

ACADEMIC JOURNAL OF HEALTH SCIENCES

MEDICINA BALEAR

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of SARS-CoV-2 vaccines

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Descriptive and correlational analysis

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A Follow-Up Study

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Patient Based Rate and Constant Gas Flow Rate

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of urinary pH and its role in kidney stone prevention

Malignant phyllodes tumor management - a case report

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El jurado calificador de los premios y becas convocados por la *Fundació Patronat Científic* del COMIB, reunido el día 7 de noviembre del presente, acordó la concesión de las siguientes becas y premios:

BECAS RELYENS-GRUP MED DE ROTACIÓN EXTERNA PARA MIR

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

- Joan Siquier Padilla, residente de la especialidad de Cardiología en el Hospital Universitario Son Espases, para una estancia de tres meses en el Servicio de Cardiología y Unidad UCI Coronaria e Insuficiencia Cardíaca del Hospital Universitari de Bellvitge en Barcelona.
- Bernat Mas Matas, residente de la especialidad de Dermatología en el Hospital Universitario Son Llàtzer, para una estancia de dos meses en el Servicio de Dermatología Pediátrica del Hospital Sant Joan de Déu en Barcelona.

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Una beca para la estancia en un hospital internacional, dotada de 3.000 euros.

- Natasha Woods Kreisler, residente de la especialidad de Pediatría y Áreas Específicas en el Hospital Universitario Son Espases, para una estancia de un mes y medio en el Servicio de Gastroenterología, Hepatología y Nutrición Pediátrica del *Hospital for Sick Children (SickKids)* en Toronto, Canadá.

BECAS DE INNOVACIÓN

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

- Carla Soldevila Verdeguer, FEA de Cirugía General y del Aparato Digestivo en el Hospital Universitario Son Espases, para una estancia de cuatro semanas en la Unidad de Carcinomatosis Peritoneal del *Mount Sinai Hospital* en Toronto, Canadá.
- Olga Claramonte Bellmunt, FEA de Cirugía General y del Aparato Digestivo en el Hospital Universitario Son Llàtzer, para una estancia de tres meses en el Servicio Cirugía Hepato-Biliar en el *Centre Hépatobiliaire. Hopital Paul Brousse* en Villejuif, Francia.

Desierta la adjudicación de las dos becas para estancias en centros sanitarios nacionales.

PREMIOS DE INVESTIGACIÓN

Tres premios de 1.500 euros.

“Premio Damià Carbó”

Al trabajo científico titulado “*Effects of six months treatment with liraglutide among patients with psoriasis and obesity, beyond metabolic control?*”, presentado por Joana Nicolau, Antoni Nadal, Pilar Sanchis, Cristina Nadal y Lluís Masmiquel.

“Premio Mateu Orfila”

Desierta la adjudicación.

“Premio Metge Matas”

Al artículo “*The coexistence of low albumin levels and obesity worsens clinical outcomes among subjects admitted for sars-cov-2 infection*”, cuyos autores son Joana Nicolau, Irene Rodríguez, Andrea Romano, Keyla Dotres, Antelm Pujol y Lluís Masmiquel.

PREMIO CAMILO JOSÉ CELA DE HUMANIDADES MÉDICAS

Un premio dotado de 1.500 euros concedido al trabajo titulado “La compasión me ha hecho ser más persona y mejor médico”, firmado por María Belén González Gragera.

PREMIO FUNDACIÓ MUTUAL MÈDICA AL MEJOR PROYECTO DE TESIS DOCTORAL

Un premio dotado de 2.000 euros al proyecto titulado “Deterioro cognitivo en la diabetes mellitus tipo 2: relación con las características clínicoepidemiológicas y papel de la dieta con especial referencia a la ingesta de fitato”, presentado por Antelm Pujol Calafat.

CERTAMEN BANCO SANTANDER DE CASOS CLÍNICOS PARA MIR

Tras la exposición de los cinco casos clínicos seleccionados como finalistas, el jurado, reunido el día 14 de noviembre del presente, acordó conceder:

- El primer premio, dotado de 1.000 euros, al caso titulado “Cuando la piel revela el diagnóstico: el rol decisivo del dermatólogo en una paciente con insuficiencia respiratoria grave”, cuya autora es Verónica Fernández Tapia.
- El segundo premio, dotado de 500 euros, al caso titulado “Neumonía necrotizante por SAMS ¿productor de PLV? A propósito de un caso”, cuya autora es Noelia Plaza Mendoza.

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ORIGINAL

Analysis of antibody immune response among patients after administration of SARS-CoV-2 vaccines

Análisis de la respuesta inmune de anticuerpos entre pacientes tras la administración de vacunas contra el SARS-CoV-2

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Abstract

The pandemic spread of SARS-COV-2 has presented a huge challenge to public health. Despite the implemented scientifically based prevention and control measures, the expected rapid control of the spread of this virus was not achieved. In the initial stage of the pandemic, there was a lack of scientific evidence on the timeframe and duration for patients to build an immune response to SARS-CoV-2. In the period August 2021-August 2022 a prospective study was conducted among 100 people who were vaccinated with vaccines against COVID-19. To evaluate the the dynamics of post-vaccination IgG antibodies and post-vaccination immune response in patients from the collection of the blood samples from 100 people was performed. To monitor the dynamics of the humoral response of the IgG antibodies the a three-point assessment was done: at the second week, at the eighth week and at the eighth month after the first dose of the vaccine.

Antibody values in the whole group show the known dynamics of class Ig G immunoglobulins after infection or vaccination. Data showed a significant slight increase, retention or decrease as early as week eight if changes between the three time points were analyzed for the shaped groups.

The greatest influence was the type and type of anti-COVID-19 vaccines. Throughout the follow-up period, there was a significant difference between the two vaccine types in favor of the mRNA vaccines, with the strongest response reported for Pfizer at day 14 and Moderna at the other measurement points.

Key words: COVID-19, antibodies, vaccