doi.org/10.1093/eurheartj/ehn570

14. Malmborg H, Lönnerholm S, Blomström-Lundqvist C. Acute and clinical effects of cryoballoon pulmonary vein isolation in patients with symptomatic paroxysmal and persistent atrial fibrillation. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2008;10(11):1277-80. doi.org/10.1093/europace/eun286

15. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Heart rhythm. 2017;14(10):e275-e444. doi.org/10.1016/j.hrthm.2017.05.012

16. Fernández-Cuadros M R-LM, Martin-Lardies MY, Laborda-Delgado A, López-Fernández J, Albaladejo-Florín MJ. Peyronie?s disease and capacitive resistive radiofrequency: pilot study and preliminary evaluation. Academic Journal of Health Sciences. 2024;39(3):129-33. doi.org/10.3306/AJHS.2024.39.03.129

17. Fernández-Cuadros ME A-FM, Pérez-Moro OS, Lorenzo-Gómez MF. Can manometry classify pelvic floor dysfunctions? Proposal and effectiveness of a therapeutic algorithm. Academic Journal of Health Sciences. 2024;39(3):53-8. doi.org/10.3306/AJHS.2024.39.03.53

18. Bulková V, Fiala M, Havránek Š, Šimek J, Škňouřil L, Januška J, et al. Improvement in Quality of Life After Catheter Ablation for Paroxysmal Versus Long-standing Persistent Atrial Fibrillation: A Prospective Study With 3-Year Follow-up. Journal of the American Heart Association. 2014;3(4):e000881. doi.org/10.1161/JAHA.114.000881

19. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, et al. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2012;14(4):528-606. doi.org/10.1093/europace/eus027

20. Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, et al. Approaches to catheter ablation for persistent atrial fibrillation. The New England journal of medicine. 2015;372(19):1812-22. doi.org/10.1056/nejmoa1408288

21. Fürnkranz A, Brugada J, Albenque JP, Tondo C, Bestehorn K, Wegscheider K, et al. Rationale and Design of FIRE AND ICE: A multicenter randomized trial comparing efficacy and safety of pulmonary vein isolation using a cryoballoon versus radiofrequency ablation with 3D-reconstruction. Journal of cardiovascular electrophysiology. 2014;25(12):1314-20. doi.org/10.1111/jce.12529

22. Linhart M, Bellmann B, Mittmann-Braun E, Schrickel JW, Bitzen A, Andrié R, et al. Comparison of cryoballoon and radiofrequency ablation of pulmonary veins in 40 patients with paroxysmal atrial fibrillation: a case-control study. Journal of cardiovascular electrophysiology. 2009;20(12):1343-8. doi.org/10.1111/j.1540-8167.2009.01560.x

23. Kühne M, Suter Y, Altmann D, Ammann P, Schaer B, Osswald S, et al. Cryoballoon versus radiofrequency catheter ablation of paroxysmal atrial fibrillation: biomarkers of myocardial injury, recurrence rates, and pulmonary vein reconnection patterns. Heart rhythm. 2010;7(12):1770-6. doi.org/10.1016/j.hrthm.2010.08.028

24. Kojodjojo P, O'Neill MD, Lim PB, Malcolm-Lawes L, Whinnett ZI, Salukhe TV, et al. Pulmonary venous isolation by antral ablation with a large cryoballoon for treatment of paroxysmal and persistent atrial fibrillation: medium-term outcomes and non-randomised comparison with pulmonary venous isolation by radiofrequency ablation. Heart

(British Cardiac Society). 2010;96(17):1379-84. doi.org/10.1136/hrt.2009.192419

25. Sorgente A, Chierchia GB, Capulzini L, Yazaki Y, Muller-Burri A, Bayrak F, et al. Atrial fibrillation ablation: a single center comparison between remote magnetic navigation, cryoballoon and conventional manual pulmonary vein isolation. Indian pacing and electrophysiology journal. 2010;10(11):486-95.

26. Andrade JG, Khairy P, Guerra PG, Deyell MW, Rivard L, Macle L, et al. Efficacy and safety of cryoballoon ablation for atrial fibrillation: a systematic review of published studies. Heart rhythm. 2011;8(9):1444-51. doi.org/10.1016/j.hrthm.2011.03.050

27. Piccini JP, Lopes RD, Kong MH, Hasselblad V, Jackson K, Al-Khatib SM. Pulmonary vein isolation for the maintenance of sinus rhythm in patients with atrial fibrillation: a meta-analysis of randomized, controlled trials. Circulation Arrhythmia and electrophysiology. 2009;2(6):626-33. doi.org/10.1161/circep.109.856633

28. Vogt J, Heintze J, Gutleben KJ, Muntean B, Horstkotte D, Nölker G. Long-term outcomes after cryoballoon pulmonary vein isolation: results from a prospective study in 605 patients. Journal of the American College of Cardiology. 2013;61(16):1707-12. doi.org/10.1016/j.jacc.2012.09.033

29. Calkins H, Reynolds MR, Spector P, Sondhi M, Xu Y, Martin A, et al. Treatment of Atrial Fibrillation With Antiarrhythmic Drugs or Radiofrequency Ablation. Circulation: Arrhythmia and Electrophysiology. 2009;2(4):349-61. doi.org/10.1161/CIRCEP.108.824789

30. Luik A, Radzewitz A, Kieser M, Walter M, Bramlage P, Hörmann P, et al. Cryoballoon Versus Open Irrigated Radiofrequency Ablation in Patients With Paroxysmal Atrial Fibrillation: The Prospective, Randomized, Controlled, Noninferiority FreezeAF Study. Circulation. 2015;132(14):1311-9. doi.org/10.1161/circulationaha.115.016871

31. Wasserlauf J, Pelchovitz DJ, Rhyner J, Verma N, Bohn M, Li Z, et al. Cryoballoon versus radiofrequency catheter ablation for paroxysmal atrial fibrillation. Pacing and clinical electrophysiology : PACE. 2015;38(4):483-9. doi.org/10.1111/pace.12582

32. Aryana A, Singh SM, Kowalski M, Pujara DK, Cohen AI, Singh SK, et al. Acute and Long-Term Outcomes of Catheter Ablation of Atrial Fibrillation Using the Second-Generation Cryoballoon versus Open-Irrigated Radiofrequency: A Multicenter Experience. Journal of cardiovascular electrophysiology. 2015;26(8):832-9. doi.org/10.1111/jce.12695

33. Hunter RJ, Baker V, Finlay MC, Duncan ER, Lovell MJ, Tayebjee MH, et al. Point-by-Point Radiofrequency Ablation Versus the Cryoballoon or a Novel Combined Approach: A Randomized Trial Comparing 3 Methods of Pulmonary Vein Isolation for Paroxysmal Atrial Fibrillation (The Cryo Versus RF Trial). Journal of cardiovascular electrophysiology. 2015;26(12):1307-14. doi.org/10.1111/jce.12846

34. Jourda F, Providencia R, Marijon E, Bouzeman A, Hireche H, Khoueiry Z, et al. Contact-force guided radiofrequency vs. second-generation balloon cryotherapy for pulmonary vein isolation in patients with paroxysmal atrial fibrillation-a prospective evaluation. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2015;17(2):225-31. doi.org/10.1093/europace/euu215

35. Squara F, Zhao A, Marijon E, Latcu DG, Providencia R, Di Giovanni G, et al. Comparison between radiofrequency with contact force-sensing and second-generation cryoballoon for paroxysmal atrial fibrillation catheter ablation: a multicentre European evaluation. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2015;17(5):718-24. doi.org/10.1093/europace/euv060

36. Natale A, Reddy VY, Monir G, Wilber DJ, Lindsay BD, McElderry HT, et al. Paroxysmal AF catheter ablation with a contact force sensing catheter: results of the prospective, multicenter SMART-AF trial. Journal of the American College of Cardiology. 2014;64(7):647-56. doi.org/10.1016/j.jacc.2014.04.072

37. Kuck KH, Hoffmann BA, Ernst S, Wegscheider K, Treszl A, Metzner A, et al. Impact of Complete Versus Incomplete Circumferential Lines Around the Pulmonary Veins During Catheter Ablation of Paroxysmal Atrial Fibrillation: Results From the Gap-Atrial Fibrillation-German Atrial Fibrillation Competence Network 1 Trial. Circulation Arrhythmia and electrophysiology. 2016;9(1):e003337. doi.org/10.1161/circep.115.003337

38. Kautzner J, Neuzil P, Lambert H, Peichl P, Petru J, Cihak R, et al. EFFICAS II: optimization of catheter contact force improves outcome of pulmonary vein isolation for paroxysmal atrial fibrillation. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2015;17(8):1229-35. doi.org/10.1093/europace/euv057

39. Reddy VY, Sediva L, Petru J, Skoda J, Chovanec M, Chitovova Z, et al. Durability of Pulmonary Vein Isolation with Cryoballoon Ablation: Results from the Sustained PV Isolation with Arctic Front Advance (SUPIR) Study. Journal of cardiovascular electrophysiology. 2015;26(5):493-500. doi.org/10.1111/jce.12626

40. Kenigsberg DN, Martin N, Lim HW, Kowalski M, Ellenbogen KA. Quantification of the cryoablation zone demarcated by pre- and postprocedural electroanatomic mapping in patients with atrial fibrillation using the 28-mm second-generation cryoballoon. Heart rhythm. 2015;12(2):283-90. doi.org/10.1016/j.hrthm.2014.11.012

41. Yorgun H, Aytemir K, Canpolat U, Şahiner L, Kaya EB, Oto A. Additional benefit of cryoballoon-based atrial fibrillation ablation beyond pulmonary vein isolation: modification of ganglionated plexi. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2014;16(5):645-51. doi.org/10.1093/europace/eut240

42. Packer DL, Kowal RC, Wheelan KR, Irwin JM, Champagne J, Guerra PG, et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. Journal of the American College of Cardiology. 2013;61(16):1713-23. doi.org/10.1016/j.jacc.2012.11.064

43. Sarabanda AV, Bunch TJ, Johnson SB, Mahapatra S, Milton MA, Leite LR, et al. Efficacy and safety of circumferential pulmonary vein isolation using a novel cryothermal balloon ablation system. Journal of the American College of Cardiology. 2005;46(10):1902-12. doi.org/10.1016/j.jacc.2005.07.046

44. Wilber DJ, Pappone C, Neuzil P, De Paola A, Marchlinski F, Natale A, et al. Comparison of Antiarrhythmic Drug Therapy and Radiofrequency Catheter Ablation in Patients With Paroxysmal Atrial Fibrillation: A Randomized Controlled Trial. JAMA. 2010;303(4):333-40. doi.org/10.1001/jama.2009.2029

45. Dagres N, Hindricks G, Kottkamp H, Sommer P, Gaspar T, Bode K, et al. Complications of atrial fibrillation ablation in a high-volume center in 1,000 procedures: still cause for concern? Journal of cardiovascular electrophysiology. 2009;20(9):1014-9. doi.org/10.1111/j.1540-8167.2009.01493.x

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ORIGINAL

Seguimiento de la obesidad infantil en un equipo de pediatría de atención primaria

Obesity monitoring children in a primary care pediatrics team

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Resumen

Introducción: La obesidad constituye la enfermedad crónica no transmisible más frecuente en la infancia y la adolescencia, y es uno de los problemas de salud pública a nivel mundial en todas las edades por su asociación con un mayor riesgo de sufrir enfermedades asociadas.
Objetivos: Se analiza una muestra de 50 niños obesos de entre 2 y 14 años durante 4 años y su posible asociación con historia familiar de obesidad, alimentación con lactancia materna, patologías acompañantes, actividad física, horas de sueño, uso de TIC y alimentación. Pretendemos conocer la edad de inicio de la obesidad y sus resultados finales en el peso.
Resultados: En los recién nacidos el 17,5% presentaban un percentil mayor o igual a 90; a los 2 años el 40% presentaban un percentil mayor o igual a 90; a los 4 años el 77,5% presentaban un percentil mayor o igual a 90; a los 6 años el 90% presentaban un percentil mayor o igual a 90; a los 9 años el 95% presentaban un percentil mayor o igual a 90 y a partir de los 12 años el 97,5% presentaban un percentil mayor o igual a 90. Las variables asociadas a la obesidad fueron: ausencia de lactancia los primeros meses (p=0,008); dormir menos horas (p=0,045); menor consumo de fruta (p=0,033) y hortalizas (p=0,019); a mayor edad más picoteos (p=0,000); a mayor edad aumento de obesidad (p=0,012) e inicio de obesidad a los 3-4 años (p=0,019).
Conclusiones: Hemos visto algunos factores que influyen en el peso de los niños con obesidad. Aún con seguimiento muy estrecho y facilitando información sobre nutrición y actividad física es muy difícil conseguir el IMC ideal para su edad en los participantes.

Palabras clave: obesidad infantil, estilo de vida, factores de riesgo.

Summary

Introduction: Obesity is the most common non-communicable chronic disease in childhood and adolescence, and is one of the public health problems worldwide at all ages due to its association with a greater risk of suffering from associated diseases.
Objectives: A sample of 50 obese children between 2 and 14 years old is analyzed for 4 years and its possible association with family history of obesity, breastfeeding, accompanying pathologies, physical activity, hours of sleep, use of ICT and nutrition. We intend to know the age of onset of obesity and its final results in weight.
Results: In newborns, 17.5% had a percentile greater than or equal to 90; At 2 years, 40% had a percentile greater than or equal to 90; At 4 years, 77.5% had a percentile greater than or equal to 90; At 6 years old, 90% had a percentile greater than or equal to 90; At 9 years old, 95% had a percentile greater than or equal to 90 and from 12 years onwards, 97.5% had a percentile greater than or equal to 90. The variables associated with obesity were: absence of breastfeeding in the first months (p=0.008); sleep fewer hours (p=0.045); lower consumption of fruit (p=0.033) and vegetables (p=0.019); the older the age, the more snacking (p=0.000); At older age, obesity increased (p=0.012) and obesity began at 3-4 years of age (p=0.019).
Conclusions: We have seen some factors that influence the weight of children with obesity. Even with very close monitoring and providing information on nutrition and physical activity, it is very difficult to achieve the ideal BMI for their age in the participants.

Key words: childhood obesity, lifestyle, risk factors.

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Introducción

Importancia del problema

La obesidad constituye la enfermedad crónica no transmisible más frecuente en la infancia y la adolescencia, y es uno de los problemas de salud pública a nivel mundial en todas las edades por su asociación con un mayor riesgo de sufrir enfermedades cardiovasculares y metabólicas[1,2], lo que impacta de manera importante en la morbimortalidad y la calidad de vida, generando un importante gasto sanitario. Los síndromes genéticos y/o endocrinológicos representan solo el 1% de la obesidad infantil, correspondiendo el 99% restante al concepto de obesidad nutricional, simple o exógena[3]. Según la Organización Mundial de la Salud (OMS) en este momento se considera la epidemia del siglo XXI[4]. En los últimos años las cifras han ido aumentando en todas las edades, sobre todo en la infancia. En Europa un 28% de los menores de 7-9 años presentan exceso de peso. En España, hemos pasado de una prevalencia del 34,1% en los niños de 5-15 años a un 40,6%[5] (**Figura 1**).

La obesidad presenta en general un gradiente norte/sur tanto en Europa como en nuestro país, de tal manera que las Comunidades Autónomas (CC.AA.) de Murcia, Canarias y Andalucía, son las que presentan cifras más elevadas[6]. Según Ortega Páez[7] hay una tendencia al aumento en la mayoría de los países europeos y de la zona ibérica. Es un problema que no solo afecta a países desarrollados, sino que también va en aumento en países en vías de desarrollo y subdesarrollados, sobre todo en medios urbanos[1]. En familias con un menor nivel de ingresos y con un nivel de estudios más bajos aumenta la prevalencia de la obesidad y la obesidad severa[5].

El mejor tratamiento de la obesidad es la prevención. Así, en España existen diferentes estrategias y programas nacionales para la prevención de la obesidad. Desde el año 2005, el Ministerio de Sanidad y Consumo elaboró la estrategia NAOS (Nutrición, Actividad Física y Prevención de la Obesidad)[5]. Es una estrategia de salud basada en una alimentación saludable y en la realización de actividad física, analizando los factores que pueden incidir en la obesidad para generar acciones para su prevención. También hay un Plan Nacional de Control de la Cadena Alimentaria (PNCOCA) para la vigilancia de comedores escolares, máquinas expendedoras y cafeterías en los centros educativos, y una Estrategia de Promoción de la salud y Prevención del Sistema Nacional de Salud con acciones específicas para menores de 15 años y mayores de 50 años[8]. Existe también tratamiento farmacológico, actualmente solo aprobado en caso de complicaciones asociadas a la obesidad: metformina, orlistat, sibutramina y glitazonas[9].

La OMS estableció para Europa una Vigilancia de la Obesidad Infantil en 2007 (Childood Obesity Surveillance Initiative: COSI), para determinar el exceso de peso en niños europeos. Intervienen 38 países y se recoge información sobre la dieta, la actividad física y el entorno escolar en menores de 6-9 años (Último informe en 2022 con 33 paises[10]. En nuestro país está recogida de datos se realiza mediante el estudio ALADINO[5] Alimentación, Actividad Física, desarrollo infantil y obesidad)[4,5]. Se puede evaluar la tendencia entre los distintos estudios y su comparación entre las distintas CC.AA. y los distintos países europeos. En 2019 se observó una prevalencia de sobrepeso del 23,3% y del 17,3% para la obesidad, el 24% son niños sedentarios y el 26,3% dedica 2 o más horas al día al uso de pantallas. La perspectiva de estos niños obesos cuando alcancen la edad adulta es algo desalentadora, ya que la mayoría acabarán siendo obesos[11,12]. En otro estudio más reciente de sobrepeso y obesidad con una muestra de mil personas entre 3 y 24 años se obtuvo una prevalencia del 30%, siendo mayor en hombres que en mujeres (sobrepeso 34,1% y obesidad 10,3%)[13].

El exceso de peso viene determinado por múltiples factores: genéticos, hormonales, estilo de vida y ambiente, siendo el estilo de vida el más relevante[1]. La ganancia de peso se inicia a edades tempranas debido a patrones de conducta y estilos de vida poco saludables. Tras la pandemia por SARS-Cov-2 se observa un empeoramiento de las cifras ya existentes, debido al cambio de los hábitos de vida, alimentación y actividad física, fomentando aún más un ambiente obesogénico.
En el Marco Global de Vigilancia en Nutrición, la OMS publicó unas metas mundiales en nutrición para 2025, donde se pretende conseguir que no aumente el sobrepeso infantil más de un 6% (meta 4)[14].

Figura 1: Exceso de peso en niños de Europa y España.

Comorbilidades asociadas.

Dentro de las comorbilidades en la obesidad infantil encontramos la muerte prematura (por eventos cardiovasculares), cáncer, discapacidad, alteraciones en el metabolismo lipídico, hipertensión arterial (HTA), hipertrofia ventricular izquierda, resistencia a la insulina, diabetes mellitus tipo 2 (DM tipo 2), síndrome metabólico, problemas respiratorios, ortopédicos, dermatológicos, hígado graso no alcohólico, colecistitis, litiasis biliar, pancreatitis, síndrome de ovario poliquístico y problemas psicológicos[15-17].

Las alteraciones metabólicas de los lípidos en la obesidad está documentada desde los clásicos estudios epidemiológicos norteamericanos, demostrando que los niños y adolescentes obesos tienen colesterol total, el colesterol de las lipoproteínas de baja densidad (c-LDL) y los triglicéridos (TG) elevados, y una disminución en el colesterol de las lipoproteínas de alta densidad (c-HDL), lo que conlleva a un mayor riesgo de presentar obesidad en la edad adulta y riesgo de aterogénesis y enfermedad vascular. Se estima que el 77%[17] de los niños obesos serán adultos obesos con el correspondiente riesgo de enfermedad vascular. Todas estas alteraciones se asocian a hiperinsulinismo que a su vez aumenta el c-LDL y el colesterol de las lipoproteínas de muy baja densidad (c-VLDL) creando un círculo vicioso.

La hipertensión arterial se cuantifica cuando tres determinaciones de la presión arterial se encuentran por encima del P (percentil) 95, siendo de riesgo cuando es mayor del P90. Se ha confirmado en numerosos estudios la asociación de ganancia de peso, porcentaje de grasa corporal, hiperinsulinismo y la hipertensión arterial. Se debería a la retención crónica de sodio en el hiperinsulinismo, el aumento de la actividad simpática y la estimulación del crecimiento del músculo liso vascular[17]. Todo esto, junto con una predisposición genética y ciertos factores ambientales predisponen a la HTA, la cual puede ser reversible con la pérdida de peso.

El riesgo de sufrir DM tipo 2 aumenta con la duración de la obesidad y la intensidad de la misma. En niños y adolescentes suele ser asintomática con hallazgos casuales como glucosuria o candidiasis vaginal. Se debería a que la obesidad induce a la resistencia a la insulina. Se sabe que la grasa visceral tiene una actividad lipolítica produciendo gran cantidad de ácidos grasos libres, leptina y resistina, que junto a las alteraciones hormonales (aumento de glucocorticoides, disminución de la hormona de crecimiento, etc) hacen que aparezca la resistencia a la insulina y dislipemia, HTA y tendencia a trombogénesis[17]. La grasa intraabdominal jugaría un papel determinante, de ahí la importancia de medir la circunferencia abdominal.

El síndrome metabólico no tiene unos criterios claros para su diagnóstico en la edad pediátrica, por lo que se ha propuesto extrapolar criterios de adultos, ajustando valores pediátricos por edad y sexo. Así pues, se han propuesto los siguientes valores: circunferencia abdominal mayor del percentil P75, TG superiores a 100 mg/ml, c-HDL < 50 mg/dl, presión arterial superior al P90 y glucemia superior a 110 mg/dl[17]. Con estos criterios se ha observado que un tercio de los adolescentes obesos norteamericanos presentan síndrome metabólico, cuando sean adultos se comprobará si estos criterios diagnósticos han sido adecuados. Su diagnóstico no nos cambiaría la forma de proceder ya que el objetivo sigue siendo tratar cada uno de los factores de riesgo independientemente de que no tenga todos los componentes del síndrome metabólico.

Los problemas ortopédicos se han descrito de forma clara en estos niños. Presentan una marcha característica por muslos voluminosos (fat tigh gait), la pierna de balanceo hace un movimiento circular y la de apoyo hace un varo de rodilla sobrecargando la parte medial. Tienen como problema principal el dolor musculoesquelético en rodillas, pies y columna lumbar (por mal desarrollo de la musculatura estabilizadora de la columna). No son capaces de aumentar la densidad ósea para compensar el exceso de carga, de tal manera que presentaban un 13% menos de densidad ósea que sus pares con normopeso[18]. También presentan con más frecuencia epifisiolisis de cadera. Por último, las deformidades angulares, sobre todo el genu valgo son más evidentes.

Dentro de las patologías psiquiátricas, los niños y adolescentes obesos tienen menor autoestima y más tendencia a la depresión, lo que influye en mantener el mayor índice de masa corporal (IMC). También tienen cambios psicológicos debidos a la inadaptación social.

La obesidad es uno de los posibles causantes del síndrome de apnea del sueño[17].

Por todo lo mencionado, debe ser prioritario en las consultas de pediatría de todos los niveles, diagnosticar y tratar la obesidad, ya que es un problema crónico de salud que para reducirlo habrá que modificar el estilo de vida de estos niños y sus familias[1,18]. La prevención debe basarse en la motivación, la dieta (dieta mediterránea. Semáforo nutricional y Nutri-score. Plato de Harvard y frecuencia de consumo KidMed) y el ejercicio[17,19] para cada edad, para que el aporte nutricional no exceda al gasto energético, manteniendo un correcto crecimiento físico y mental. Este es el motivo por el que he realizado este Trabajo Fin de Grado (TFG).

Factores para el desarrollo de la obesidad

La prevención de la obesidad en la infancia debe ser una prioridad en cualquier sistema sanitario, implicando instituciones públicas y privadas, centros educativos, profesionales sanitarios y familias[8].

Factores individuales

No modificables.

Edad, sexo, raza y genética. Se han determinado genes relacionados con la obesidad, aun así, algunos

estudios demuestran que en el 99% de la población que presenta obesidad estos genes no son determinantes, dándose una modulación por factores ambientales (dieta y actividad física). El sexo masculino presenta un mayor riesgo de exceso de peso[14].

Modificables.
Factores maternos: peso materno al inicio de la gestación o ganancia ponderal durante la misma, tabaquismo materno y diabetes gestacional.

Factores del recién nacido: peso al nacimiento, edad gestacional e incremento de peso posnatal.

Factores en la adolescencia: rebote adiposo o incremento rápido de peso respecto a la talla en niños de 2-6 años[20]. La pubertad es un período con tendencia a la obesidad.

Relación, apego y salud mental de los progenitores.

Estilo de vida y nivel socioeconómico (peor en hogares con menos ingresos)[21].

Ansiedad, estrés, autoestima, depresión, alteración de la imagen corporal o búsqueda de satisfacción con la ingesta.

Las nuevas tecnologías (TIC) presentan una serie de inconvenientes que favorecen la obesidad por el ocio sedentario. El 98% de españoles mayores de 13 años dispone de teléfono móvil, con una media de 2 horas de uso en redes sociales y 6 horas diarias de internet[22]. Sin embargo, internet también dispone de multitud de recursos para profesionales sanitarios y para familias que se pueden utilizar para el manejo de la obesidad[15].

Factores ambientales
Alimentos poco saludables, comida rápida, tecnologización de la vida diaria y publicidad. En España el 69,1% de los padres de escolares con exceso de peso lo valoran como normal[5].

Objetivos

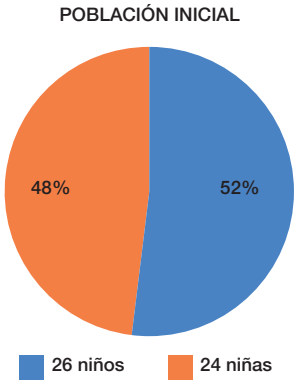
El objetivo principal de este estudio es analizar una muestra de 50 niños con obesidad, sus principales características y su relación con historia familiar de obesidad, lactancia materna, patologías acompañantes, actividad física diaria, tipo de alimentación, horas de descanso diario y tiempo dedicado a los videojuegos, móviles u otras tecnologías similares. Después se irán controlando durante cuatro años en la consulta.

Material y método

Muestra
Se trata de un estudio observacional longitudinal prospectivo desde el año 2020 al 2024. Se realiza sobre una muestra de 50 niños obesos de entre 2 y 14 años, con controles periódicos en el Programa del Niño Sano, en una consulta de pediatría de un centro de salud urbano de atención primaria en Albacete con un total de 1200 niños. La muestra fue escogida de forma aleatoria con un riesgo alfa de 0,05 calculado sobre una prevalencia del 21% aproximadamente.

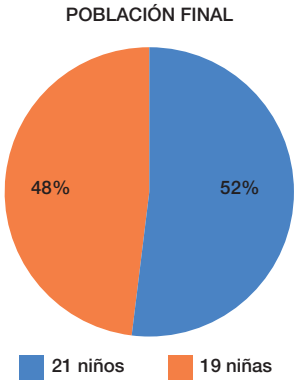
El muestreo se inició durante los meses de enero, febrero y marzo de 2020, con posterior seguimiento en el Programa de Niño Sano. De los 50 niños estudiados, 26 (52%) fueron de sexo masculino y 24 (48%) de sexo femenino (**Figura 2**).

Figura 2: Población inicial por sexos.



Durante estos años cuatro años no hemos podido evaluar 10 niños, debido al cambio de Centro de salud, a que han pasado al control por parte del Médico de Familia o a la no participación en su seguimiento durante esos años en los distintos controles. De los 40 niños que siguieron el estudio las proporciones han sido prácticamente las mismas: 21 niños (52,5%) y 19 niñas (47,5%) (**Figura 3**).

Figura 3: Población final por sexos.



Recogida de datos
Para la recogida de datos se accedió por parte de su pediatra a las historias clínicas de los pacientes y

cuando fue necesario se completaron con llamadas telefónicas a los padres o citas presenciales en el centro de salud, previo consentimiento verbal informado. Los datos que se recogieron en una hoja Excel de forma anonimizada fueron: sexo, edad, número de hermanos y su percentil de IMC, edad y peso de los padres, antecedentes familiares de obesidad, diabetes, HTA, colesterol, enfermedades cardiovasculares, diabetes gestacional, semanas de gestación, peso y talla al nacimiento, lactancia materna y duración, peso, talla y percentiles de IMC, patologías acompañantes, horas semanales de actividad física, horas diarias de sueño y horas diarias de uso de tecnologías de información y comunicación (TIC): videoconsolas, móviles, redes sociales y similares. También se realizó una encuesta, por parte de su pediatra o enfermera de pediatría, SI/NO sobre los grupos de alimentos que ingieren los niños a lo largo de la semana según la pirámide saludable de alimentos: leche y derivados; carne, huevos y pescado; verduras y hortalizas; fruta; cereales y azúcar; grasas. En el cuestionario también se preguntaba por el uso de picoteos entre horas.

En los cuatro años de seguimiento se han seguido cogiendo datos sobre sexo, edad, número de hermanos y su percentil de IMC, peso y talla, percentiles de IMC, horas semanales de actividad física, horas diarias de sueño y horas diarias de uso de tecnologías de información y comunicación (TIC): videoconsolas, móviles, redes sociales y similares. También se han seguido evaluando los grupos de alimentos que ingieren los niños a lo largo de la semana según el plato saludable de Harvard[26]: leche y derivados; carne, huevos y pescado; verduras y hortalizas; fruta; cereales y azúcar; grasas. En el cuestionario se seguía preguntando por el uso de picoteos entre horas

Análisis estadístico

Los datos estadísticos se procesaron mediante el programa SPSS 20.0. Las variables cuantitativas se presentaron como mediana y rango intercuartílico, las cualitativas como frecuencias absolutas y relativas. Para la evaluación del significado estadístico se utilizaron las pruebas CHI cuadrado, ANOVA y medidas de asociación. Se consideró significativo un valor de p menor o igual a 0,05.

Aspectos éticos

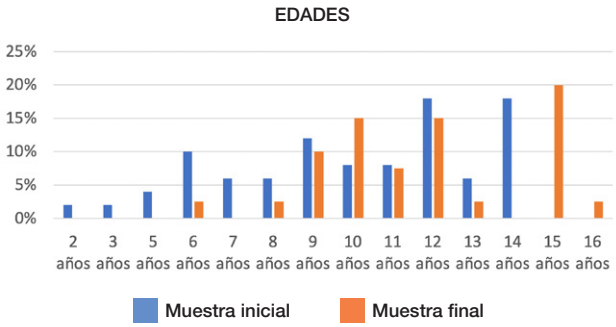
El estudio se ha realizado según las normas deontológicas y las normas de buena práctica clínica. Los datos fueron protegidos de usos no permitidos por personas ajenas a la investigación y se respetó la confidencialidad sobre la protección de datos de carácter personal y la Ley 41/2002, de noviembre, Ley básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica. Por tanto, la información generada en este estudio ha sido considerada estrictamente confidencial entre las partes participantes.

Resultados

La muestra inicial de 50 niños escogidos al azar, se distribuyó por edades de la siguiente manera: 2 años (2%), 3 años (2%), 5 años (4%), 6 años (10%), 7 años (6%), 8 años (6%), 9 años (12%), 10 años (8%), 11 años (8%), 12 años (18%), 13 años (6%) y 14 años (18%).

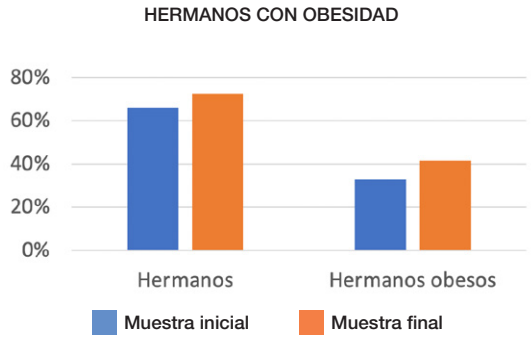
De los 40 finales la distribución por edades fue: 6 años (2,5%), 8 años (2,5%), 9 años (10%), 10 años (15%), 11 años (7,5%), 12 años (15%), 13 años 2,5%), 15 años (20%) y 16 años (2,5%) (**Figura 4**).

Figura 4: Distribución por edades.



Del total de la muestra inicial, 33 (66%) tenían hermanos y 11 (33,3%) de ellos tenían hermanos con un peso por encima el P 97 para su edad. Se encontró relación entre el número de hermanos y el peso de los niños (p=0,011), de tal manera que cuando los niños no tenían hermanos sus pesos eran mayores. No hubo relación entre el peso de los niños y el peso de sus hermanos (p=0,32). De la muestra final 29 (72,5%) tenían hermanos y 12 (41,38%) de ellos tenían hermanos con peso por encima del P 97, sin encontrarse ninguna asociación estadística significativa, ya que de los 12 niños el 50% (6 casos) de ellos eran niños y el otro 50% (6 casos) niñas (**Figura 5**).

Figura 5: Hermanos con obesidad.



De los 40 niños finales, de recién nacidos (RN) el 17,5% (7 casos) presentaban un P mayor o igual a 90 y el 30% (12 casos) un P menor o igual a 10; a los 2 años el 40% (16 casos) presentaban un P mayor o igual a 90 y el 10% (4 casos) un P menor o igual a 10; a los 4 años el 77,5%

(31 casos) presentaban un P mayor o igual a 90; a los 6 años el 90% (36 casos) presentaban un P mayor o igual a 90; a los 9 años el 95% (38 casos) presentaban un P mayor o igual a 90 y a partir de los 12 años el 97,5% (39 casos) presentaban un P mayor o igual a 90.

Un caso (2,5%) consiguió bajar a un P 85 pero luego volvió a engordar y otros 2 casos consiguieron unos P de 75 y 50 al final del estudio (**Figura 6**).

La media de edad de las madres fue 38,98 años y la de los padres 40,66 años. La media del IMC de las madres fue de 24,14 siendo la moda 24 (36%). El porcentaje de madres con IMC igual o superior a 25 (sobrepeso) fue del 34% del total. La media del IMC de los padres fue de 25,62 siendo la moda 25 (32%). El porcentaje de padres con IMC igual o superior a 25 fue del 80% del total. Se encontró relación significativa entre la edad de la madre y el peso de los niños (p=0,025). No sucedió lo mismo con la edad del padre ni con el IMC de ambos.

Todos los niños tenían antecedentes familiares de riesgo cardiovascular, excepto uno, por sus abuelos principalmente. Los padres no tenían patología relacionada con obesidad que se hubiera reflejado en la historia clínica. Con las medidas de asociación, se detectó relación entre el peso de los niños y los antecedentes familiares (p=0,049). Solo una de las madres tuvo diabetes gestacional tratada con dieta.

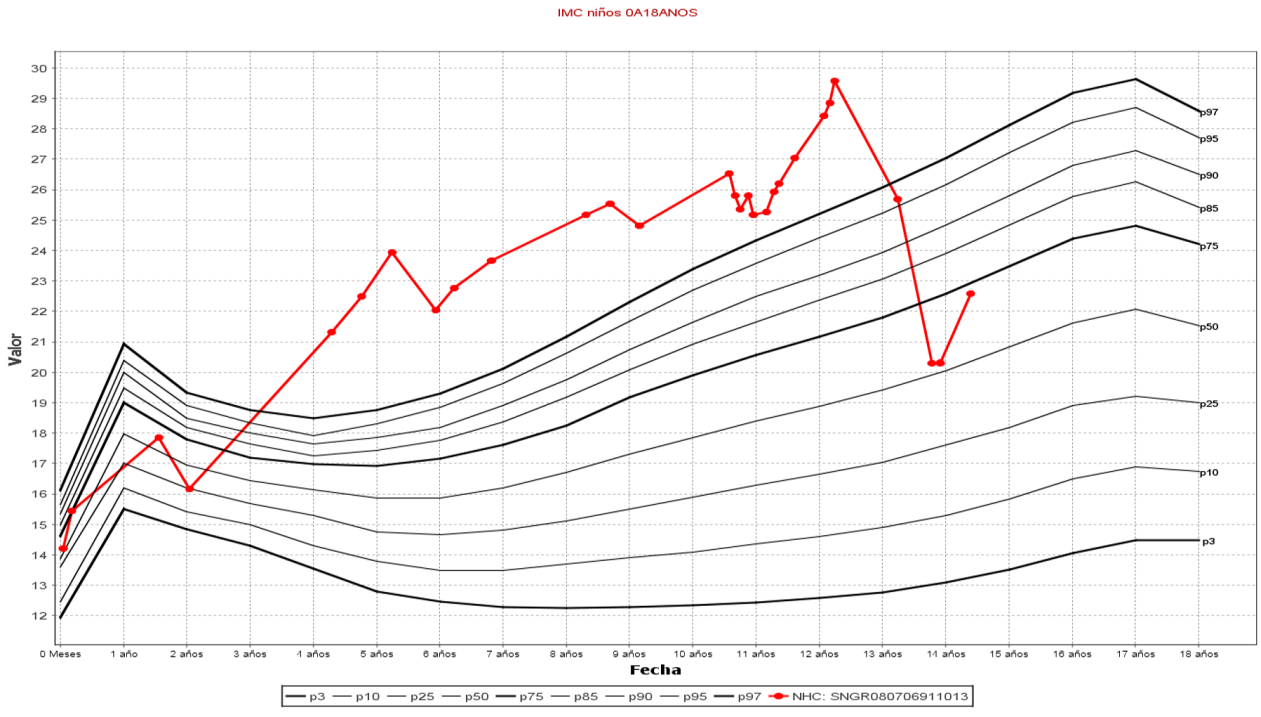
Todos los niños nacieron a término excepto uno (33 semanas), el 64% de la muestra nacieron entre las 39-40 semanas, con una media de 39,6 semanas de gestación al nacimiento. La media de peso al nacimiento fue de 3,351 kg. Tres niños nacieron con un peso inferior a 2,5 kg y otros 2 niños con un peso superior a 4 kg. El 90% nació con un peso entre 2,5 y 4 kg. En cuanto a la talla, la media al nacimiento fue de 49,93 cm. Tanto las semanas como el peso al nacimiento no mostraron relación con el peso posterior de los niños.

Respecto a la lactancia materna 29 niños (58%) se alimentaron con ella con una media de duración de 5 meses. En el estudio de asociación se observó una relación estadísticamente significativa (p=0,008). La duración de la lactancia también se vio relacionada pero no de manera estadísticamente significativa (p=0,098). Todos los niños del estudio presentaban un percentil de peso mayor del P90 para su edad, mostrando correlación con su IMC. Los niños diagnosticados de alguna enfermedad fueron 10 (20%): 4 asma, 3 epilepsia, 1 hipotiroidismo, 1 celiaquía y 1 Asperger. No se estableció relación estadística entre la patología y el peso de los niños.

La mayoría de los niños no realizaban actividad física fuera de las horas escolares (82%). Con edades mayores bajó al 62%. El peso de los niños y el ejercicio físico realizado estaban relacionados, pero no estadísticamente significativa (p=0,096). Los de 14 años (45%), seguidos de los 6 años (22%) fueron los que más actividad física realizaban. Estas proporciones se mantuvieron a lo largo del estudio.

Las horas de descanso nocturno de todos los niños eran superiores a las 8 horas, con una media de 8,62 horas.

Figura 6: Evolución favorable del IMC.



Si encontramos asociación significativa entre el peso y el número de horas que duermen los niños (p=0,045). En los años siguientes, al ser niños de mayor edad presentaban unas horas de sueño algo superiores con una media de 9,15 horas.

Tos los niños usaban TIC de 1 a 3 horas diarias, siendo la media de 2,02 horas y la moda de 2 horas diarias, en los fines de semana aumentaba el uso hasta una media de 3,5 horas. A mayor edad se observa un aumento en las horas de uso: media 2,53 horas diarias y 5,18 horas los fines de semana. Hay asociación entre el peso y las horas de juego sin llegar a ser estadísticamente significativa.

En cuanto al consumo por grupos de alimentos se observó que todos tomaban leche y derivados, y cereales y azúcares. El 98% tomaba carne, huevos y pescado; al separar por sexos se vio que había una relación entre consumo y peso (p=0,033), de tal manera que ser niño multiplicaba por 1,128 el consumo. También se vio que con el aumento de la edad había más consumo (p=0,035). El 58% tomaban verduras y hortalizas, habiendo una fuerte relación entre su consumo y el peso (p=0,019); desglosado por sexo las niñas multiplicaban por 2,611 el consumo. No había asociación estadísticamente significativa entre la edad y consumo, pero a mayor edad se multiplicaba por 1,71 el consumo. El 40% tomaba fruta con una asociación estadística (p=0,033); a mayor edad mayor consumo (p=0,011). El 96% tomaban grasas, lo que estaba asociado estadísticamente significativo con el peso (p=0,000).

El 74% comían entre horas (picoteos), aunque mostró relación con el peso, no fue estadísticamente significativa (p=0,067); desglosado por sexo las niñas multiplicaban por 1,934 el riesgo de comer entre horas y a mayor edad mayor tendencia a los picoteos (p=0,000) de tal manera que por encima de los 6 años se multiplica por 12 el comer entre horas. Con los años se consiguió alguna mejora en la ingesta de fruta y verduras y hortalizas, así como en la reducción de picoteos pero sin significación estadística (**Figura 7**), lo que se observaba en las curvas de su IMC con la aparición de descensos alternantes (**Figura 8**).

Figura 7: Consumo por grupos de alimentos.

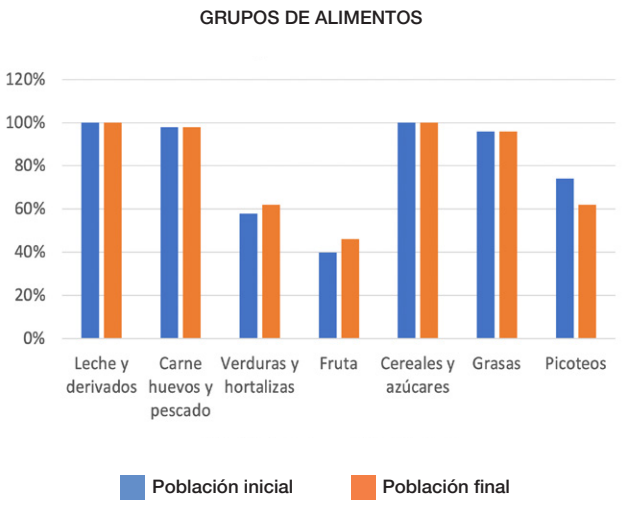
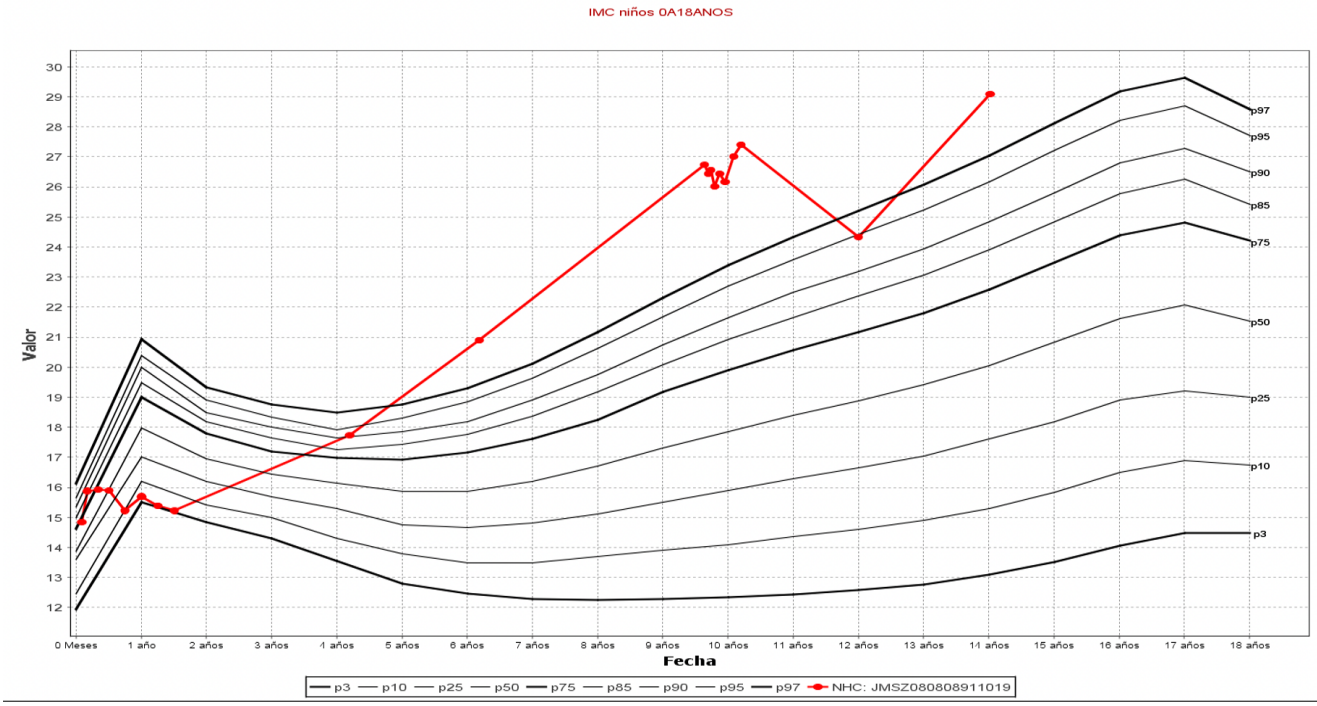


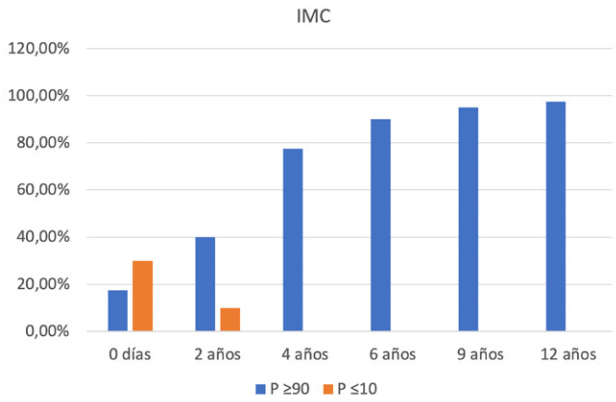
Figura 8: Ejemplo de evolución del IMC en un caso.



En la evolución del IMC durante estos años de estudio, vamos a dar datos de 8 momentos del estudio: RN, 2 años, 4 años, 6 años, 9 años,12 años, 13 años y 14 años. En los RN, solo el 17,5% (7 casos) presentaba un percentil por encima de 90 y un 30% (12 casos) menor del 10. A los 2 años, por encima del 90 un 40% (16 casos) y menor del 10 el 10% (4 casos). A los 4 años, el 77,5% (31 casos) presentaba percentil superior a 90. A los 6 años eran el 90% (36 casos) y a los 9 y 12 años el 97,5% (39 casos) presentaron percentil mayor de 90 (**Figura 9**).

En las variables asociadas encontramos que a mayor edad se aprecia un aumento de obesidad en los 2 sexos (p=0,012) y que la edad de inicio de la obesidad comienza a los 3-4 años (p=0,019).

Figura 9: IMC por edades en tanto por ciento.



Discusión

La obesidad infantil es una patología que cada vez está más presente en la sociedad. Su aumento progresivo se ha visto favorecido tras la pandemia provocada por el COVID-19 (18). Aunque en los últimos años se ha trabajado mucho en las causas que la producen y en su prevención, parece que la población no le da la importancia que debería, muchos piensan que la obesidad solo es una condición física que afecta al exterior de la persona. Poco a poco, en el seguimiento de los pacientes, se les va concienciando sobre las consecuencias de la obesidad a largo plazo y su potencial peligrosidad.

Para darle visualización a este problema se comenzó este estudio, para comprobar que estilos de vida seguían estas familias. Sabemos que la mejor forma de atacar esta enfermedad es educando a nuestros pacientes y sus familias desde muy pequeños, promocionando hábitos de vida saludables, lo que hay que hacer en los distintos controles en el CC.SS mediante educación para la salud de forma individualizada[27,28]. Se pretende que en un futuro los niños de ahora sean adultos sanos sin patologías derivadas de la obesidad, ya que el exceso de peso es una condición que afecta a todos los sistemas del menor, por lo que es fundamental el asesoramiento desde el primer contacto en la consulta de Atención Primaria.

Las publicaciones demuestran que los niños y adolescentes que realizan actividad física y se encuentran en normopeso para su edad y talla, tienen una dieta más saludable[29]. Por eso consideramos que para luchar contra la obesidad hay que hacerlo desde un punto de vista multidisciplinar.

Dentro de la evaluación diagnóstica de la obesidad es fundamental una buena somatometría del niño, con peso, talla e IMC, cuyos datos serán comparados con curvas de percentiles/z-score. Es útil la realización de cuestionarios sobre la alimentación, la actividad física, horas de sueño y uso de TIC como más adelante comentaremos.

Lactancia materna.

Los niños que han recibido menos meses de lactancia materna o que solo han recibido lactancia artificial, muestran pesos mayores que los que han recibido lactancia materna exclusiva[30]. En nuestro estudio también hemos encontrado esa correlación de protección de la lactancia materna frente a la obesidad, tanto en su uso como con su duración.

En la literatura científica encontramos numerosos estudios que proponen que la lactancia materna puede ser un factor de protección frente a la obesidad, no solo desde el aspecto nutricional, sino también desde un punto de vista psicológico y emocional[31]. Las leches artificiales cada vez se parecen más a la leche materna, pero nunca llegarán a ser lo mismo, por eso, salvo raras excepciones de contraindicación en la lactancia materna (imposibilidad de la madre, VIH, tuberculosis bacilífera positiva, galactosemia, etc) debemos recomendarla siempre.

Obesidad y la familia

En nuestro estudio hemos comprobado que más de la mitad de sus padres presentaban sobrepeso, demostrando esa asociación de peso de los padres y de sus hijos como en otros estudios publicados[32]. Más importante todavía es el peso de las madres, sobre todo antes del embarazo según Nicola Heslehurst[33], se observa un aumento del 264% en las probabilidades de obesidad infantil cuando las madres presentan obesidad antes del embarazo. En nuestro estudio no hemos encontrado esta relación dado que la mayoría de nuestras madres presentaban sobrepeso o normopeso. Si que hemos visto relación entre la edad de las madres y los pesos de los niños, de tal manera que a mayor edad de la madre los niños presentan un mayor IMC. Cuando se trata de hijo único hay un 27,5% de obesidad (11 casos), mientras que cuando

tienen hermanos (29 casos) el 41,38% de ellos (12 casos) son obesos.

Con todo vemos la gran importancia el abordaje familiar en el tratamiento de la obesidad[34] ya que hay una relación del peso de los componentes de la unidad familiar con el peso del niño. Habrá más probabilidad en el niño de presentar obesidad cuando los demás componentes de la familia sean obesos. Es por esto que el niño tiene un patrón de referencia familiar sobre la alimentación al que imita, siendo a los 3-4 años cuando empieza a materializarse con mayor claridad.

Actividad física

Está clara la relación directa entre actividad física, la condición física[35] y el IMC[36,37]. A mayor actividad física, mayor gasto energético y menor peso. Sabemos que el mayor gasto energético lo realiza el metabolismo basal, el cual es difícil de modificar, por eso hay que promocionar la actividad física.

En este trabajo hemos podido ver que al principio, solo el 18% de los encuestados realizaban actividad física fuera del horario escolar. Con el aumento de la edad ascendió hasta el 38%. Como el horario de educación física en los colegios es de 2 horas semanales, vemos que el ejercicio es escaso. Las recomendaciones de ejercicio para los niños serían las mismas que para los adultos. En los niños más pequeños es recomendable que tengan alguna actividad extraescolar que los mantenga activos y les enseñe a socializar.

La actividad física es una de las herramientas más eficaces para prevenir morbimortalidad en la edad adulta[38]. Hacer deporte desde la infancia mejora la adopción de hábitos de vida activa y saludable[39,40]. Según diferentes estudios se observa que la condición física es un biomarcador y predictor del estado de salud desde edades tempranas, contribuyendo a la prevención y el retraso en la aparición de enfermedades cardiovasculares, y se encuentra relacionada con la calidad de la dieta y los patrones de sedentarismo (36). Un ambiente familiar en donde los padres incentiven el ejercicio fomentará que en la vida adulta lo siga practicando con el consiguiente factor protector de múltiples enfermedades.

Sueño

En un metaanálisis se resumieron los datos de 12 estudios transversales que demostraban evidencia moderada de que la duración del sueño podía estar relacionada de forma inversa con el riesgo de sobrepeso y obesidad en niños y adolescentes[41]. En nuestro trabajo también hemos obtenido esa relación, por lo que deberíamos transmitir a las familias la importancia de un buen descanso desde edades tempranas.

TIC

Cada vez observamos como estas tecnologías de la información y el conocimiento se introducen de forma más temprana en la infancia, sobre todo el uso de móviles como forma habitual de juego. De esta forma, los juegos que requieren actividad física son menos utilizados comparado con los niños de otras generaciones anteriores, lo que supone el aumento del sedentarismo.

En un estudio realizado en 2014 con 2371 alumnos de Educación Secundaria Obligatoria (ESO) y 1º de Bachillerato[42] se constató que más del 80% de los participantes hacían uso del móvil y de visdeoconsolas. En nuestro trabajo, todos los niños usaban estas tecnologías como forma de juego y las seguían utilizando en años posteriores. La media diaria fue de 2,02 horas diarias que no es mucho comparado con otros estudios[8].

Al poner los padres las TIC como forma de juego desde edades pequeñas, quitan actividades de esfuerzo físico y socialización, creando hábitos de conducta poco saludables con sus correspondientes daños a nivel físico y mental. Es por esto que hay que enseñar a los padres como hacer un uso razonable de las TIC con sus hijos.

El uso excesivo de aparatos digitales para el ocio aumenta la prevalencia de sobrepeso y obesidad en la infancia[43].

Alimentación

La alimentación es un pilar básico en el estilo de vida saludable[44-46]. En nuestro trabajo quisimos ver si los padres seguían los consejos sobre nutrición que les ofrecíamos en las distintas consultas de seguimiento. Salvo leche y derivados, cereales y azúcares que todos consumían, sí que pudimos sacar conclusiones con otros grupos de alimentos.

Los niños consumían más carne, huevos y pescado que las niñas, además a mayor edad mayor consumo. En cuanto al consumo de vegetales, las niñas multiplicaban por dos su consumo frente a los niños sin cambios con la edad. Sólo consumían fruta el 40% y aumentaba con la edad. El consumo de grasa estaba relacionado con el peso. Por último, el picoteo estaba relacionado con el peso y las niñas multiplicaban por dos el comer entre horas y a mayor edad mayor número de picoteos en ambos sexos.

Con los años se consiguió alguna mejora en la ingesta de fruta y verduras y hortalizas, así como en la reducción de picoteos, pero sin significación estadística.

Tenemos pues información nutricional de como modificar hábitos alimenticios en nuestros niños para conseguir una dieta no obesogénica[38]. El conseguir hábitos alimenticios sanos en la familia es algo fundamental a la hora de una buena nutrición. Con esta intención en 2021 se llevó a cabo el estudio EsNuPi para conocer los patrones de alimentación en la infancia[47].

Comorbilidades

Por último, remarcar que, en los adultos, hay que prevenir las comorbilidades de la obesidad desde la infancia, ya que la obesidad se suele acompañar de patologías como la diabetes tipo 2, hipercolesterolemia, HTA, etc. En la infancia no suele ser así, debido probablemente a que no les ha dado tiempo a desarrollarlas. Lo que si podemos constatar es que este aumento en la obesidad infantil conllevará la aparición de estas patologías de una manera más precoz. En nuestra muestra encontramos niños mayoritariamente sanos, el caso del asma no lo consideramos como una causa de la obesidad (aunque si hay estudios que demuestran que niños obesos tienen más riesgo de padecer asma más grave), pero si un peor control con exacerbaciones y mayor resistencia a los corticoides por ser un niño obeso. Aunque en los niños se ha estudiado menos, hay relación entre una adecuada intervención nutricional y su correspondiente pérdida de peso mejorando la función pulmonar y el control del asma[48].

Por tanto, hay que informar a los padres de que el normopeso previene de enfermedades y además mejora las que pueda tener el niño.

Conclusiones

1. Los niños con obesidad en edades tempranas, llegan a la adolescencia con obesidad.

2. El percentil de IMC al nacimiento no nos orienta a cuál va a ser su estado nutricional en edades mayores.

3. La obesidad en el entorno familiar está muy relacionada con la obesidad infantil.

4. A partir de los 4 años es cuando realmente se observa la tendencia personal a la obesidad. Probablemente relacionada con una mayor autonomía personal.

5. Los malos hábitos nutricionales y la menor actividad física (muchas veces relacionada con el uso/abuso de TIC) predisponen a la obesidad.

6. Los resultados de este trabajo son muy prometedores, ya que hemos visto algunos factores que influyen en el peso de los niños con obesidad. Pero por otra parte hemos visto que aún con seguimiento muy estrecho y facilitando información sobre nutrición y actividad física es muy difícil conseguir el IMC ideal para la edad de los participantes. De todas maneras, estos resultados nos animan para seguir estos niños en una consulta específica para obesidad y animarlos e incentivarlos para que su desarrollo como personas que llegarán a la edad adulta sea con unas mayores ventajas sobre su calidad de vida personal y social.

Conflicto de intereses

Los autores declaran no tener conflicto de intereses.

Bibliografía

1. Tárraga López PJ, Tárraga Marcos ML, Panisello Royo JM, Rosich Domenech N, Castell Panisello E, Carbayo Herencia JA, et al. Resultados de una intervención motivacional con niños obesos o con sobrepeso y sus familias: estudio piloto. Rev Esp Nutr Humana Dietética. diciembre de 2017;21(4):313-9.

2. Urgell MR. Libro blanco de la nutrición infantil en España [Internet]. Prensas de la Universidad de Zaragoza; 2015 [citado 22 de abril de 2024]. Disponible en: https://dialnet.unirioja.es/servlet/libro?codigo=654905

3. Moreno Aznar LA, Lorenzo Garrido H. Obesidad infantil. En: Tratamiento en Gastroenterología, Hepatología y Nutrición Pediátrica, 2021, ISBN 9788417844998, págs 843-850 [Internet]. Ergon; 2021 [citado 29 de abril de 2024]. p. 843-50. Disponible en: https://dialnet.unirioja.es/servlet/articulo?codigo=8223309

4. Obesidad y sobrepeso [Internet]. [citado 21 de abril de 2024]. Disponible en: https://www.who.int/es/news-room/fact-sheets/detail/obesity-and-overweight

5. Aesan - Agencia Española de Seguridad Alimentaria y Nutrición [Internet]. [citado 26 de abril de 2024]. Disponible en: https://www.aesan.gob.es/AECOSAN/web/nutricion/detalle/aladino_2019.htm

6. Scribd [Internet]. [citado 21 de abril de 2024]. Obesidad Infantil | PDF | Obesidad | Obesidad infantil. Disponible en: https://es.scribd.com/document/611052452/obesidad-infantil

7. La prevalencia del exceso de peso debe disminuir en los países mediterráneos [Internet]. [citado 26 de abril de 2024]. Disponible en: https://evidenciasenpediatria.es/articulo/7473/la-prevalencia-del-exceso-de-peso-debe-disminuir-en-los-paises-mediterraneos-

8. García Mérida M J, Castell Miñana, M. (2023). Obesidad infantil: la otra pandemia. In Congreso de Actualización en Pediatría (pp. 127-139). [citado 26 abril de 2024].

9. Axon E, Atkinson G, Richter B, Metzendorf MI, Baur L, Finer N, et al. Drug interventions for the treatment of obesity in children and adolescents. Cochrane Database Syst Rev.2016 [citado 21 de abril de 2024].

10. Aesan - Agencia Española de Seguridad Alimentaria y Nutrición. [citado 21 de abril de 2024]. Disponible en: https://www.aesan.gob.es/AECOSAN/web/noticias_y_actualizaciones/noticias/2022/COSI.htm

11. Simmonds M, Llewellyn A, Owen CG, Woolacott N. Predicting adult obesity from childhood obesity: a systematic review and meta-analysis. Obes Rev Off J Int Assoc Study Obes. febrero de 2016;17(2):95-107.

12. Albañil Ballesteros MR, Rogero Blanco ME, Sánchez Martín M, Olivas Domínguez A, Rabanal Basalo A, Sanz Bayona MT. Riesgo de mantener obesidad desde la infancia hasta el final de la adolescencia. Pediatría Aten Primaria. junio de 2011;13(50):199-211.

13. Aranceta-Bartrina J, Gianzo-Citores M, Pérez-Rodrigo C. Prevalencia de sobrepeso, obesidad y obesidad abdominal en población española entre 3 y 24 años. Estudio ENPE. Rev Esp Cardiol. 1 de abril de 2020;73(4):290-9.

14. Corella Piquer D, Coltell Simón O, Ordovás Muñoz JM. Genética y epigenética de la obesidad. An Real Acad Nac Farm. 2016;82(Extra 2):129-36.

15. Sanidad ultima el Plan de prevención de la obesidad infantil [citado 21 de abril de 2024]. Disponible en: https://www3.gobiernodecanarias.org/noticias/sanidad-ultima-el-plan-de-prevencion-de-la-obesidad-infantil-en-menores-de-12-anos-en-canarias/

16. Fontaine KR, Redden DT, Wang C, Westfall AO, Allison DB. Years of life lost due to obesity. JAMA. 8 de enero de 2003;289(2):187-93.

17. Dalmau Serra J, Alonso Franch M, Gómez López L, Martínez Costa C, Sierra Salinas C. Obesidad Infantil. Recomendaciones del Comité de Nutrición de la Asociación Española de Pediatría. Parte II. Diagnóstico. Comorbilidades. Tratamiento. An Pediatría. 1 de marzo de 2007;66(3):294-304.

18. Amo MLG, Gonzalez E, López-Gil JF, Montoya MR de A, Marcos LT, López PJT. Análisis de la obesidad en niños de 6 a 12 años de Albacete durante la pandemia COVID19. J Negat No Posit Results. 13 de febrero de 2021;6(4):665-82.

19. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J Sports Med. diciembre de 2020;54(24):1451-62.

20. Geserick Mandy, Vogel Mandy, Gausche Ruth, Lipek Tobias, Spielau Ulrike, Keller Eberhard, et al. Acceleration of BMI in Early Childhood and Risk of Sustained Obesity. N Engl J Med. 4 de octubre de 2018;379(14):1303-12.

21. Obesidad y pobreza infantil .radiografia de una doble desigualdad. [citado 26 de abril de 2024].

22. Uso de tecnología en los hogares españoles. [citado 26 de abril de 2024]. Disponible en: https://www.ontsi.es/es/publicaciones/uso-tecnologia-hogares-espanoles-2022

23. Algoritmos AEPap [Internet]. [citado 21 de abril de 2024]. Disponible en: https://algoritmos.aepap.org/index.php

24. Arriba Muñoz A de, López Úbeda M, Rueda Caballero C, Labarta Aizpún JI, Ferrández Longás Á. Valores de normalidad de índice de masa corporal y perímetro abdominal en población española desde el nacimiento a los 28 años de edad. Nutr Hosp. agosto de 2016;33(4):887-93.

25. Yeste D, Clemente M, Campos A, Fábregas A, Mogas E, Soler L, et al. Precisión diagnóstica del índice de masa triponderal (kg/m3) para identificar el fenotipo de riesgo metabólico en pacientes obesos. An Pediatría. 1 de febrero de 2021;94(2):68-74.

26. Avenue 677 Huntington, Boston, Ma 02115. The Nutrition Source. 2015 [citado 21 de abril de 2024]. El Plato para Comer Saludable (Spanish). Disponible en: https://www.hsph.harvard.edu/nutritionsource/healthy-eating-plate/translations/spanish/

27. Argelich E, Alemany ME, Amengual-Miralles B, Argüelles R, Bandiera D, Barceló MA, et al. Los equipos de pediatría ante la obesidad infantil: un estudio cualitativo dentro del proyecto STOP. An Pediatría. 1 de septiembre de 2021;95(3):174-85.

28. Rodríguez Delgado J. El papel clave de la pediatría de atención primaria en el manejo de la obesidad infantil. An Pediatría. 1 de septiembre de 2021;95(3):137-8.

29. Rosa Guillamón A, Carrillo López PJ, García Cantó E, Perez Soto JJ, Tarraga Marcos L, Tarraga López PJ. Mediterranean diet, weight status and physical activity in schoolchildren of the Region of Murcia. Clin E Investig En Arterioscler Publicacion Of Soc Espanola Arterioscler. 2019;31(1):1-7.

30. Yan J, Liu L, Zhu Y, Huang G, Wang PP. The association between breastfeeding and childhood obesity: a meta-analysis. BMC Public Health. 13 de diciembre de 2014;14:1267.

31. Aguilar Cordero MJ, Sánchez López AM, Madrid Baños N, Mur Villar N, Expósito Ruiz M, Hermoso Rodríguez E. Lactancia materna como prevención del sobrepeso y la obesidad en el niño y el adolescente: revisión sistemática. Nutr Hosp. febrero de 2015;31(2):606-20.

32. Iguacel I, Escartín L, Fernández-Alvira JM, Iglesia I, Labayen I, Moreno LA, et al. Early life risk factors and their cumulative effects as predictors of overweight in Spanish children. Int J Public Health. mayo de 2018;63(4):501-12.

33. Heslehurst N, Vieira R, Akhter Z, Bailey H, Slack E, Ngongalah L, et al. The association between maternal body mass index and child obesity: A systematic review and meta-analysis. PLoS Med. junio de 2019;16(6):e1002817.

34. El abordaje familiar en el tratamiento del sobrepeso y la obesidad en la infancia mejora los resultados en el entorno familiar [Internet]. [citado 21 de abril de 2024]. Disponible en: https://evidenciasenpediatria.es/articulo/8209/el-abordaje-familiar-en-el-tratamiento-del-sobrepeso-y-la-obesidad-en-la-infancia-mejora-los-resultados-en-el-entorno-familiar

35. Evaluación de los dominios de la actividad física y los componentes de la condición física en niños de 4-5 años en un centro de salud [Internet]. [citado 21 de abril de 2024]. Disponible en: http://pap.es/articulo/13969/evaluacion-de-los-dominios-de-la-actividad-fisica-y-los-componentes-de-la-condicion-fisica-en-ninos-de-4-5-anos-en-un-centro-de-salud

36. Mestre-Font M, Busquets-Cortés C, Ramírez-Manent JI, Tomás-Gil P, Paublini H, López-González AA. Influence of sociodemographic variables and healthy habits on the values of overweight and obesity scales in 386,924 Spanish workers. Academic Journal of Health Sciences 2024; 39 (1):27-35 doi: 10.3306/AJHS.2024.39.01.27

37. Mestre-Font M, Busquets-Cortés C, Ramírez-Manent JI, Tomás-Gil P, Paublini H, López-González AA. Influence of sociodemographic variables and healthy habits on the values of type 2 diabetes risk scales. Academic Journal of Health Sciences 2024; 39 (2):99-106 doi: 10.3306/AJHS.2024.39.02.99

38. Rosa Guillamon A, Garcia Canto E, Rodríguez García PL, Pérez Soto JJ, Tárraga Marcos ML, Tárraga López PJ. [Physical activity, physical fitness and quality of diet in schoolchildren from 8 to 12 years]. Nutr Hosp. 14 de septiembre de 2017;34(5):1292-8.

39. Moral García JE, Agraso López AD, Pérez Soto JJ, Rosa Guillamón A, Tarraga Marcos L, García Canto E, et al. [Phisical activity practice according to adherence to the Mediterranean diet, alcohol consumption and motivation in adolescents]. Nutr Hosp. 10 de abril de 2019;36(2):420-7.

40. Pérez Solís D, Díaz Martín JJ, Álvarez Caro F, Suárez Tomás I, Suárez Menéndez E, Riaño Galán I. Efectividad de una intervención escolar contra la obesidad. An Pediatría. 1 de julio de 2015;83(1):19-25.

41. Ruan H, Xun P, Cai W, He K, Tang Q. Habitual Sleep Duration and Risk of Childhood Obesity: Systematic Review and Dose-response Meta-analysis of Prospective Cohort Studies. Sci Rep. 5 de noviembre de 2015;5:16160.

42. Fernández Á del B. Los adolescentes y el uso de los teléfonos móviles y de videojuegos. Rev INFAD Psicol Int J Dev Educ Psychol. 27 de septiembre de 2014;3(1):563-70.

43. El uso excesivo de aparatos digitales para el ocio aumenta la prevalencia de sobrepeso y obesidad en la infancia [Internet]. [citado 21 de abril de 2024]. Disponible en: https://evidenciasenpediatria.es/articulo/8098/el-uso-excesivo-de-aparatos-digitales-para-el-ocio-aumenta-la-prevalencia-de-sobrepeso-y-obesidad-en-la-infancia

44. Dalmau J, Moráis A, Martínez V, Peña-Quintana L, Varea V, Martínez MJ, et al. Evaluación de la alimentación y consumo de nutrientes en menores de 3 años. Estudio piloto ALSALMA. An Pediatría. 1 de julio de 2014;81(1):22-31.

45. Riutord Sbert P, Riutord Fe B, Riutord Fe N, Arroyo Bote S, López González AA, Ramírez Manent JI. Relationship between physical activity and adherence to the mediterranean diet with metabolic syndrome, hypertriglyceridemic waist phenotype and hypertensive waist. Academic Journal of Health Sciences 2022;37 (6): 33-38 doi: 10.3306/AJHS.2022.37.06.33

46.Riutord Sbert P, Riutord Fe B, Riutord Fe N, Arroyo Bote S, López González AA, Ramírez Manent JI. Relationship between healthy habits and sociodemographic variables in the values of different atherogenic indices. Academic Journal of Health Sciences 2022;37 (2):22-7 doi: 10.3306/AJHS.2022.37.02.22

47. Madrigal Arellano C, Hernández Ruiz Á, Soto Méndez MJ, Gil Á, Madrigal Arellano C, Hernández Ruiz Á, et al. Estudio Nutricional en Población Infantil Española (EsNuPI): actualización de hallazgos y primeras conclusiones. Nutr Hosp. 2021;38(SPE2):23-6.

48. Álvarez Zallo N, Guillen Grima F, Aguinaga-Ontoso I, Hermoso-de-Mendoza-Cantón J, Marín Fernández B, Serrano-Monzó I, et al. Estudio de prevalencia y asociación entre síntomas de asma y obesidad en la población pediátrica de Pamplona. Nutr Hosp. septiembre de 2014;30(3):519-25.

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ORIGINAL

LncRNA regulation in human oocytes obtained from patients with polycystic ovaries

Regulación de la lncRNA en ovocitos humanos obtenidos de pacientes con ovarios poliquísticos

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Summary

Introduction: Polycystic ovary syndrome (PCOS) is a common endocrine disorder among women of reproductive age. It often causes ovarian cysts, ovulation issues and infertility. PCOS also causes diabetes, obesity, hyperandrogenism, insulin resistance and other problems. PCOS is the leading cause of infertility in females and affects 4-20% of reproductive-age women. Long non-coding RNAs (lncRNAs) regulate the expression of target genes.
Methods: Thus, in this study, a number of lncRNA expression levels were investigated in human meiosis II stage oocytes obtained from patients with polycystic ovaries (PCO) relative to women without PCO. The oocytes were obtained from the Near East University Hospital IVF Clinic. The oocytes were grouped as the PCO and the control groups, respectively. Experiments were performed on a total of 13 samples, seven of which were obtained from PCO patients. RNAs were extracted and then used to make cDNAs. Real-time PCR was used to measure lncRNA expression level. Data was then statistically analyzed.
Results: Results from this study showed that MALAT1, AOC4P, and NEAT1 lncRNAs were expressed in human meiosis II stage oocytes. However, there was no statistical difference between the expression patterns of these three lncRNAs in oocytes samples obtained from PCO patients relative to the non-PCO patients.
Conclusions: Our results suggest that these particular lncRNAs may not be involved in the development of polycystic ovaries. To our knowledge, this is the first study investigating lncRNA expression in PCO oocytes rather than ovaries or endometrial wall.

Key words: PCOS, lncRNA, gene expression, oocytes, RT-PCR.

Resumen

Introducción: El síndrome de ovario poliquístico (SOP) es un trastorno endocrino frecuente entre las mujeres en edad reproductiva. Suele causar quistes ováricos, problemas de ovulación e infertilidad. El SOP también causa diabetes, obesidad, hiperandrogenismo, resistencia a la insulina y otros problemas. El SOP es la principal causa de infertilidad femenina y afecta al 4-20% de las mujeres en edad reproductiva. Los ARN no codificantes largos (lncARN) regulan la expresión de genes diana.
Material y métodos: Así, en este estudio, se investigaron varios niveles de expresión de lncRNAs en ovocitos humanos en estadio de meiosis II obtenidos de pacientes con ovarios poliquísticos (PCO) en relación con mujeres sin PCO. Los ovocitos se obtuvieron de la Clínica de FIV del Hospital Universitario Near East. Los ovocitos se agruparon como grupo PCO y grupo control, respectivamente. Se realizaron experimentos con un total de 13 muestras, siete de las cuales procedían de pacientes con OPC. Se extrajeron los ARN y se utilizaron para obtener ADNc. Se utilizó la PCR en tiempo real para medir el nivel de expresión de los lncARN. A continuación, los datos se analizaron estadísticamente.
Resultados: Los resultados de este estudio mostraron que los lncRNAs MALAT1, AOC4P y NEAT1 se expresaban en ovocitos humanos en estadio de meiosis II. Sin embargo, no hubo diferencias estadísticas entre los patrones de expresión de estos tres lncRNAs en muestras de ovocitos obtenidas de pacientes con PCO en relación con las pacientes sin PCO.
Conclusiones: Nuestros resultados sugieren que estos lncRNAs en particular pueden no estar implicados en el desarrollo de ovarios poliquísticos. Hasta donde sabemos, este es el primer estudio que investiga la expresión de lncRNAs en ovocitos PCO en lugar de ovarios o pared endometrial.

Palabras clave: SOP, lncRNA, expresión génica, ovocitos, RT-PCR.

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Introduction

Polycystic ovary syndrome (PCOS) is a disorder characterized by an aberrant androgen production in the ovaries. Normally, there is trace amounts of male sex hormone, androgen present in the female body, which ensures that the reproductive system functions properly. Due to an overabundance of androgen in the ovaries, cysts (fluid-filled sacs) grow, from which the name of the syndrome originates. PCOS is a widespread endocrine condition. It affects 4-20% of reproductive-age women worldwide[1,2]. PCOS is a well-known culprit in female infertility[3]. Excess androgen in the ovaries interferes with follicle development and egg release during ovulation, causing ovarian cysts. This causes menstrual difficulties such amenorrhea or oligomenorrhea (< 6-8 periods per year). Other consequences of PCOS include but not limited to acnes, obesity, insulin resistance, hyperandrogenism, and polycystic ovaries[4]. PCOS patients are more prone to type II diabetes. PCOS produces elevated blood insulin and glucose levels due to weak or non-functioning insulin receptors[5]. Obesity, hyperglycemia, and hyperinsulinemia are known to rise as a direct result of this[6]. Obese women are more likely to develop hyperandrogenism, which exacerbates PCOS symptoms[7]. Following menopause, ovaries are pacified and thus, the level of androgens descends, which may improve the symptoms brought about by PCOS. Despite this development, PCOS patients have been shown to possess elevated insulin resistance and androgen hormones in comparison with normal postmenstrual females[8].

PCOS follows multifactorial characteristics where it can arise from genetics, environment, and epigenetics, but most likely as a combination of at least two of these factors. The influence of genetics is quite prominent in PCOS as cases are observed in clusters in families. Furthermore, hyperandrogenemia and hyperinsulinemia are also shown to be heritable disorders[9,10]. To what extent genetics play a role in PCOS as well as its specific mechanism of action are yet to be discovered. It is highly likely that more than a single gene is responsible in the incarnation of this disease[9,11].

Long non-coding RNAs (lncRNAs) have a key role in cell proliferation, apoptosis, differentiation, and cancer by modifying chromatin, RNA-binding proteins, and endogenous competitive RNA (ceRNA)[12,13]. Previous investigations have shown that lncRNAs are critical for follicle growth. lncRNA NEAT1 knockout prevented a successful animal pregnancy (KO). Because of corpus luteum malfunction and low serum progesterone[14]. Previous research examined lncRNA expression in PCOS leukocytes. Higher lncRNA H19 expression was shown to increase the PCOS risk[15]. Thus, increased lncRNA H19 levels may be a biomarker for PCOS patients.

Thus, the pathophysiology of PCOS is complex and many genetic factors are involved in the development of PCOS. While studies on cumulus cells, endometrial cells and blood samples are present, to our knowledge there are no investigations present that directly focus on human oocytes. Thus, in our study we aimed to identify the differences in the expression levels of lncRNAs NEAT1, MALAT1 and AOC4P, if any, that occur between oocytes obtained from patients with polycystic ovaries compared to the ones from non-polycystic ovaries.

Materials and Methods

The study was approved by the Near East University ethical committee (YDU/2019/75-920) and informed consent was obtained from all the participants prior to sample collection. The samples were collected in two groups. The first group included oocytes from patients with polycystic ovaries (PCO) and the second group consisted of oocytes from non-PCO individuals (control group). Seven PCO samples and six control samples were collected. RNA was isolated from single human oocytes using a DNA/RNA extraction kit (Norgen DNA/RNA purification kit, Canada). The manufacturer protocol was followed with no modifications. Nanodrop analysis was used to assess the quality and quantity of the extracted RNA samples. cDNA was generated from extracted RNA samples (Transcript First Strand cDNA Synthesis kit, Canada). cDNA synthesis was performed by following the manufacturer's protocol. Real-time PCR was used to examine MALAT1, NEAT1 and AOC4P expression levels in both groups. ACTB was used as the housekeeping gene. Optimized PCR conditions comprised of 0.5µM to 2.5µM final primer concentrations and a range of 56°C to 62°C annealing temperatures for durations ranging from 10 to 30 seconds (**Table I**). lncRNA expression levels were detected using SYBR green mix (Lightcycler SYBR Green, Roche, Germany). A negative control containing

Table I: PCR Settings For LncRNAs (MALAT1, NEAT1, and AOC4P).

PCR Steps	Temperature/Time	Cycles
Initial Denaturation	95°C for 10min	1
Denaturation	95°C for 10sec	40
Annealing	56°C (*MALAT1* and **NEAT1**) / 62°C (*AOC4P*) for 20sec	
Elongation	72°C for 30sec	

no DNA template was used in each run. The Ct value (cycle of threshold), indicative of the number of cycles required to exceed the background level and gives off fluorescent signal above the threshold level, was obtained using the software program of the real time PCR equipment. The ΔCt value was calculated as the difference in the Ct values of the specified lncRNA and the housekeeping gene ACTB. Delta delta Ct (ΔΔCt) values were calculated from the difference between the ΔCt values of the oocytes obtained from the PCO and the control group, respectively. Using ACTB as a housekeeping gene, the ΔΔCt method was employed to normalize the level of gene expression. ΔΔCt values were then evaluated using unpaired student's T-test and one-way ANOVA on GraphPad prism software.

Results

This study was conducted on a total of 13 human meiosis II stage oocytes. Seven of which were obtained from patients with PCO undergoing IVF treatment and the remaining six from patients without PCO. RNA was successfully extracted from single oocytes, and the concentration and purity are shown in **table II**. The results of this study showed that all these lncRNAs were expressed in human meiosis II stage oocytes.

The real time PCR analysis was conducted to determine the expression level of each gene. The expression patterns of MALAT1, AOC4P, and NEAT1 were investigated in two groups. Normalization was conducted using the housekeeping gene. Delta CT method was applied to investigate the statistical significance between two groups. The results of the statistical analysis indicate that these lncRNAs are expressed at similar levels in oocytes from PCO patients and the control group ($p>0.005$, **table III**).

Discussion

PCOS is mainly a hormonal imbalance disorder that affects women of reproductive age. PCOS is one of the causes of infertility[3]. The condition can be brought about by various factors although its major cause is yet to be identified. It is suspected however, that both genetic and environmental factors contribute to its development. In the field of genetics, the topic of non-coding RNAs represent a very hot topic lately, following the recognition of their roles in many regulatory processes. Impact of non-coding RNAs and specifically long non-coding RNAs, is thus currently being investigated in many different areas. Despite that, associations between lncRNAs and PCOS is not well established yet. Therefore, in our study we aimed to investigate whether PCOS is a condition that can affect the levels of lncRNAs compared to individuals that do not suffer from such syndrome.

Previously published studies suggest that there is a correlation between PCOS and expression of a number of lncRNAs, although the definitive nature of these relationships is yet to be determined. Huang et al.,[16] showed that many lncRNA levels were altered in cumulus cells obtained from PCOS patients. Furthermore, Qin et al.[15] reported an association between H19 lncRNA in leukocytes obtained from PCOS patients. Nevertheless, to our knowledge, there is no previous research conducted in this field on oocytes directly.

Our results suggest there is no significant changes in the levels of NEAT1, AOC4P and MALAT1 lncRNAs between oocytes obtained from patients with PCO compared to patients with no PCO indication. Thus, it is possible that these lncRNAs are not directly associated with the oocyte maturation and development. Previously published data on NEAT1 knockout mice suggested that such an intervention would disrupt corpus luteum

Table II: Patient Details Including Polycystic Ovary Status, Age And BMI.

Patient's No.	Groups	Female's Age	BMI	Concentration (ng/µl)	260/280
1	Study group	22	27	10.0	1.52
2	Study group	29	22	11.0	1.48
3	Study group	26	19	12.7	1.46
4	Study group	23	21	11.0	1.50
5	Study group	21	19	9.7	1.51
6	Study group	27	16	9.9	1.52
7	Study group	28	34	12.5	1.53
8	Control group	23	22	10.9	1.56
9	Control group	21	19	10.3	1.53
10	Control group	21	19	10.0	1.52
11	Control group	25	18	10.9	1.56
12	Control group	29	18	11.5	1.51
13	Control group	27	23	10.0	1.52

Table III: P And T Values Of LncRNAs (MALAT1, AOC4P And NEAT1) From Unpaired T-test.

LncRNA	P values	T values
MALAT1	0.5026	0.7067
AOC4P	0.3563	0.9629
NEAT1	0.2438	1.232

development preventing natural pregnancies in such mice. However, the same study suggests that if the oocytes from those mice were to be implanted in pseudo-pregnant mice, the resulting embryos would be normal, i.e., NEAT1 knockout may not be directly affecting the oocyte quality[14]. Thus, it is a possibility that these lncRNAs have an impact on the endometrial maturation or follicle development. Therefore, it would be interesting to perform further experiments using endometrial samples or cumulus cells. One of the limitations of this study is the low sample size. This might have undermined the quality of the results to an extent. However, since it is almost impossible to perform any experiments on human meiosis II stage oocytes, this study proves to be precious. Combined with our results, this might suggest NEAT1 and AOC4P may be affecting structures such as cumulus cells and/or the endometrium to bring about infertility problems in PCOS, rather than directly altering oocyte quality. Moreover, MALAT1, also known as NEAT2, can be considered in a similar fashion as it is a lncRNA closely related to NEAT1.

Conclusion

All in all, we present that NEAT1, MALAT1 and AOC4P levels in oocytes are unaffected in patients with polycystic ovaries in comparison with control oocytes. However, further experiments are required to understand this phenomenon beyond our current level. Future improvements can include an extended sample size as well as possibly including various cell types, such as cumulus cells and endometrial cells in addition to oocytes.

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Conflict of Interest
The authors have no relevant financial or non-financial interests to disclose.

Author Contribution Statement
Warda Rai performed the molecular parts of the experiments, analyzed the data including the statistical analysis and wrote the manuscript.
Hakan Aytacoglu performed the molecular parts of the experiments, analyzed the data including the statistical analysis and wrote the manuscript.
Burcu Özbakır was involved in patient evaluation and sample collection. She approved the final version of the manuscript.
Cenk Serhan Özverel was involved in the primer selection and primer design. He approved the final version of the manuscript.
Emine Kandemis was involved in the primer selection and primer design. He approved the final version of the manuscript.
Pinar Tulay supervised the project. She was involved in the study design, analysis and approved the final version of the manuscript.

Ethical approval
The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

References

1. Deswal R, Narwal V, Dang A, Pundir CS. The Prevalence of Polycystic Ovary Syndrome: A Brief Systematic Review. J Hum Reprod Sci. 2020;13(4):261. doi:10.4103/JHRS.JHRS_95_18

2. Mazinani M, Sangy S, Sangy S, Safavi H. Evaluation of the effectiveness of herbal composition (fennel, anise and bamboo cane) in the treatment of polycystic ovaries. Academic Journal of Health Sciences. 2022;37(4):90-93.

3. Mohammad MB, Seghinsara AM. Polycystic Ovary Syndrome (PCOS), Diagnostic Criteria, and AMH. Asian Pac J Cancer Prev. 2017;18(1):17. doi:10.22034/APJCP.2017.18.1.17

4. Rojas J, Chávez M, Olivar L, et al. Polycystic Ovary Syndrome, Insulin Resistance, and Obesity: Navigating the Pathophysiologic Labyrinth. Int J Reprod Med. 2014;2014:719050. doi:10.1155/2014/719050

5. Wilcox G. Insulin and Insulin Resistance. Clinical Biochemist Reviews. 2005;26(2):19. Accessed November 25, 2022. /pmc/articles/PMC1204764/

6. Martyn JAJ, Kaneki M, Yasuhara S. Obesity-induced Insulin Resistance and Hyperglycemia Etiologic Factors and Molecular Mechanisms. Anesthesiology. 2008;109(1):137-148. doi:10.1097/ALN.0B013E3181799D45

7. Pasquali R. Obesity and androgens: facts and perspectives. Fertil Steril. 2006;85(5):1319-1340. doi:10.1016/J.FERTNSTERT.2005.10.054

8. Hsu MI. Changes in the PCOS phenotype with age. Steroids. 2013;78(8):761-766. doi:10.1016/J.STEROIDS.2013.04.005

9. Franks S, Mccarthy M. Genetics of Ovarian Disorders: Polycystic Ovary Syndrome. Rev Endocr Metab Disord. 2004;5:69-76.

10. Legro RS, Driscoll D, Strauss JF, Fox J, Dunaif A. Evidence for a genetic basis for hyperandrogenemia in polycystic ovary syndrome. Proceedings of the National Academy of Sciences. 1998;95(25):14956-14960. doi:10.1073/PNAS.95.25.14956

11. Franks S, Gharani N, Waterworth D, et al. The genetic basis of polycystic ovary syndrome. Human Reproduction. 1997;12(12):2641-2648. doi:10.1093/HUMREP/12.12.2641

12. Flynn RA, Chang HY. Long Noncoding RNAs in Cell-Fate Programming and Reprogramming. Cell Stem Cell. 2014;14(6):752-761. doi:10.1016/J.STEM.2014.05.014

13. Quinn JJ, Chang HY. Unique features of long non-coding RNA biogenesis and function. Nat Rev Genet 2015 17:1. 2015;17(1):47-62. doi:10.1038/nrg.2015.10

14. Nakagawa S, Shimada M, Yanaka K, et al. The lncRNA Neat1 is required for corpus luteum formation and the establishment of pregnancy in a subpopulation of mice. Development. 2014;141(23):4618-4627. doi:10.1242/DEV.110544

15. Qin L, Huang CC, Yan XM, Wang Y, Li ZY, Wei XC. Long non-coding RNA H19 is associated with polycystic ovary syndrome in Chinese women: a preliminary study. Endocr J. 2019;66(7):587-595. doi:10.1507/ENDOCRJ.EJ19-0004

16. Huang X, Hao C, Bao H, Wang M, Dai H. Aberrant expression of long noncoding RNAs in cumulus cells isolated from PCOS patients. J Assist Reprod Gen. 2016;33(1):111-121. doi:10.1007/S10815-015-0630-Z/FIGURES/5

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CASE REPORT

Niña con síndrome coronario agudo de causa alérgica (Síndrome de Kounis): a propósito de un caso

A girl with acute coronary syndrome of allergic cause (Kounis syndrome): a case report

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Resumen

El síndrome de Kounis (SK) es una nueva entidad clínica definida como la aparición simultánea de síntomas alérgicos y de un síndrome coronario agudo. Desde su descripción inicial en el año 1991 se han ido sumando revisiones y descripciones de casos que están permitiendo conocer mejor su patogénesis. Actualmente hay descritos en la literatura tres subtipos: el tipo I sin enfermedad coronaria, el tipo II con enfermedad coronaria y el tipo III en pacientes que sufren trombosis de un stent farmacoactivo. La epidemiología es desconocida y no existen guías de práctica clínica que establezcan el tratamiento de elección. Presentamos un caso clínico de Síndrome de Kounis tipo I diagnosticado en nuestro centro cuya particularidad es que tuvo lugar en una paciente de edad pediátrica.

Palabras clave: Síndrome de Kounis, alergia, pediatría, infarto de miocardio.

Summary

The Kounis syndrome (KS) is a new clinical entity defined as the simultaneous occurrence of allergic symptoms and acute coronary syndrome. Since its initial description in 1991, there have been additional reviews and case descriptions that are helping to better understand its pathogenesis. Currently, there are three subtypes described in the literature: type I in patients without coronary artery disease, type II in patients with coronary artery disease, and type III in patients experiencing thrombosis of a drug-eluting stent. The epidemiology is unknown, and there are no clinical practice guidelines establishing the treatment of choice. We present a clinical case of Type I Kounis Syndrome diagnosed, with the particularity that it occurred in a pediatric patient.

Key words: Kounis Syndrome, allergy, childhood, myocardial infarction.

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Descripción del caso

Adolescente de 14 años de edad sin alergias conocidas en seguimiento en Traumatología Infantil por escoliosis congénita que ingresa de forma programada para intervención quirúrgica. No presenta otros antecedentes personales de interés. El estudio preoperatorio que incluye analítica, pruebas de función respiratoria y estudio cardiológico con electrocardiograma y ecocardiograma, resulta anodino. La cirugía se lleva a cabo sin incidencias y tras la misma, la paciente se mantiene ingresada con tratamiento analgésico, protección gástrica y vitamina K (en el contexto de protocolo de la Unidad de Cuidados Intensivos Pediátricos). Se traslada a planta donde al tercer día de ingreso durante la administración vitamina K, presenta de forma súbita inestabilidad hemodinámica con desaturación de oxígeno, taquipnea, taquicardia e hipotensión arterial mantenida. Dada la sospecha de reacción alérgica, se inician maniobras de estabilización con oxigenoterapia y cargas de suero salino fisiológico. Se administra dexclorfeniramina intravenosa y adrenalina intramuscular. Tras ello persiste inestable, por lo que se traslada de nuevo a la Unidad de Cuidados Intensivos Pediátricos. En dicha unidad se realiza un electrocardiograma en el que se objetiva alteración en la repolarización con onda T aplanada en derivaciones precordiales izquierdas sugestiva de isquemia subendocárdica (**Imagen 1**) y una analítica sanguínea en la que destaca una elevación marcada de troponina I así como del NT-proBNP con valores de triptasa sérica normales, entre otras pruebas complementarias.

Ante dichos hallazgos, se realiza ecocardiograma en el que se observa disfunción ventricular sistólica leve (fracción de eyección del ventrículo izquierdo del 47%) (**Imagen 2**). Durante su estancia en UCIP, se inicia perfusión de adrenalina que se desciende en pocas horas sin incidencias y se mantiene tratamiento con dexclorfeniramina y corticoterapia. Presenta mejoría progresiva a nivel hemodinámico y cardiaco con normalización de los parámetros analíticos de daño miocárdico y de la función ventricular en control ecocardiográfico a las 24 horas del evento.

Discusión

El Síndrome de Kounis es una enfermedad infradiagnosticada. En los casos publicados se ha llegado al diagnóstico por sospecha clínica ya que se han podido objetivar síntomas alérgicos agudos coincidentes en el tiempo con eventos coronarios[1-6]. Cualquier fármaco podría desencadenar un Síndrome de Kounis. La etiología de este síndrome no se conoce en la actualidad y se postula la implicación de los mediadores mastocitarios como histamina, serotonina, triptasa y leucotrienos como agentes vasoactivos capaces de generar un vasoespasmo coronario o angina microvascular[7,8]. La triptasa es un buen indicador de la presencia de descarga masiva de mediadores procedentes de mastocitos. Los altos niveles de triptasa junto con síntomas alérgicos apoyan la sospecha de la implicación farmacológica como desencadenante del cuadro. El tratamiento es controvertido puesto que no hay guías clínicas en la actualidad[9,10].

En nuestro caso existen varios puntos de discusión. En primer lugar, la determinación de triptasa en la analítica sanguínea al inicio del episodio fue normal. Si bien es el parámetro más útil para el diagnóstico de reacción alérgica, su normalidad no es excluyente de la misma. En el caso de nuestra paciente no se realizaron determinaciones seriadas ni se amplió estudio analítico con otros factores como IgE o complemento. En segundo lugar, existen consideraciones especiales en cuanto al manejo de este síndrome ya que el tratamiento de cada entidad por separado de forma simultánea presenta incompatibilidades[9]. Es el caso de la adrenalina, que estaría contraindicada en el caso de eventos coronarios agudos ya que puede inducir mayor isquemia, aparición de arritmias o empeorar el vasoespasmo coronario. En nuestro caso se mantuvo su administración. Cabe plantearse entonces que la persistencia de inestabilidad inicial podría tener relación con la administración de esta droga. Por otra parte, la expansión de volumen debe hacerse de forma cautelosa debido a la disfunción ventricular aguda que puede desencadenarse. Como se ha mencionado inicialmente, por el momento existe poca información y estudios al respecto de la entidad y de la idoneidad de su tratamiento.

Imagen 1: Electrocardiograma de la paciente.

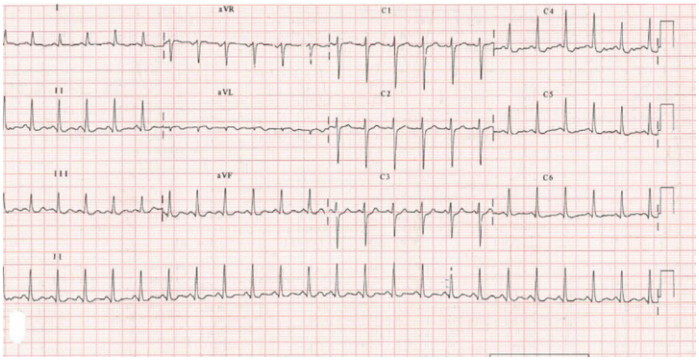
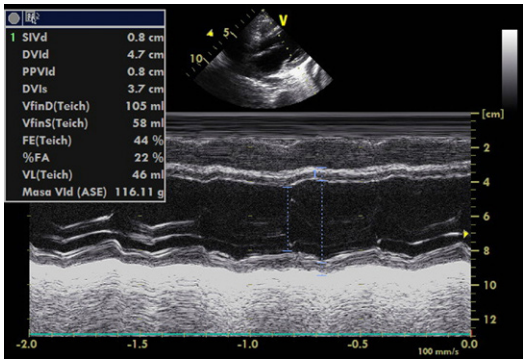


Imagen 2: Ecocardiograma en el que se observa disfunción ventricular sistólica leve.



Juicio clínico final

Dada la forma de presentación, las características y la evolución del episodio, el juicio diagnóstico final fue de síndrome de Kounis. El diagnóstico de esta entidad es clínico y se puede realizar tras objetivar simultáneamente síntomas y signos sugestivos de reacción anafiláctica y un evento coronario agudo. A pesar de la singularidad del síndrome y de la dificultad de la orientación diagnóstica, fue posible su detección y manejo exitoso. La paciente actualmente ha sido dada de alta por parte de Cardiología Infantil por normalización de función cardiaca sin secuelas y se ha declarado alérgica a vitamina K, por lo que ha cumplido las expectativas de pronóstico que se describen en los casos similares en la bibliografía[1].

Conflicto de intereses

Los autores declaran no tener conflicto de intereses.

Bibliografía

1. Biteker M, Duran NE, Biteker FS, Civan HA, Kaya H, Gökdeniz T, et al. Allergic myocardial infarction in childhood: Kounis syndrome. Eur J Pediatr. 2010 Jan;169(1):27-9. doi: 10.1007/s00431-009-0965-5. Epub 2009 Mar 11. PMID: 19277706

2. Molina Anguita M, García Rodríguez C, Méndez Díaz Y, Galindo Bonilla PA. Síndrome de Kounis, urgencia diagnóstica. Semergen. 2016 Oct;42(7):e133-e135. Spanish. doi: 10.1016/j.semerg.2015.11.007. Epub 2016 Jan 29. PMID: 26831543

3. Méndez Betancourt JL, Ramírez Ramos CF, López Guevara OA, Osorio Carmona HE. Síndrome de Kounis, a propósito de un caso. Acta Med Perú. 2018;35(1):65-70

4. Garcipérez Vargas FJ, Mendoza J, Sánchez Calderón P, et al. Shock cardiogénico secundario a síndrome de Kounis tipo II inducido por metamizol. Rev Esp Cardiol. 2012;65:1134-42

5. Rodríguez González M, Castellano Martínez A. Vasoespasmo coronario en un niño alérgico al látex: síndrome de Kounis. Arch Argent Pediatr 2019;117(5):e514-e518

6. Pampín F, Rial Prado MJ, Vázquez Vigo R, González Guzmán LA Síndrome coronario agudo por hipersensibilidad: Síndrome de Kounis. Galicia Clin 2014; 75 (1): 31-32

7. Kounis NG. Kounis syndrome: an update on epidemiology, pathogenesis, diagnosis and therapeutic management. Clin Chem Lab Med. 2016 Oct 1;54(10):1545-59. doi: 10.1515/cclm-2016-0010. PMID: 26966931

8. Kounis NG. Coronary hypersensitivity disorder: the Kounis syndrome. Clin Ther. 2013 May;35(5):563-71. doi: 10.1016/j.clinthera.2013.02.022. Epub 2013 Mar 13. PMID: 23490289

9. Gómez Canosa MS, Castro Orjales MJ, Rodríguez Fariñas FJ, García Jiménez A, Gutiérrez Cortés JM. Tratamiento del síndrome de Kounis. Med Intensiva. 2011 Nov;35(8):519-20. Spanish. doi: 10.1016/j.medin.2011.01.010. Epub 2011 Feb 26. PMID: 21354655

10. Douedi S, Odak M, Mararenko A, Ross J, Sealove B. Kounis Syndrome: A Review of an Uncommon Cause of Acute Coronary Syndrome. Cardiol Rev. 2023 Jul-Aug 01;31(4):230-232. doi: 10.1097/CRD.0000000000000436.

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CASE REPORT

Spontaneous rectus muscle hematoma from inferior epigastric artery hemorrhage

Hematoma espontáneo del músculo recto por hemorragia de la arteria epigástrica inferior

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Abstract

The epigastric arteries are important to consider during several surgical procedures such as trocar placement in laparoscopic surgeries, inguinal hernia repair, paracentesis and drain placements. Bleeding from inferior epigastric artery may result in abdominal wall hematomas that may require surgery. Although trauma is the most common cause for inferior epigastric artery bleeding there have been several cases of spontaneous rupture of an inferior epigastric artery. Predisposing factors may include anticoagulation, hematological disease, previous abdominal operation, injection of drugs and increased intra-abdominal pressure or pregnancy. Ultrasonography (USG) and computed axial tomography with intravenous enhancement is the best diagnostic methods in a hemodynamically stable patient. The treatment can include surgery, endovascular embolization or in selective cases conservative management. We present a case of spontaneous inferior epigastric artery bleeding that required surgery and ligation of the bleeding vessel.

Key words: rectus muscle, inferior epigastric artery, hematoma, hemorrhage.

Resumen

Es importante tener en cuenta las arterias epigástricas durante varios procedimientos quirúrgicos, como la colocación de trocares en cirugías laparoscópicas, la reparación de hernias inguinales, la paracentesis y la colocación de drenajes. La hemorragia de la arteria epigástrica inferior puede dar lugar a hematomas de la pared abdominal que pueden requerir cirugía. Aunque el traumatismo es la causa más frecuente de hemorragia de la arteria epigástrica inferior, se han dado varios casos de rotura espontánea de una arteria epigástrica inferior. Los factores predisponentes pueden incluir anticoagulación, enfermedad hematológica, operación abdominal previa, inyección de fármacos y aumento de la presión intraabdominal o embarazo. La ultrasonografía y la tomografia axial computarizada con realce intravenoso son los mejores métodos diagnósticos en un paciente hemodinámicamente estable. El tratamiento puede incluir cirugía, embolización endovascular o, en casos selectivos, tratamiento conservador. Presentamos un caso de hemorragia espontánea de la arteria epigástrica inferior que requirió cirugía y ligadura del vaso sangrante.

Palabras clave: músculo recto, arteria epigástrica inferior, hematoma, hemorragia.

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Introduction

The inferior epigastric artery branches from the external iliac artery and plays an important role in vascular supply of the anterior abdominal wall. It ascends medial to the deep inguinal ring in the subperitoneal tissue and penetrates the transversalis fascia. It gives off muscular branches and anastomoses with the superior epigastric branch of the internal mammary and lower intercostal arteries in the umbilical region[1]. There are numerous vascular variations of the abdomen and its wall that should be taken into account during different invasive and diagnostic procedures[2,3]. The epigastric arteries are important to consider during several surgical procedures such as trocar placement in laparoscopic surgeries, inguinal hernia repair, paracentesis, and drain placements. Bleeding may result in abdominal wall hematomas that require surgery to stop the bleeding vessel. Epigastric arteries can also be used for arterial perforation in case of trans-rectus abdominis muscle (TRAM) flap[2].

Although trauma is the most common cause for inferior epigastric artery bleeding there have been several cases of spontaneous rupture of an inferior epigastric artery[4]. The clinical picture can present with vague symptoms, making the diagnosis difficult. The treatment can include surgery, endovascular embolization or in selective cases conservative management. We present a case of spontaneous inferior epigastric artery management that required surgery.

Case report

A 68-year-old female, was urgently admitted to the hospital on September 20, 2023 with complaints of pain and appearance of a large palpable mass on the left side of the abdomen. The patient considered herself ill during the last 3 hours, when the pain first appeared with no apparent reason. Upon admission her hemoglobin level was 118 g/l (normal reference 120-160 g/l), erythrocytes 4.0*1012 (normal reference 4.2-5.4*1012), hematocrit 39% (normal reference 40-54%). No other changes were found in laboratory tests and she previously did not have any operations.

During ultrasound examination there was a partially delimited mass of an irregular ovoid shape, measuring 105*71*50 mm in the projection rectus muscle. In some areas, the mass was not clearly demarcated from the muscle tissue (infiltration). The structure of the mass was heterogeneous, with alternating areas of medium and low echogenicity, as well as inclusions of anechoic liquid component. There were no areas of active vascularization in the Doppler mode.

Ultrasonography with a higher frequency sensor (linear) (**Figure 1**), provide detailed picture of the structure allowed isolation of a pulsating hematoma, as well as differential diagnoses of a hematoma and fluid accumulations with a solid mass. In cases of large masses, as well as their topographic assessment, it is recommended to use a low-frequency convex sensor as in the current case (**Figure 2**).

The CT scan with intravenous enhancement revealed a heterogeneous cluster of 107*71*43 mm (volume ~170 cm^3) in the anterior abdominal wall on the right. The mass presented inclusions of hemorrhagic content with layers of liquid within the rectus muscle. The inferior epigastric artery slowly accumulated contrast, with signs of extravasation, probably from the branches of the epigastric artery. The patient also had an inguinal hernia of 22x22 mm, the contents of which was a strand of the omentum with no signs of ischemia.

The patient undergone surgery under general anesthesia on September 20. An incision was performed along the right side of the rectus sheath. During revision there was

Figure 1: Ultrasound scanning of the soft tissues of the anterior abdominal wall, transverse section at the mesogastric level with a linear sensor. The hematoma is indicated by an arrow.

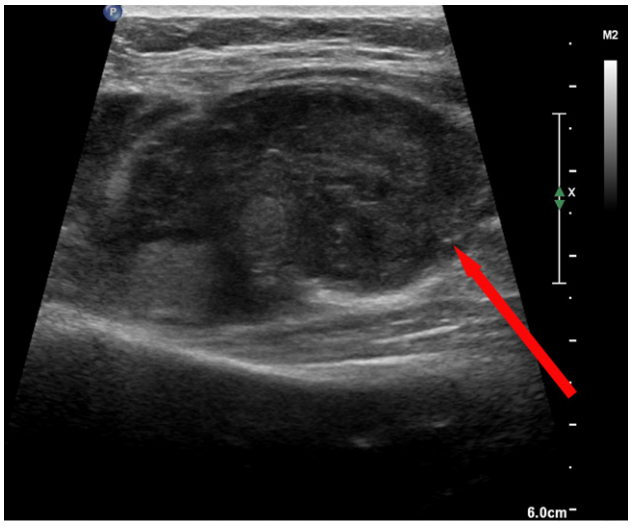
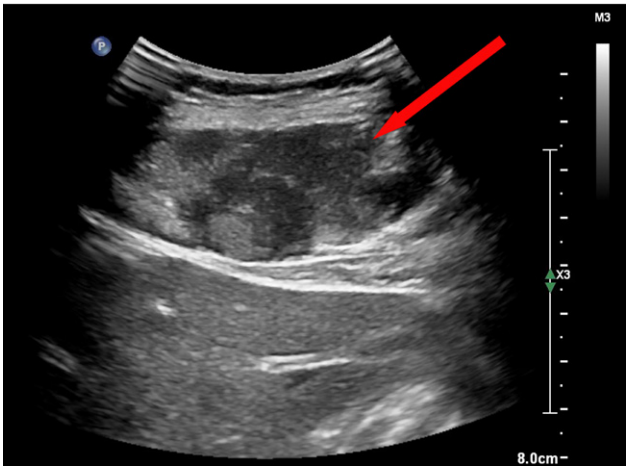


Figure 2: Ultrasound scanning of the soft tissues of the anterior abdominal wall, transverse section at the mesogastric level with a slight cranial tilt with a convex sensor. The hematoma is indicated by an arrow.



a hematoma approximately 200 cm^3 within the rectus muscle, at the bottom of which there was and actively bleeding inferior epigastric artery. The vessel was ligated and the incision was sutured in layers with and active drain. The patient received NSAIDS for postoperative pain in the postoperative period and 1 g of cefotaxime as antibiotic prophylaxis before surgery. The drainage was removed after 24 hours and the patient was discharged 2 days after the operation. There were no signs of complications during postoperative evaluation after 1 and 2 months.

Discussions

The rectus abdominis muscles represent two parallel vertically aligned muscles that begin at the level of superior ramus of the pubis and insert in the ventral aspect of the fifth, sixth, and seventh costal cartilages and the xiphoid process. The middle boundary is represented by the linea alba and the lateral by the linea semilunaris. The arcuate line is located about 5 cm below the umbilicus and functionally separates the rectus sheath into superior and inferior portions. Anatomical particularities of the rectus sheath make it possible for blood accumulation and distribution in a relatively wide area due to weaker support of the rectus abdominis by transversalis fascia and peritoneum below the linear semicircularis[6]. The area of inferior epigastric artery most susceptible to trauma is when it penetrates the rectus muscle and can undergo traction. During contractions of the rectus abdominis muscle, the length of the muscle changes, and the artery must glide with the muscle to avoid tearing[4,6].

Spontaneous rectus muscle hematoma due to inferior epigastric artery rupture is a rare entity. The most common cause is trauma, however in rare cases it can occur without an apparent reason. Predisposing factors may include anticoagulation, hematological disease, previous abdominal operation, injection of drugs and increased intra-abdominal pressure or pregnancy[4,5]. One of the hypothesis is that minor trauma such as cough, sneezing or other can cause small vessel damage that leads to spontaneous rupture. One of the main predisposing factors is anticoagulant therapy that is seen in up to 25% of patients with spontaneous rectus sheath hematomas[7,8].

The first case of inferior epigastric artery rupture was reported in 1857 by Richardson[9,10]. The patient usually presents with a painful lower abdominal mass that does not cross the midline and appeared suddenly. Carnett's test is performed by raising the patient's head off the bed while palpating the painful abdominal mass. Tensing up the rectus muscle protects the viscera and lessens the pain from intra-abdominal origin; however, if the source is in the abdominal wall, the pain will remain the same or increase in severity[4]. Ultrasonography is the optimal diagnostic modality as it is fast and can be performed at bedside. A linear probe is better for assessment of the mass while a convex probe can provide a better evaluation in case of large hematomas as in the presented case. CT scan with intravenous enhancement is considered the golden standard in case of bleeding as it can provide better information on extravasation.

There are two main treatment options. The majority of patients undergo surgery to find and ligate the bleeding artery. However, in selective cases conservative non-operative approach may be as effective that includes. abdominal compressive devices, blood transfusion, procoagulation therapy and coagulation parameter correction. Nevertheless, conservative approach is associated with a risk of continued and worsening bleeding, abscess formation, calcification and chronic pain (**Table I**)[10]. Another possible treatment option is endovascular embolization that can be less invasive[11]. Although, it seems that the inferior epigastric artery has a small diameter one retrospective review revealed 20 cases over a 12-year period, with a 30-day mortality rate of 30%[12].

Figure 3: CT scan of the abdomen (arrow indicates the area of hematoma with inferior epigastric artery). A – axial plane, B – sagittal plane.

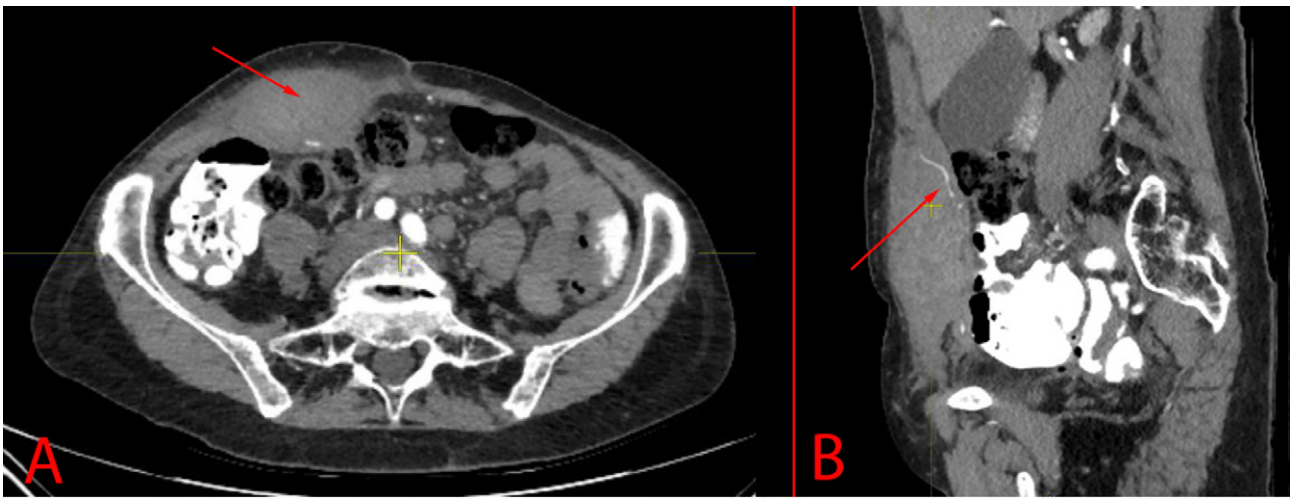


Table I: Management of spontaneous rectus sheath hematoma

Procedure	Advantages	Disadvantages
Conservative	Less invasive	The possibility remains of continuous bleeding, abscess formation, calcification and severe pain
USG-guided drainage	Less invasive than surgery	The possibility remains of continuous bleeding
Embolization	Less invasive than surgery	Requires specialized personnel and is not possible in some settings. There are risks of contrast-induced complications.
Surgery	Most definitive treatment for bleeding as it allows visual control of the sight of bleeding and direct ligation of the vessel	Invasive procedure that is associated with postoperative complications

To date there is no consensus on the management of this group of patients. Angeramo and coworkers have proposed an algorithm for rectus muscle sheet hemorrhage treatment based on an artificial neural network[13]. The patients can be subdivided into three groups (Berna I, II or III) based on the risk factors. Berna I are patients who are less than 65 years old and rectus muscle hematoma less than 1000 ml. Berna II are patients who older than 65 years and have change in hematocrit of more than 10% and decrease in hemoglobin more than 4 g/dl. Berna III are patients with signs of active extravasation[13]. Management of patients with hemorrhage should involve a multidisciplinary approach as the mortality and morbidity in this group of patients is high[14].

Conclusions

Spontaneous rectus sheath hematoma is a rare condition that requires timely diagnosis and treatment. It usually appears due to inferior epigastric artery tear and bleeding. Several treatment options can be implemented in this case, while surgery is still considered as the gold standard.

Conflict of interest

The authors declare that they have no competing interests.

References

1. Al-Talalwah W. The Inferior Epigastric Artery: Anatomical Study and Clinical Significance. International Journal of Morphology, 2017;35(1):7-11. doi:10.4067/S0717-95022017000100001

2. Kandinata N, Van Fossen K. Anatomy, Abdomen and Pelvis: Epigastric Artery. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537156/

3. Mazuruc N, Covantev S, Belic O. A Case of Unusual Vascularization of Upper Abdominal Cavity' Organs. Case Rep Vasc Med. 2018;31;2018:5738037. doi: 10.1155/2018/5738037.

4. Siu WT, Tang CN, Law BK, Chau CH, Li MK. Spontaneous rectus sheath hematoma. Can J Surg. 2003;46(5):390.

5. Zainea GG, Jordan F. Rectus sheath hematomas: their pathogenesis, diagnosis, and management. Am Surg 1988;54:630-3.

6. Casey RG, Mahmoud M, Carroll K, Hurley M. Rectus sheath hematoma: an unusual diagnosis [review]. Ir Med J 2000;93:90-2.

7. Cherry WB and Mueller PS: Rectus sheath hematoma: Review of 126 cases at a single institution. Medicine (Baltimore). 85:105-10. 2006.

8. Sobkin PR, Bloom AI, Wilson MW, LaBerge JM, Hastings GS, Gordon RL, et al. Massive abdominal wall hemorrhage from injury to the inferior epigastric artery: a retrospective review. J Vasc Interv Radiol. 2008;19:327-32.

9. Herrman C. Rupture of the deep epigastric vessels. Am J Surg, 1946;71:553-5

10. Sulkowski K, Young C. Case Report: Spontaneous Rupture of Inferior Epigastric Artery Masquerading as Inguinal Hernia. Clin Pract Cases Emerg Med, 2020;4(4):607-609. doi: 10.5811/cpcem.2020.9.48629.

11. Chen Y, Huang C, Shih M and Wang J: Transcatheter arterial embolization as an effective treatment for spontaneous inferior epigastric artery bleeding caused by anticoagulant therapy: Case reports. World Acad Sci J 2: 28, 2020

12. Abrashev H, Ananiev J, Georgieva E. Case Report: Spontaneous Left Inferior Epigastric Artery Injury in a COVID-19 Female Patient Undergoing Anticoagulation Therapy. J Clin Med. 2023, 25;12(5):1842. doi: 10.3390/jcm12051842.

13. Angeramo CA, Méndez P, Eyheremendy EP, Schlottmann F. Rectus sheath hematoma: conservative, endovascular or surgical treatment? A single-center artificial neural network analysis. Eur J Trauma Emerg Surg. 2022;48(3):2157-2164. doi:10.1007/s00068-021-01854-2

14. Shabunin AV, Lebedinsky IN, Dolidze DD, Bagatelia ZA, Covantsev S, Bocharnikov DS, et al. Giant bleeding post-traumatic thoracic sarcoma management: A case report. Front Surg. 2022; 8;9:1044077. doi: 10.3389/fsurg.2022.1044077.

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CASE REPORT

Mass-Like Lesions Leading to a Tumor-Like Appearance in the Right Atrium: Two Case Reports

Lesiones masivas con aspecto tumoral en la aurícula derecha: Dos casos clínicos

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Abstract

Introduction/Background: The majority of cardiac masses classified as benign, malignant, or tumor-like masses are composed of benign masses. In addition, another common cause of intracardiac masses is thrombi. Here, we present two cases of right atrial masses with different clinical manifestations.

Case 1: The first case was a 47-year-old patient with a history of chronic myeloid leukemia (CML) who was followed in the intensive care unit due to acute respiratory distress syndrome (ARDS). Transthoracic echocardiography (TTE) revealed an isoechoic thrombus with dimensions of 4.4x3.8 cm. The patient, who underwent surgery by the department of cardiovascular surgical, was found to have a histopathological examination consistent with a blood fibrin mass and hematoma structure.

Case 2: The second case was a 39-year-old patient who presented to the hospital with shortness of breath and palpitations approximately one year after undergoing secundum-type atrial septal defect (ASD) surgery. The transthoracic echocardiography (TTE) revealed a mobile mass in the right atrium with dimensions of 3.2x3.2 cm, consistent with a thrombus. The patient underwent surgery conducted by the Cardiovascular Surgery Department. The post-surgical pathology examination confirmed the removed mass as an organized thrombus formation. Causes of cardiac thrombus include diseases such as underlying valve diseases, arrhythmia, cardiomyopathy, malignancy or deep vein thrombosis. In the cases we shared, the first patient's history of CML and the second patient's ASD surgery as risk factors for right atrial thrombus development. The most commonly confused masses in the differential diagnosis of right atrial thrombi are myxomas. The distinction here was made with histopathological evaluation after resection.

Conclusion: Right cardiac thrombi can present as masses with a tumor-like appearance. Rapid diagnosis and treatment are life-saving.

Key words: cardiac mass, cardiac thrombus, case report, chronic myeloid leukemia, secundum-type atrial septal defect.

Resumen

Introducción/antecedentes: La mayoría de las masas cardíacas clasificadas como benignas, malignas o tumorales están compuestas por masas benignas. Además, otra causa frecuente de masas intracardiacas son los trombos. Aquí presentamos dos casos de masas auriculares derechas con manifestaciones clínicas diferentes.

Caso 1: El primer caso era un paciente de 47 años con antecedentes de leucemia mieloide crónica (LMC) que fue seguido en la unidad de cuidados intensivos debido a un síndrome de dificultad respiratoria aguda (SDRA). La ecocardiografía transtorácica (ETT) reveló un trombo isoecoico de dimensiones 4,4x3,8 cm. El paciente, que fue intervenido quirúrgicamente por el departamento de cirugía cardiovascular, presentaba un examen histopatológico compatible con una masa de fibrina sanguínea y estructura de hematoma.

Caso 2: El segundo caso era un paciente de 39 años que acudió al hospital con disnea y palpitaciones aproximadamente un año después de someterse a una intervención quirúrgica de comunicación interauricular (CIA) de tipo secundum. La ecocardiografía transtorácica (ETT) reveló una masa móvil en la aurícula derecha con unas dimensiones de 3,2x3,2 cm, compatible con un trombo. La paciente fue intervenida quirúrgicamente por el Servicio de Cirugía Cardiovascular. El examen patológico posquirúrgico confirmó que la masa extirpada era un trombo organizado. Las causas de los trombos cardíacos incluyen enfermedades como valvulopatías subyacentes, arritmias, miocardiopatías, neoplasias o trombosis venosa profunda. En los casos que compartimos, los antecedentes de LMC de la primera paciente y la cirugía de la CIA de la segunda como factores de riesgo para el desarrollo de trombos en la aurícula derecha. Las masas más comúnmente confundidas en el diagnóstico diferencial de los trombos auriculares derechos son los mixomas. En este caso, la distinción se realizó con la evaluación histopatológica tras la resección.

Conclusiones: Los trombos cardiacos derechos pueden presentarse como masas de aspecto tumoral. Un diagnóstico y tratamiento rápidos pueden salvar vidas.

Palabras clave: masa cardiaca, trombo cardiaco, caso clínico, leucemia mieloide crónica, comunicación interauricular de tipo secundum.

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Introduction

Cardiac masses are classified as benign, malignant, tumor-like masses, and pericardial tumors[1]. The incidence of primary cardiac tumors varies from 1.38 to 30 per 100,000 individuals annually, with the majority (up to 75-90%) being benign masses[1-4]. The most common benign cardiac tumor in adults is myxoma, with approximately 75% originating from the left atrium and 10-15% from the right atrium[2,4]. Another common intracardiac mass etiology is thrombi, which can occur in various regions of the heart, although they are often found in the left atrium[2]. Thrombi can develop due to various underlying causes, including malignancies, and can result in different clinical presentations depending on the location within the heart. This article presents two cases of right atrial masses with different clinical presentations.

Case Presentations

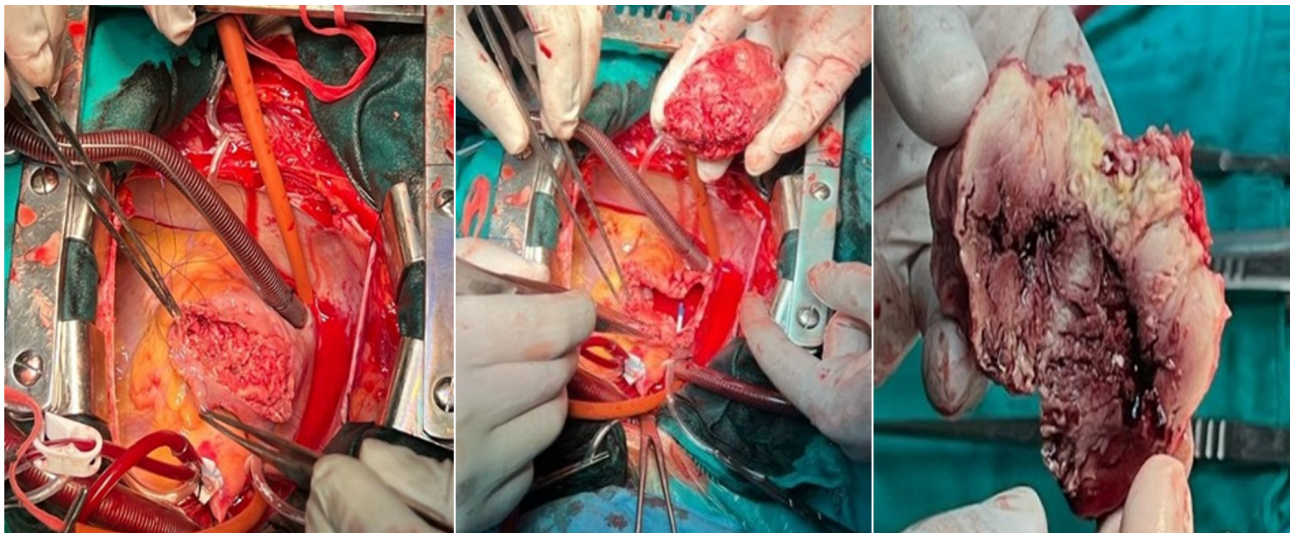
Case 1

A 47-year-old male with a known diagnosis of chronic myeloid leukemia (CML) was admitted to the internal medicine intensive care unit in May 2023 with a preliminary diagnosis of acute respiratory distress syndrome (ARDS). He was intubated and followed for one month. Transthoracic echocardiography (TTE) performed after extubation revealed a mobile isoechoic thrombus measuring 4.4x3.8 cm within the right atrium. The patient was consulted to the cardiovascular surgery (CVS) department and admitted to the CVS intensive care unit (ICU) in June 2023 for mass excision.

The preoperative evaluation revealed a history of Acinetobacter baumannii detected in tracheal aspirate culture, for which the patient had received treatment with meropenem, colistin, ampicillin-sulbactam, and vancomycin. There was no known history of allergies. The patient had a pleuroken placed due to left pleural effusion. His vital signs were stable, with fine rales heard on lung auscultation. Laboratory values on preoperative examination were as follows: WBC: 4.53x103/uL, hemoglobin: 8.6 g/dL, hematocrit: 26.7%, platelet: 100x103/uL, AST: 1899 U/L, ALT: 570 U/L, with other laboratory values within normal ranges. Electrocardiography (ECG) showed normal sinus rhythm, and chest X-ray revealed effusion in the left side but no other abnormalities. On repeat TTE during the preoperative period, an isoechoic thrombus measuring 4.4x3.8 cm was confirmed within the right atrium, along with an ejection fraction (EF) of 50%, globally hypokinetic heart, mild-to-moderate mitral regurgitation, mild-to-moderate aortic regurgitation, and right atrial enlargement. The patient received the necessary consultations, and recommended treatments were administered, leading to a decision to perform surgery with American Society of Anesthesiologists 3 (ASA) classification.

The patient underwent surgery, with general anesthesia and a median sternotomy incision. Cardiopulmonary bypass and cardiac arrest were initiated, followed by opening the right atrium, where a mass measuring approximately 4x3 cm near the interatrial septum was found (**Figure 1**). After excision of the mass, the operation was successfully completed, and the patient was transferred to the CVS ICU in intubated condition. In the postoperative period, the patient experienced active bleeding from the chest tube and developed tamponade, leading to an emergency reoperation. After opening the mediastinum, the hemorrhagic fluid and hematoma were evacuated, and the bleeding sources were managed. Surgical procedures were completed with bleeding control, and the patient was again transferred to the CVS ICU while intubated. Extubation was performed on the second postoperative day, and the patient was transferred to the internal medicine ICU. He experienced no issues during follow-up and was discharged after one month of hospitalization. The pathology report of the mass revealed a composition of fibrin clot and hematoma.

Figure 1: Intraoperative images of the mass in the first case.



Case 2

A 39-year-old male with no known comorbidities underwent surgery for secundum-type atrial septal defect (ASD) in September 2022. In June 2023, he presented to the hospital with complaints of shortness of breath and palpitations. Transthoracic echocardiography showed a mobile thrombus within the right atrium, measuring 3.2x3.2 cm, which appeared consistent with a mass. The TTE also revealed moderate tricuspid regurgitation, dilation of the right heart chambers, and a pulmonary artery pressure of 40-45 mmHg. The patient was evaluated by the CVS department and was recommended for surgical excision of the right atrial mass.

The preoperative evaluation showed no specific medical history other than the previous secundum-type ASD surgery. Physical examination, vital signs, and laboratory values were within normal limits. The ECG revealed sinus tachycardia at 115 bpm and ventricular extrasystoles. Preoperative preparations were completed, and the patient was classified as ASA 3 for surgery.

The patient underwent surgery with general anesthesia and a median sternotomy incision. After opening the pericardium, cardiopulmonary bypass and cardiac arrest were initiated, followed by exploration of the right atrium. The mass was excised, and any remaining fragments within the right atrium were removed (**Figure 2**). The operation was completed without complications, and the patient was transferred to the CVS ICU in intubated condition. Extubation was performed 6 hours postoperatively, and the patient was transferred to the general ward on the second postoperative day. He experienced no issues during ward stay and was discharged following recommendations on the seventh postoperative day. Pathological examination of the mass revealed organized thrombus formation.

Figure 2: Intraoperative images of the mass in the second case.

Discussion

Most primary cardiac tumors are located on the left side of the heart, making up the majority of benign tumors[4-5]. However, the majority of right atrial masses are also benign tumors. Thrombi are another significant etiology for right atrial masses[2,6,7]. Right atrial thrombi are often associated with underlying conditions such as valvular diseases, arrhythmias, cardiomyopathy, intravenous instrumentation, malignancies, or diseases causing hypercoagulability, such as deep venous thrombosis[2,8]. In the cases presented here, the first patient had a critical condition due to CML and had recently been extubated. The second patient had presented with dyspnea and palpitations approximately 10 months after undergoing ASD surgery, making them both at risk for right atrial thrombus development. A similar case to our second patient was reported by Arif et al. [9], where they shared a case of a large, spherical, and stalked right atrial mass in a patient who had undergone extensive secundum-type ASD surgery 11 months earlier.

The differential diagnosis of right atrial thrombi often includes myxomas. Right atrial myxomas can be

asymptomatic or present with various symptoms depending on the size and location of the mass (fatigue, fever, dyspnea, etc.)[10]. Similarly, thrombi can present with different symptoms based on their size and location within the heart[2]. In both of our cases, myxoma and thrombus were initially considered as differential diagnoses, and the definitive diagnosis was made only after histopathological evaluation following surgical resection.

There is no consensus on the treatment of right atrial thrombi, and the choice of treatment should be individualized for each patient. Surgical excision, medical therapy, and percutaneous techniques have all been applied in the treatment of right atrial thrombi. Direct-acting oral anticoagulants have been reported to be safely used in malignancy patients with venous thromboembolism[1,2]. However, surgical thrombectomy may be indicated in cases of hemodynamic deterioration or recurrent embolization. Surgical thrombectomy is a low-risk and effective treatment providing complete cure[1,2]. In our cases, surgical excision was preferred over oral anticoagulant therapy due to the systemic thromboembolic risk.

Conclusion

While the majority of benign cardiac tumors are located in the left atrium, right atrial thrombi can rarely occur due to various clinical reasons. Right cardiac thrombi are masses that can mimic a life-threatening tumor-like appearance depending on their location and size. Rapid diagnosis and treatment are life-saving.

Written informed consent has been obtained from both patients featured in the case reports.

Conflict of interest

The authors declare that they have no competing interests.

References

1. Bussani R, Castrichini M, Restivo L, Fabris E, Porcari A, Ferro F, et al. Cardiac Tumors: Diagnosis, Prognosis, and Treatment. Curr Cardiol Rep. 2020;22(12).

2. Poterucha TJ, Kochav J, O'Connor DS, Rosner GF. Cardiac Tumors: Clinical Presentation, Diagnosis, and Management. Curr Treat Options Oncol. 2019;20(8):1-15.

3. Hoffmeier A, Sindermann JR, Scheld HH, Martens S. Cardiac Tumors—Diagnosis and Surgical Treatment. Dtsch Arztebl Int. 2014;111(12):205-11.

4. Maleszewski JJ, Basso C, Bois MC, Glass C, Klarich KW, Leduc C, Padera RF, Tavora F. The 2021 WHO Classification of Tumors of the Heart. J Thorac Oncol. 2022 Apr;17(4):510-8.

5. Shah Z, Alraies MC, Harp A, Khalil S, Kaki A, Elder M. A right atrial mass. Cleve Clin J Med. 2019;86(7):445-7.

6. Kate Y, Syed MP, Doshi A, Patil S, Kumar D. Atrial Mass Versus Thrombus. Balkan Med J 2020;37:166-7

7. Chen Z, Xu G, Lin H. Eggshell right atrial mass. J Card Surg. 2018;1-2.

8. Nagatomi S, Matsumoto K, Imoto Y. Spherical right atrial thrombus with a fibrous capsule and stalk. Asian Cardiovasc Thorac Ann. 2018;26(7):580-1.

9. Arif S, Aktuerk D, Barron DJ. Giant, pedunculated right atrial thrombus formation after surgical atrial septal defect repair. J Thorac Cardiovasc Surg. 2015;149(3):e46-8.

10. Ma G, Wang D, He Y, Zhang R, Zhou Y, Ying K. Pulmonary embolism as the initial manifestation of right atrial myxoma: A case report and review of the literature. Med (United States). 2019;98(51):1-7.

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CASE REPORT

Pérdida de peso y deterioro del control glucémico en persona de edad avanzada y con diabetes tipo 2: ¿más allá de lo esperado? A razón de un caso clínico

Weight loss and deterioration of glycemic control in an elderly person with type 2 diabetes: beyond expectations? A clinical case report

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Resumen

La pérdida de peso involuntaria en adultos presenta una incidencia del 15-20% cuando las personas tienen más de 65 años. La pérdida de peso involuntaria es de gran relevancia clínica por aumentar la mortalidad, dependencia, riesgo de caídas y hospitalizaciones, entre otros efectos adversos. Esta puede ser un reto diagnóstico por el amplio abanico diagnóstico diferencial a realizar. Presentamos el caso de un varón de 79 años con empeoramiento del control glucémico, pérdida de peso severa en 3 meses y sintomatología digestiva. El diagnóstico esconde una afectación de alta prevalencia y probablemente, infradiagnosticada. El manejo de la terapia nutricional del paciente será decisivo en la reducción de la morbilidad y mortalidad de nuestro paciente.

Palabras clave: pérdida de peso, control glucémico, diabetes tipo 2.

Abstract

Unintentional weight loss in adults has an incidence of 15-20% when people are over 65 years of age. Unintentional weight loss is of great clinical relevance due to increased mortality, dependence, risk of falls and hospitalization, among other adverse effects. This can be a diagnostic challenge due to the wide range of differential diagnoses to be made. We present the case of a 79-year-old man with worsening glycemic control, severe weight loss in 3 months and digestive symptoms. The diagnosis hides a highly prevalent and probably underdiagnosed condition. The management of the patient's nutritional therapy will be decisive in reducing the morbidity and mortality of our patient.

Key words: Weight loss, glycemic control, diabetes tipo 2.

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Introducción

La pérdida peso involuntaria en adultos presenta una incidencia del 13%[1] aumentando la incidencia a 15-20% cuando las personas tienen más de 65 años[2]. Aunque no existe una única definición, se define pérdida de peso involuntaria patológica cuando la pérdida de peso es superior al 5% del peso corporal en menos de 3 meses o del 10% en seis meses o más[3]. La pérdida de peso involuntaria es de gran relevancia clínica por aumentar la mortalidad, dependencia, riesgo de caídas y hospitalizaciones, entre otros efectos adversos[4].

La fisiopatología de la pérdida de peso involuntaria consta de los siguientes mecanismos: reducción de la ingesta calórica, aumento de las necesidades calóricas por aumento de los requerimientos metabólicos y/o pérdida calórica por orina o heces[5].

La pérdida de peso involuntaria es un reto diagnóstico por el amplio abanico de diagnóstico diferencial a realizar. Las etiologías más frecuentes son: procesos malignos, procesos gastrointestinales, causas psiquiátricas, caquexia asociada a fallo orgánico, endocrinopatías, procesos infecciosos, medicaciones o factores socioeconómicos[6].

En este trabajo, presentamos el caso de un varón de 79 años que es derivado a consultas externas de endocrinología y nutrición por empeoramiento del control glucémico y pérdida de peso severa en 3 meses. La pérdida de peso podría ser consecuencia del mal control metabólico pero el paciente y sus familiares reportan cambios en el ritmo deposicional, dolor abdominal y un acentuado aumento de los requerimientos insulínicos. Lo explicado condicionará que nos hagamos más preguntas con interesantes respuestas.

Caso clínco

Varón de 79 años con antecedentes relevantes de fumador de 20 cigarrillos al día durante 40 años y posteriormente 1-2 cigarrillos al día en el momento actual, diabetes mellitus tipo 2 (DM2) desde el 2005, dislipidemia probable fenotipo IIa, esofagitis grado A y policitemia vera gen JAK2 positivo (controlado de forma estrecha por Hematología estando estable) por los cuáles recibe tratamiento con Metformina/Dapaglifozina 1000/5 mg cada 12 horas, Alogliptina 25mg/día, Insulina Glargina U200 14U/día, Atorvastatina 40mg/día, Interferon y Pantoprazol 20mg/día que es remetido a consulta de Endocrinología por mal control glucémico.

En la entrevista clínica, el paciente y sus familiares refieren un empeoramiento progresivo del control glucémico con hiperglucemias post-pandriales e hipoglucemias nocturnas asociado también a una pérdida de peso (5kg en 3 meses hecho que supondría más del 10% del peso de paciente) sin disminución del apetito, sin disminución de la ingesta calórica habitual, sin aumento de la actividad física y con presencia de dolor abdominal post-pandrial con sensación de plenitud y dificultad en realizar la digestión con diarreas post-comidas de aspecto pseudo-esteatorreico. El paciente y sus familiares no refiere sangre en heces, ni episodios de hipotensión arterial, ni tos, ni otra sintomatología por aparatos ni sistemas.

En la exploración física destaca presión arterial de 121/70mmHg y frecuencia cardíaca de 85lpm, peso actual de 46,5kg (peso habitual de 52kg), IMC actual de 17,9, estigmas de caquexia, dinamometría de 12 kg en mano dominante y 11kg en mano no-dominante, sin otros hallazgos reseñables.

Realizamos en consulta una valoración morfofuncional mediante impedancia bioeléctrica vectorial (Nutrilab Akern®) y ecografía nutricional ®junto con dinamometría y test de valoración funcional. Los resultados de estos fueron los siguientes:

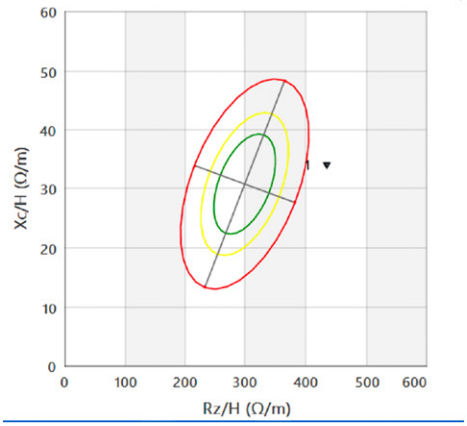
- Ecografía nutricional®: Recto femoral del cuádriceps a 13 centímetros de la rótula. Objetivamos Valores cuantitativos: área 2,21cm^2, circunferencia 7,40cm, eje X 3,29cm, eje Y 0,63cm, eje Y en contracción 0,71 cm y tejido adiposo subcutáneo 0,78cm. Respecto las variables cualitativas existe presencia de mioesteatosis y de mionecrosis. Entre el apéndice xifoides y el ombligo objetivamos: grasa abdominal subcutánea total de 0,47cm con superficial 0,27cm y grasa preperitoneal de 0,2cm.

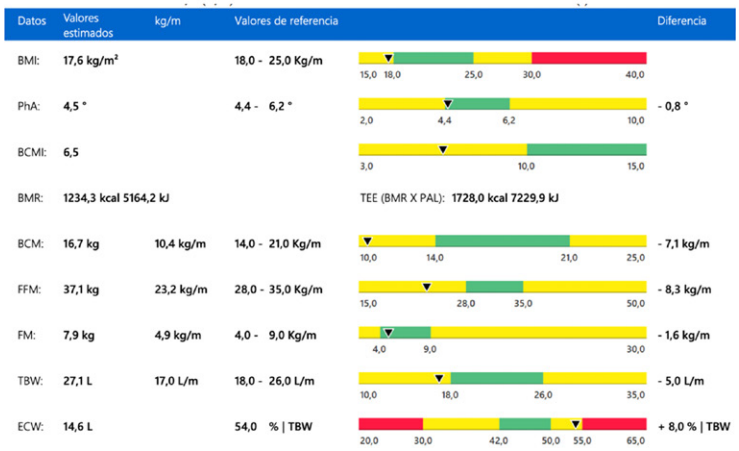
- Impedancia bioeléctrica vectorial (Nutrilab Akern®): Resistencia 696,5 ohm, reactancia 54,5 ohm, ángulo de fase 4,5º, hidratación del 73,1%, agua corporal total de 27,1L, agua extracelular 14,6L, masa libre de grasa 37,1kg, masa grasa 7,9kg, masa celular total 16,7kg, masa muscular esquelética apendicular 13.6kg e índice de masa muscular esquelética apendicular 7,1 kg/m^2.

- Test de velocidad de la marcha: 0,7m/s

Por tanto, nuestro paciente siguiendo los criterios del European Working Group on Sarcopenia in Older People (EWGPO2)[7] en su última revisión presenta una sarcopenia probable (medida mediante dinamometría con resultado inferior a 27kg en mano dominante), confirmamos la baja masa muscular mediante bioimpedancia vectorial (índice de masa muscular esquelética (SMI) < 8,31 kg/m^2 [8] en este caso SMI de 7,1 kg/m^2) y ecografía nutricional (área del recto femoral anterior del cuádriceps < 7,2cm^2 [9] en este caso 2,21 cm2) y añadimos la etiqueta de sarcopenia severa por bajo rendimiento físico (test de velocidad de la marcha <0,8)[10]. Siguiendo los criterios GLIM, estamos delante un paciente con desnutrición calórico-proteica severa con sarcopenia severa. Además, establecemos el diagnóstico de diabetes mellitus tipo 2 con mal control glucémico y pérdida de peso a estudio.

Imagenes 1 y 2: Representación gráfica del ángulo de fase y el análisis de la composición corporal obtenidos mediante impedancia bioelectríca en visita inicial.





Ajustamos insulinoterapia disminuyendo la insulina basal (objetivo: reducción de hipoglucemias nocturnas), asociamos pauta conservadora de insulina con análogos de acción rápida según glucémica capilar (objetivo: evitar excursiones post-pandriales), damos recomendaciones nutricionales para aumentar aporte calórico proteico, pautamos suplementos hipercalóricos e hiperproteicos en merienda de la mañana y merienda de la tarde, damos recomendaciones de ejercicio de fuerza y solicitamos pruebas complementarias para el estudio etiológico de la pérdida de peso de cara a la siguiente visita. Los resultados de las pruebas complementarias son:

- **Radiografía postero-anterior y lateral de tórax**: Normal.
- **Estudio de sangre oculta en heces:** Negativo.
- **Estudio de celiaquía en el adulto:** Negativo.
- **Ecografía abdominal completa:** Normal.
- **Elastasa fecal:** 15,60 µg/gr (Normal> 200µg/gr)
- **Analítica de sangre:** Leucocitos 3,36 10^9/L (4,00-11,0), Neutrófilos absolutos 1,91 10^9/L (1,80-7,50), Linfocitos absolutos 1,07 10^9/L (1,00-4.5), Hemoglobina 13,90 g/dL (13,00-16,7),Plaquetas 76,70 10^9/L *(150,00-400,00), Glucosa 64 mg/dL* (70-110), Creatinina 0,7 mg/dL* (0,72-1,25), Filtrado Glomerular 87 mL/min, Sodio 137,6 mmol/L (136-145), Potasio 4,33 mmol/L (3,6-5,3), Cloro 106 mmol/L (101,00-110,00), Calcio 9,20 mg/dL (8,80-10,20), Fosfato 2,70 mg/dL (2,30-4,70), Magnesio 1,79 mg/dL (1,60-2,60), Triglicéridos 176 mg/dL * (0-150), Colesterol Total 130 mg/dL (110,00-200,00), Proteínas totales 70,00 g/L (64,00-83,00), Albúmina 44,00 g/L (35,00-55,00), Hierro 67 µg/dL (65-175), Transferrina 237 mg/dL (174-364), Índice de Saturación de Transferrina 20,34 % (20,0-40,0), Ferritina 87,63 ng/mL (20-274), AST/ GOT 38 U/L *(5-34), ALT/ GPT 31 U/L (1-55), Fosfatasa Alcalina 66U/L (40-150) GGT 95 U/L* (12-64), CK 27 U/L * (30-200), Hemoglobina Glicosilada 8,5 % *(3,8-6,2), Prealbúmina 14,00mg/dL *(16,00-42,00), Cortisol 12 µgr/dL (antes 10 am: 3,7-19,4), Vitamina C 1,48 mg/dL (0,4-2), TSH 4,18 µUI/mL (0.35-4.95), FT4 0,88 ng/dL (0,7-1,48), Proteína C Reactiva 1 mg/dL*(0,00 - 0,50), Vitamina D 25 OH 9 ng/mL*.

En la siguiente visita, 1 mes después:

El paciente refiere escasa tolerancia a suplementos hipercalórico e hiperproteicos con diarreas y malestar gastrointestinal asociados. Le ha sido muy difícil seguir las recomendaciones nutricionales, hecho que ha condicionado que haya seguido perdiendo peso, en la consulta de 45 kg (1 kg menos que en visita anterior).

Por otro parte, el ajusto de la insulinoterapia ha reducido las hipoglucemias nocturnas (desde última visita sin otras hipoglucemias) pero persiste con excursiones hiperglucémicas. Informamos al paciente de los resultados objetivados en las pruebas complementarias, destacando la insuficiencia pancreática exocrina severa que presenta.

Dado los resultados de las pruebas complementarias se decide:

- Iniciamos suplementación con enzimas pancreáticas con recubrimiento entérico (Kreon®) a razón de 40.000U antes de desayuno-comida-cena y 20.000U antes de las meriendas.
- Cambiamos la fórmula de nutrición enteral por una fórmula peptídica a razón de 2 suplementos al día.
- Ajustamos insulinoterapia.
- Iniciamos suplementos de vitamina D.
- Se solicita screening de déficits vitamínicos.
- Solicitamos una resonancia magnética pancreática.

En la siguiente visita 1 mes después:

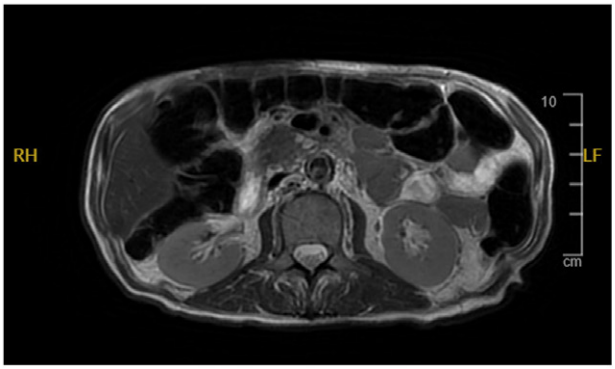
Gran mejoría de la tolerancia a la nutrición y suplementación enteral, con mejoría de las diarreas con aumento de la consistencia y disminución de la frecuencia (sólo 1-2 veces por día). Correcta adherencia a enzimas pancreáticas. Refieren él y sus familiares una mejoría de su estado general. Ha empezado a seguir recomendaciones de ejercicio físico también. El peso refleja esta mejoría con una ganancia ponderal de 2kg en 1 mes.

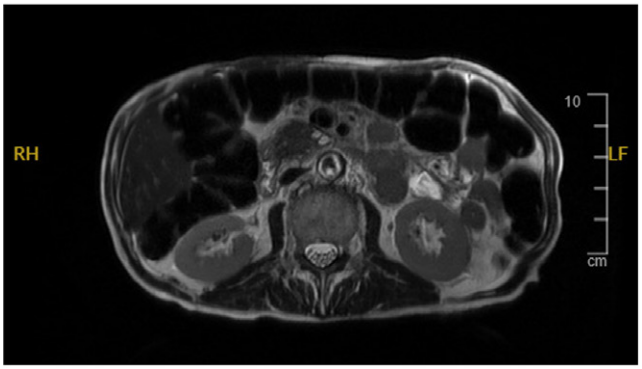
Por otra parte, el control glucémico ha mejorado notablemente, especialmente en las glucemias post-pandriales sin requerir ajuste posterior.

Screening déficits vitamínicos: Vitamina A 0,79 mg/L (0,3-1,00), Vitamina E 9,40 mcg/mL (5-20), Vitamina C 1,48 mg/dL (0,4-2), Vitamina D 25 OH 9 ng/mL*, Vitamina K 0.4ng/mL (0,2-1)

En la Resonancia Magnética Pancreática sin contraste endovenoso se objetivan pequeñas formaciones quísticas agrupadas que se extienden a lo largo del borde medial de la cabeza hasta el proceso uncinado del páncreas en relación con cistoadenoma seroso (30-35mm de eje longitudinal en el plano coronal).

Imagenes 3 y 4: Plano coronal para visualización de cistoadenoma pancreático.





Se informa al paciente de los resultados y dado la evolución decidimos:

- Interconsulta a Digestivo y Cirugía para valoración.
- Mismo tratamiento.
- Se acuerda visita telefónica en 1 mes.
- Cita presencial en 3 meses con analítica asociada.

En la siguiente visita (6 meses desde la primera visita), persiste la gran mejoría de la tolerancia a la nutrición y suplementación enteral, actualmente con deposiciones normales y controles glucémicos sin hipoglucemias y manteniendo valores entre 150-250mg/dL. Mejor estado general mejor, realiza más actividad física (va en bici a la cafetería) y cumple con las recomendaciones de ejercicio físico proporcionadas en consulta. El peso refleja esta mejoría con una ganancia ponderal de 1,8kg durante estos tres meses. Esta mejoría se refleja en el peso.

Por otra parte, el control glucémico ha mejorado notablemente, especialmente en las glucemias post-pandriales sin requerir ajuste posterior.

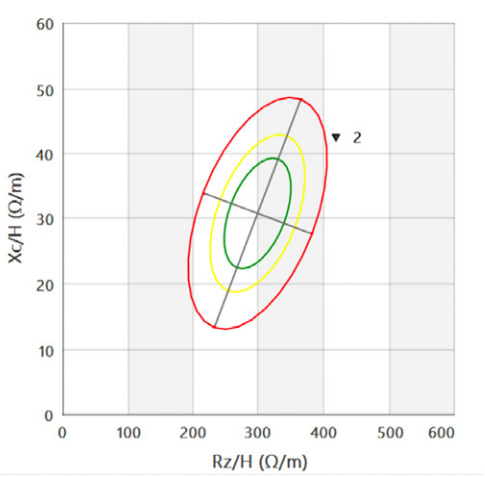
En la exploración física destaca presión arterial de 125/78mmHg y frecuencia cardíaca de 82lpm, peso actual de 47,8kg (peso al inicio de 45kg), IMC actual de 18,7 Kg/m^2, sin otros hallazgos reseñables.

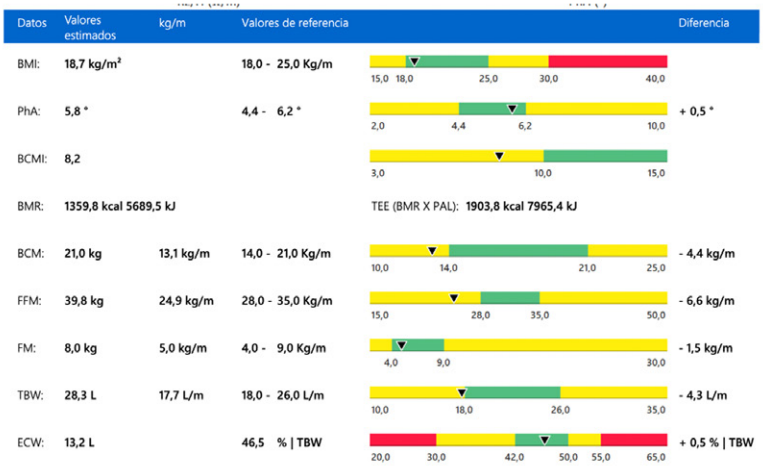
Realizamos en consulta una valoración morfofuncional mediante impedancia bioeléctrica vectorial (Nutrilab Akern®) y ecografía nutricional® junto con dinamometría y test de valoración funcional.

Los resultados de estos fueron los siguientes:

- **Ecografía nutricional®:** Recto femoral del cuádriceps a 13 centímetros de la rótula. Objetivamos valores cuantitativos: área 2,71cm^2, circunferencia 8,88cm, eje X 3,95cm, eje Y 0,76cm, eje Y en contracción 0,85 cm y tejido adiposo subcutáneo 0,79cm. Respecto las variables cualitativas existe presencia de mioesteatosis y de mionecrosis. Entre el apéndice xifoides y el ombligo objetivamos: grasa abdominal subcutánea total de 0,46 cm con superficial 0,26cm y grasa preperitoneal de 0,19cm.
- **Impedancia bioeléctrica vectorial (Nutrilab Akern®):** Resistencia 670,2 ohm, reactancia 68,3 ohm, ángulo de fase 5,8º, hidratación del 71,1%, agua corporal total de 28,3 L, agua extracelular 13,2 L, masa libre de grasa 39,8 kg, masa grasa 80kg, masa celular total 21,0 kg, masa muscular esquelética apendicular 16,2 kg e índice de masa muscular esquelética apendicular 8,42 kg/m^2.
- Dinamometría de 14 kg (previamente de 12kg) en mano dominante y 13kg (previamente de 11kg) en mano no-dominante.
- **Test de velocidad de la marcha:** 0,85 m/s.
- En la analítica de sangre destaca: Linfocitos absolutos 1,52 10^9/L (1,00-4,5), Hemoglobina 13,90 g/dL (13,00-16.,7), Glucosa 145 mg/dL* (70-110), Creatinina 0,75 mg/dL (0,72-1,25), Filtrado Glomerular 89 mL/min, Colesterol Total 150 mg/dL (110,00-200,00), Hemoglobina Glicosilada 7,5 % *(3,8-6,2), Prealbúmina 35,00mg/dL (16,00-42,00), Proteína C Reactiva 0.2 mg/dL (0,00-0,50), Vitamina D 25 OH 30 ng/mL.

Imagenes 5 y 6: Representación gráfica del ángulo de fase y el análisis de la composición corporal obtenidos mediante impedancia bioeléctrica en visita final.





Por tanto, objetivamos que la terapia nutricional ha conseguido una recuperación ponderal de 3 kg respecto la visita inicial con una mejoría del ángulo de fase de 1,3 puntos, una magnitud se describe como significativa para la reducción de la mortalidad[11]. Este aumento del ángulo de fase es consecuencia de un aumento tanto de la masa celular total como de la masa muscular. Correspondientemente, se produce un viraje del agua total disminuyendo la proporción de agua extracelular hecho que se asocia a una mejor salud celular[10]. El aumento de la masa muscular, objetivado mediante ecografía nutricional e impedancia bioeléctrica se ha acompañado con un aumento de la funcionalidad del músculo principalmente objetivada por el test de velocidad de la marcha que también ha mejorado. La dinamometría, a pesar de que es una herramienta de screening y no de funcionalidad, también ha mejorado. A nivel bioquímico, los niveles de prealbúmina se han normalizado, la proteína C reactiva ha disminuido, entrando en rango de normalidad y el control metabólico ha mejorado significativamente. En la siguiente tabla, encontramos parámetros biológicos importantes pre y post-intervención:

Tabla I: parámetros biológicos relevantes pre y post intervención

Variables biológicas	Pre-intervención	Post-intervención
Peso corporal	45kg	47,8kg
IMC	17,6 Kg/m²	18,7 Kg/m²
Dinamometría	12kg mano dominante/11kg	14kg mano dominante/13kg
Ángulo de fase	4,5º	5,8º
Masa libre de grasa	37,1kg	39,8kg
Índice masa muscular apendicular	7,1 kg/m²	8,42 kg/m²
Masa grasa	7,9kg	8,0kg
Agua corporal total	27,1L	28,3L
Agua extracelular	14,6L	13,2L
Test de velocidad de la marcha	0,7m/s	0,85m/s
Prealbúmina	14,00mg/dL	35,00mg/dL
Proteína C-Reactiva	1 mg/dL	0,2 mg/dL

Discusión

Describimos un caso de una desnutrición calórico-proteica severa con sarcopenia severa por insuficiencia pancreática exocrina (IPE) probablemente causada por la presencia de un cistoadenoma seroso pancreático y por una diabetes mellitus tipo 2 de larga evolución. El tratamiento con enzimas pancreáticas junto con el abordaje nutricional y de ejercicio físico han conseguido una recuperación ponderal progresiva con la mejoría del estado general del paciente y de su control metabólico.

La insuficiencia pancreática exocrina está presente entre el 30-50% de pacientes con diabetes mellitus tipo 2 insulinodependientes[12]. Esta entidad en los pacientes con diabetes mellitus tipo 2 está infradiagnosticada en esta población[13]. La etiología de la insuficiencia pancreática exocrina en pacientes con diabetes tipo 2 no está completamente esclarecida[12,13]. Se postula que existe una infiltración grasa pancreática (como ocurre con el enfermedad metabólica hepática) que puede

conducir a la fibrosis[14]; una disregulación de las hormonas secretadas por el páncreas, con hiperglucagonemia e hipersomatostatinemia, que inhiben la producción de amilasa, lipasa, tripsina y bicarbonato[15]; la infiltración por células inmunitarias producto de la inflamación crónica de bajo grado causada por la diabetes[16]; desregulación de los péptidos gastrointestinales, que promueve la liberación de las enzimas pancreáticas y reducción de la perfusión pancreática por la microangiopatía diabética[12]. De hecho, la *American Gastroenterological Association* (AGA) en su reciente documento de consenso publicado en 2023, considera a la diabetes mellitus tipo 2 insulinodependiente de larga evolución como una entidad con riesgo moderado-alto a desarrollar insuficiencia pancreática exocrina[17]. Por ello, el tratamiento de la insuficiencia pancreática exocrina en paciente con diabetes mellitus tipo 2 mejoría significativamente su control metabólico[13]. Al igual que el caso de nuestro paciente.

El cistoadenoma seroso pancreático representa la causa más común de lesiones benginas pancreáticas[18]. El diagnostico radiológico puede ser un reto para diferenciar las características de benignidad versus malignidad[18]. El *American College of Gastroenterology* (ACG) no recomienda seguimiento para los cistoadenomas serosos asintomáticos, aunque no define claramente los síntomas[19]. El *European Study Group on Cystic Tumors of the Pancreas* sugieren un seguimiento anual, y la resección quirúrgica solo se indica en presencia de síntomas de obstrucción[20]. El *American College of Radiology* (ACR) también desaconseja la vigilancia continua a menos que haya síntomas, pero sugiere considerar la resección quirúrgica para los cistoadenoma seroso asintomáticos mayores de 4cm[21].

En conclusión, consideramos nuestro caso de especial relevancia clínica al poner de manifiesto la no despreciable prevalencia y la importancia de sospecha de insuficiencia pancreática exocrina en pacientes con clínica compatible y diabetes mellitus tipo 2 de larga evolución e insulinodependientes. El correcto diagnóstico y tratamiento nutricional mejorará el estado nutricional y el control metabólico de nuestro paciente hecho que, inevitablemente acompañará una reducción de la morbimortalidad.

Conflicto de intereses

Los autores declaran no tener conflicto de intereses.

Bibliografía

1. Stajkovic S, Aitken EM, Holroyd-Leduc J. Unintentional Weight Loss in Older Adults. *CMAJ* 2011, 183, 443-9, doi:10.1503/cmaj.101471.

2. Alibhai SMH, Greenwood C, Payette H. An Approach to the Management of Unintentional Weight Loss in Elderly People. *CMAJ* 2005, 172, 773-80, doi:10.1503/cmaj.1031527.

3. Gilmore SA, Robinson G, Posthauer ME, Raymond J. Clinical Indicators Associated with Unintentional Weight Loss and Pressure Ulcers in Elderly Residents of Nursing Facilities. *J Am Diet Assoc* 1995, 95, 984-92, doi:10.1016/S0002-8223(95)00271-5.

4. Duan R, Zhang Q, Zhu J, Sun Y, Ye K, Li S, et al. The Association between GLIM Criteria-Defined Malnutrition and 2-Year Unplanned Hospital Admission in Outpatients with Unintentional Weight Loss: A Retrospective Cohort Study. *JPEN J Parenter Enteral Nutr* 2023, 47, 624-34, doi:10.1002/jpen.2506.

5. Thompson MP, Morris LK. Unexplained Weight Loss in the Ambulatory Elderly. *J Am Geriatr Soc* 1991, 39, 497-500, doi:10.1111/j.1532-5415.1991.tb02496.x.

6. McMinn J, Steel C, Bowman A. Investigation and Management of Unintentional Weight Loss in Older Adults. *BMJ* 2011, *342*, d1732, doi:10.1136/bmj.d1732.

7. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: Revised European Consensus on Definition and Diagnosis. *Age Ageing* 2019, *48*, 16-31, doi:10.1093/ageing/afy169.

8. Masanes F, Culla A, Navarro-Gonzalez M, Navarro-Lopez M, Sacanella E, Torres B, et al. Prevalence of Sarcopenia in Healthy Community-Dwelling Elderly in an Urban Area of Barcelona (Spain). *J Nutr Health Aging* 2012, *16*, 184-7, doi:10.1007/s12603-011-0108-3.

9. Ozturk Y, Deniz O, Coteli S, Unsal P, Dikmeer A, Burkuk S, et al. Global Leadership Initiative on Malnutrition Criteria with Different Muscle Assessments Including Muscle Ultrasound with Hospitalized Internal Medicine Patients. *JPEN J Parenter Enteral Nutr* 2022, *46*, 936-45, doi:10.1002/jpen.2230.

10. Valoración Morfofuncional de la Desnutrición Relacionada con la Enfermedad de José Manuel García Almeida | España | Editorial Médica Panamericana Available online: https://www.medicapanamericana.com/co/libro/valoracion-morfofuncional-de-la-desnutricion-relacionada-con-la-enfermedad (accessed on 3 February 2024).

11. Mattiello R, Amaral MA, Mundstock E, Ziegelmann PK. Reference Values for the Phase Angle of the Electrical Bioimpedance: Systematic Review and Meta-Analysis Involving More than 250,000 Subjects. *Clin Nutr* 2020, *39*, 1411-7, doi:10.1016/j.clnu.2019.07.004.

12. Kunovský L, Dítě P, Jabandžiev P, Eid M, Poredská K, Vaculová J, et al. Causes of Exocrine Pancreatic Insufficiency Other Than Chronic Pancreatitis. *J Clin Med* 2021, *10*, 5779, doi:10.3390/jcm10245779.

13. Radlinger B, Ramoser G, Kaser S. Exocrine Pancreatic Insufficiency in Type 1 and Type 2 Diabetes. *Curr Diab Rep* 2020, *20*, 18, doi:10.1007/s11892-020-01304-0.

14. Ou HY, Wang CY, Yang YC, Chen MF, Chang CJ. The Association between Nonalcoholic Fatty Pancreas Disease and Diabetes. *PLoS One* 2013, *8*, e62561, doi:10.1371/journal.pone.0062561.

15. Barreto SG, Carati CJ, Toouli J, Saccone GTP. The Islet-Acinar Axis of the Pancreas: More than Just Insulin. *Am J Physiol Gastrointest Liver Physiol* 2010, *299*, G10-22, doi:10.1152/ajpgi.00077.2010.

16. Kobayashi T, Nakanishi K, Kajio H, Morinaga S, Sugimoto T, Murase T, et al. Pancreatic Cytokeratin: An Antigen of Pancreatic Exocrine Cell Autoantibodies in Type 1 (Insulin-Dependent) Diabetes Mellitus. *Diabetologia* 1990, *33*, 363-70, doi:10.1007/BF00404641.

17. Whitcomb DC, Buchner AM, Forsmark CE. AGA Clinical Practice Update on the Epidemiology, Evaluation, and Management of Exocrine Pancreatic Insufficiency: Expert Review. *Gastroenterology* 2023, *165*, 1292-301, doi:10.1053/j.gastro.2023.07.007.

18. Ning K, Salamone A, Manos L, Lafaro KJ, Afghani E. Serous Cystadenoma: A Review on Diagnosis and Management. *J Clin Med* 2023, *12*, 7306, doi:10.3390/jcm12237306.

19. Elta GH, Enestvedt BK, Sauer BG, Lennon AM. ACG Clinical Guideline: Diagnosis and Management of Pancreatic Cysts. *Am J Gastroenterol* 2018, *113*, 464-79, doi:10.1038/ajg.2018.14.

20. European Study Group on Cystic Tumours of the Pancreas European Evidence-Based Guidelines on Pancreatic Cystic Neoplasms. *Gut* 2018, *67*, 789-804, doi:10.1136/gutjnl-2018-316027.

21. Megibow AJ, Baker ME, Morgan DE, Kamel IR, Sahani DV, Newman E, et al Management of Incidental Pancreatic Cysts: A White Paper of the ACR Incidental Findings Committee. *J Am Coll Radiol* 2017, *14*, 911-23, doi:10.1016/j.jacr.2017.03.010.

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CASE REPORT

Síndrome de Kabuki. Presentación de un caso

Kabuki syndrome. Presentation of a case

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Resumen

El síndrome de Kabuki fue descrito por primera vez en 1981 por los autores Niikawa y Kuroki. En un inicio fue descrito en japoneses, pero cada vez se diagnostican más casos tanto dentro como fuera de Japón. El propósito de este trabajo es presentar un caso esporádico sin relación familiar de un niño con síndrome de Kabuki, cuadro de baja frecuencia en nuestro servicio. A nuestro entender sería el segundo caso publicado en Ecuador. Se hace énfasis en los hallazgos polimalformativos y en especial el aspecto facial único referidos en la literatura vigente. Genéticamente nos fue imposible realizar un estudio específico para su diagnóstico, por lo cual nos basamos en los criterios fenotípicos establecidos en especial las manifestaciones faciales y oftalmológicas, siendo estas últimas estar presentes en 100% de los casos. Es importante fomentar el conocimiento de este síndrome para llegar a un diagnóstico temprano y ofrecer una mejor expectativa de vida.

Palabras clave: Síndrome de Kabuki, KMT2D, KDM6A, Ecuador.

Summary

Kabuki syndrome was first described in 1981 by authors Niikawa and Kuroki. It was initially described in Japanese, but more and more cases are being diagnosed both inside and outside Japan. The purpose of this paper is to present a sporadic case with no family relationship of a child with Kabuki syndrome, a low frequency picture in our service. To our knowledge it would be the second case published in Ecuador. Emphasis is made on the polymalformative findings and especially the unique facial aspect, referred to in the current literature. Genetically it was impossible for us to perform a specific study for diagnosis, so we rely on the established phenotypic criteria, especially the facial and ophthalmologic manifestations, the latter being present in 100% of the cases. It is important to promote awareness of this syndrome in order to reach an early diagnosis and offer a better life expectancy.

Key words: Kabuki's syndrome, KMT2D, KDM6A, Ecuador.

Introducción

El síndrome de Kabuki (SK) (OMIM 147920 300867), se caracteriza por anomalías congénitas múltiples/trastorno del neurodesarrollo poco frecuente caracterizado por cinco características principales: discapacidad intelectual (típicamente leve a moderada), endocrinológicas como retraso del crecimiento y retraso psicomotor; malformaciones viscerales (con frecuencia defectos cardíacos congénitos), persistencia de las yemas de los dedos fetales, baja estatura posnatal, anomalías esqueléticas (braquimesofalangia, braquidactilia V, anomalías de la columna vertebral y clinodactilia del quinto dedo) y rasgos faciales específicos (cejas arqueadas y anchas, fisuras palpebrales largas, eversión de la párpado inferior, orejas grandes y prominentes, ahuecadas, punta nasal deprimida y columela corta). Con frecuencia se observan varias características adicionales[1].

El SK suele deberse a variantes patógenas de novo en aproximadamente el 70% de los pacientes que cumplen los criterios diagnósticos. En la mayoría de los pacientes (56 a 75 %), el SK se debe a mutaciones en KMT2D (12q13.12) y en la minoría de pacientes (5%), el SK se debe a mutaciones en KDM6A (xp11.2).[1,2]

Los *Criterios de Diagnóstico de Consenso Internacional* para el SK fueron desarrollados en 2019 con el objetivo de facilitar el proceso de diagnóstico de esta condición. Estos criterios han sido publicados en diversas fuentes, como en un artículo científico en PubMed[12] y en una guía médica específica del SK[15]. El diagnóstico clínico de este síndrome se basa en el reconocimiento de características principales descritas, como hipotonía en la infancia, retraso psicomotor o discapacidad

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intelectual[12]. El Síndrome de Kabuki se manifiesta típicamente con hipotonía neonatal y dificultades en la alimentación, afectando a más del 70% de los casos. Los criterios se los aplican en pacientes de cualquier edad que tengan antecedentes de hipotonía infantil, retraso en el desarrollo y cumplan al menos uno de los criterios más importantes:[12]

1. Variantes no patógenas o potencialmente patógenas en KMT2D o KDM6A.
2. Las características dismórficas típicas incluyen párpados alargados, ectropión de los párpados inferiores y algunos de los siguientes:
   a. Las cejas son arqueadas y anchas, con muescas o escasas.
   b. Columela corta y punta nasal hundida
   c. Orejas grandes, protuberantes o en forma de cuenco.
   d. Almohadillas duraderas para las yemas de los dedos.

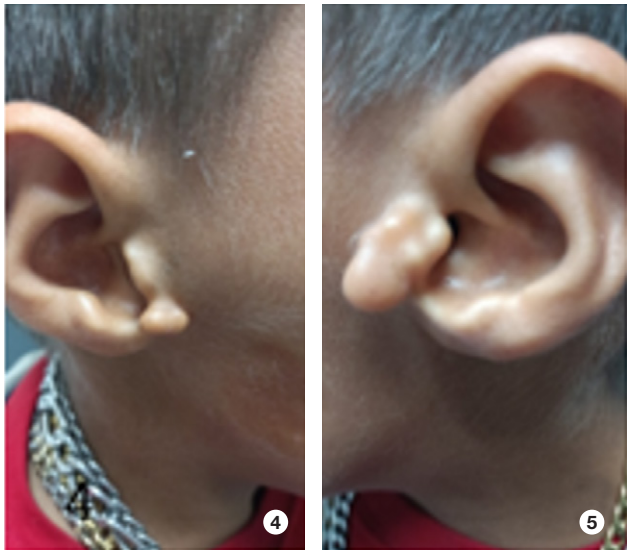
El SK, también conocido como síndrome de maquillaje Kabuki (Kabuki make-up), fue descrito por primera vez de manera simultánea en 1981 por los autores japoneses Niikawa y colaboradores[3] y Kuroki y colaboradores[4]. El término kabuki significa cantar (ka), bailar (bu), y habilidad (ki). Frecuentemente se traduce kabuki como "el arte de cantar y bailar". La denominación de este síndrome, dada por Kiikawa en su trabajo, se debe al parecido de estos niños con el maquillaje de los actores del teatro tradicional japonés Kabuki, especialmente, por el aspecto de la eversión del borde inferior externo de los párpados. Este síndrome fue descrito inicialmente en personas de origen japonés, si bien es cierto es el lugar donde más comúnmente se presenta, con una frecuencia estimada de 1/32,000 recién nacidos vivos, cada vez se diagnostican más casos tanto dentro como fuera de Japón[3]. Se informa en la bibliografía sobre dos series en España: una con de 18 casos[4] y otra con cinco[5]; un informe en Arabia saudita y algunos otros casos esporádicos en otras regiones del mundo como Australia, Ecuador, Brasil, el norte de Europa y Nueva Zelanda[3]. Sólo encontramos un caso ecuatoriano informado en 2006[6]. El propósito de este artículo es presentar el caso clínico de un niño con diagnóstico de SK en Ecuador.

Reporte de caso

Paciente masculino de 10 años de edad, remitido a consulta de cirugía estética por presentar rasgos dismórficos faciales muy peculiares, que invitaban a pensar en una displasia. Progenitores sin características semiológicas del hijo. Producto de primera gestación, nacido por parto normal y a término, con peso y talla adecuados para la edad. Conocemos muy poco en cuanto al desarrollo psicomotor y del lenguaje. Al examen físico: facie con rasgos dismórficos que le daban aspecto oriental que comprendía boca extremadamente grande con macroglosia, ojos almendrados, raíz nasal ancha, pabellones auriculares grandes y de implantación baja, con lóbulos adicionales, cabello igualmente baja implantación. A nivel de tórax se encontró mamilas anormalmente separadas, algunos roncus diseminados, respiración algo ruda y soplo sistólico foco aórtico. Tórax y abdomen: tórax simétrico con *pectus carinatum* en el tercio inferior. Se observan la braquidactilia y la clinodactilia del quinto dedo de ambas manos.

Imágenes 1, 2 y 3: Evidente dismorfia facial: Boca extremadamente grande y amplia (boca en carpa); macroglosia. Fisuras palpebrales elongadas, discreta eversión del tercio lateral del párpado inferior, hipertelorismo y telecanto y el aspecto almendrado de los ojos; cejas arqueadas con tercio lateral más despoblado. Caos y apiñamiento dental con columela baja y puente nasal ancho y deprimido.

Imágenes 4 y 5: Orejas displásicas, grandes con pabellón auricular de baja implantación con varios lóbulos adicionales en el trago en la oreja izquierda, y a nivel del trago y del lóbulo de la oreja derecha; orejas algo rotadas posteriormente.



Imágenes 6 y 7: Extremidades: dedos muy cortos, que a persistencia de rehabilitación parece ser que tubo almohadillas en el pulpejo de los dedos, en especial del medio que se lo ve un poco en flexión permanente. Fenotípicamente nos permitió filiar al paciente dentro de este síndrome. Se ordenó un cariotipo de bandas G, RMN de cerebro, serie ósea, y exámenes de rutina sanguínea. Lamentablemente el paciente se perdió de la consulta. (Colaboración del Dr. Mario Delgado Panchana, Cirujano Plástico (Complejo de Hospitales de la Honorable Junta de Beneficencia de Guayaquil-Ecuador).

Discusión

Los hallazgos en el paciente coinciden con los descriptos en la bibliografía, lo que nos permitió concluir que el paciente presentaba el SK. La presencia de un fenotipo de "aspecto oriental" a nivel facial, la cardiopatía congénita apoyada en la presencia de un soplo sistólico a la altura del área aortica, la baja talla, nos certificó nuestra sospecha inicial. Aunque nos fue imposible una valoración integral no descartamos haber encontrado algunas otras anomalías como las urinarias, por ejemplo, no representó una dificultad para arribar al diagnóstico. El progreso de la talla y la búsqueda de anomalías genitales se deberían tener en cuenta en los controles futuros.

Bien es cierto que, el SK se caracteriza por una fisonomía peculiar con un conjunto de rasgos únicos dismórficos, que dan a los niños una apariencia oriental muy típica, retraso mental de leve a moderado, retraso del crecimiento posnatal, anomalías esqueléticas y estrías. La primera serie publicada señaló que las malformaciones viscerales eran raras[2]. Sin embargo, con la aparición de nuevos casos, una proporción importante de estos niños desarrolla estas anomalías, que afectan principalmente a los sistemas cardiovascular, renal y genitourinario. Ohdo et al[7] fueron los primeros en llamar la atención sobre la asociación entre la cardiopatía congénita y el SK. En este contexto, en los casos de alta sospecha clínica o confirmación diagnóstica de SK, se recomienda el seguimiento en diferentes etapas de la vida.

En una serie española publicada recientemente por Galán y cols.[8], cuatro de los cinco pacientes (80%) tenían cardiopatía; pero tan sólo uno de ellos presentaba coartación de aorta. En cuanto a las anomalías reno-urogenitales, éstas pueden ser muy variadas (riñón en herradura, pelvis renal bífida, fístula rectovaginal, micropene, criptorquidia) y no parece que ninguna se asocie con más frecuencia que el resto. La presencia de un riñón único, como ocurría en nuestro paciente, no ha sido previamente descrita. El retraso mental leve a moderado es común en este síndrome, pero se sabe poco sobre las manifestaciones neurológicas infantiles y las anomalías cerebrales en estos pacientes. Aunque las características principales de este síndrome en las poblaciones orientales son similares a las de otras regiones, algunos síntomas neurológicos como hipotonía, disfagia de succión e hipermovilidad articular parecen ser más importantes y más comunes en pacientes no japoneses[5,9].

Hallazgos sobre cambios neuroconductuales y retrasos globales en el desarrollo motor desde los primeros meses de vida no se han informado previamente y pueden ayudar a caracterizar mejor las condiciones neurológicas en la primera infancia. Se ha informado microcefalia en el 36% de los pacientes no japoneses[5] y atrofia cerebral en el 4% de los pacientes japoneses[3]. Sin embargo, no está claro si estas anomalías están presentes en el nacimiento u ocurren más tarde debido a problemas con malformaciones orgánicas asociadas con el síndrome y en qué medida son responsables de un desarrollo neurológico deficiente. En nuestro paciente debido a la negativa de sus progenitores en iniciar una investigación más exhaustiva nos privó de encontrar hallazgos descritos.

Desde el punto de vista genético, la mayoría de los casos que se reportan son de *novo*, por lo que el riesgo de recurrencia es bajo para la descendencia de una pareja con un hijo afectado, aunque se han descrito casos familiares con herencia dominante[10,11]. Las mutaciones del gen KMT2D (en el cromosoma 12) 12,13 y KDM6A (en el cromosoma X) se han asociado a SK, pero debido a la existencia de casos con diagnóstico de SK, en ausencia de estas, se infiere que pueden existir otros genes involucrados.

Recientemente, tras el descubrimiento de microdeleciones en el brazo largo del cromosoma 22 en el llamado síndrome CATCH 22, se ha sugerido que algunos casos previamente descritos como SK pueden corresponder a este trastorno[14]. La mayoría de los casos publicados anteriormente se diagnosticaron al final de la infancia y antes de la adolescencia. Sin embargo, la presencia de rasgos faciales característicos –un aspecto general oriental– ya desde la primera etapa de la vida, junto con un retraso en el crecimiento posnatal y desviaciones tempranas en el desarrollo psicomotor, permiten la detección temprana de sospechas diagnósticas.

La supervivencia suele ser normal. Los primeros casos descritos tienen actualmente 30 años de edad. Todavía son pocos los casos conocidos fuera de Japón, encontramos casos esporádicos informados en América del Norte, Brasil, Filipinas, Vietnam, Arabia, India y África[12]. Por ello, creemos importante concienciar sobre este

síndrome no sólo a los distintos especialistas pediátricos que puedan estar implicados (neurólogos, cardiólogos, nefrólogos, etc.), sino también a neonatólogos y pediatras generales, para que puedan detectar este síndrome. temprano diagnóstico y así poder orientar a los padres sobre el pronóstico, manejo y futuro de estos niños.

Conclusión

Es muy importante que los médicos de cabecera comprendan que las características dismórficas de los pacientes con SK pueden parecer similares, pero el cuadro clínico completo puede variar significativamente de un paciente a otro; el genotipo no se corresponde al fenotipo, como sucede con la mayoría de las enfermedades raras. Esto es especialmente cierto cuando se consideran aspectos relacionados con sistemas de órganos específicos. El diagnóstico genético temprano para identificar el síndrome subyacente es fundamental porque puede confirmar el SK y clasificar los subtipos de SK. La identificación temprana de problemas médicos inusuales en pacientes con SK es importante para prevenir complicaciones y mejorar el pronóstico, especialmente dado que ciertas enfermedades en pacientes con SK no se tratan de manera diferente que en pacientes sin SK. Un mayor conocimiento de las manifestaciones clínicas del SK permitirá a los médicos brindar atención primaria de calidad a los pacientes y sus familias. Los estudios futuros deberían centrarse en los mecanismos genéticos específicos de las diversas condiciones clínicas para desarrollar potencialmente nuevos fármacos y enfoques terapéuticos multidisciplinarios. Se están investigando modelos de ratón y de ordenador. Los tratamientos existentes, como la suplementación con hormona del crecimiento, deberían ser otro tema de investigación. Como los resultados actuales aún son limitados, se debe reclutar un mayor número de pacientes con SK para estudios longitudinales. Finalmente, se necesita un análisis en profundidad de la calidad de vida de los pacientes con SK para descubrir las tecnologías más útiles para mejorar la calidad de vida y, con suerte, preparar era de la terapia génica que ya estamos viviendo.

Declaraciones éticas

Protección de personas: Los autores declaran que los procedimientos seguidos se conformaron a las normas éticas del comité de experimentación humana responsable y de acuerdo con la Asociación Médica Mundial y la Declaración de Helsinki.

Consentimiento de publicación

Los autores han obtenido el consentimiento informado de los tutores del paciente referido en el artículo. Para su protección hemos cubierto parcialmente la cara para que se pueda visualizar las características faciales, muy importantes para el diagnóstico.

Conflictos de intereses

Los autores declaran no tener conflictos de intereses.

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Bibliografía

1 Síndrome de Kabuki. Disponible en: https:// orpha.net/es/disease/detail/2322

2. Li Y, Bogerhausen N, Alanay Y, Kiper PO, Plume N, Keupp K, et al. A mutation screen in patients with Kabuki syndrome. Hum. Genet. 2011;130:715-724. doi: 10.1007/s00439-011-1004-y.

3. Niikawa N, Kuroki Y, Kajii T. Kabuki make-up (Niikawa-Kuroki) Syndrome: a study of 62 patients. Am J Med Genet 1988; 31:565-589.

4. Kuroki Y, Suzuki Y, Chio H, Hata A, Matsui I: A new malformation Syndrome of long palpebral fissures, large ears, depressed nasal tip, and skeletal anomalies associated with postnatal dwarfism and men tal retardation. J Pediatr 1981; 99:570-573.

5. Schrander-Stumpel C, Meinecke P, Wilson G, et al: The Kabuki (Niikawa-Kuroki) Syndrome: Further delineation of the phenotype in 29 non-Japanese patients. Eur J Pediatr 1994; 155:438-445.

6. Guzmán-Acurio AM, Tumbaco R, Jaramillo L. Síndrome de Kabuki. Rev. Ecuat. Neurol. VOL 13 Nº 3, 2004.

7. Ohdo S, Makodoro H, Sonoda T. Kabuki make-up Syndrome (Niikawa-Kuroki Syndrome) associated with congenital heart disease. J Med Genet 1985; 22:126-7.

8 Galán-Gómez E, Cardesa-García JJ, Campo-Sampedro FM, Salamanca Maeso C, Martínez- Frías ML, Frías JL. Kabuki make-up (Niikawa Kuroki) Syndrome in five Spanish children. Am J Med Genet 1995; 59:276-282.

9. Philip N, Meinecke P, David A, Dean J, Ayme S, Clark R, Gross-Kieselstein E, Hosenfeld D, Moncla A, Muller D, et al. Kabuki make-up (Niikawa-Kuroki) syndrome: a study of 16 non-Japanese cases. Clin Dysmorphol. 1992 Apr;1(2):63-77.

10. Schott Da, Blok MJ, Gerver WJ, Devriendt K, Zimmermann lJ, Stumpel CT. Growth pattern in Kabuki syndrome with a KMt2D mutation. Am J Med Genet A 2016;170:3172–9.

11. Micale L, Augello B, Fusco C, Selicorni A, Loviglio MN, Silengo MC, et al. Mutation spectrum of MLL2 in a cohort of Kabuki syndrome patients. Orphanet J Rare Dis. 2011 Jun 9;6:38. doi: 10.1186/1750-1172-6-38.

12. Adam MP, Hudgins L. Kabuki Syndrome: a review. Clin Genet 200;67(3):209-19.

13. Suarez Guerrero JL, Ordónez Suarez AA, Contreras García GA. Síndrome de Kabuki. An Pediatr (Barc) 2012;77(1):51-6 doi: 10.1016/j.anpedi.2012.01.016.

14. Wang LC, Chiu IS, Wang PJ, Wu MH, Wang JK, Hung YB, et al. Kabuki make-up syndrome associated with congenital heart disease. Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi. 1994 Jan-Feb;35(1):63-9.

15. Síndrome de Kabuki: información para padres y guía de manejo. Disponible en: SKInformacionPadresGuiaManejo2019.pdf (sindromekabuki.es)

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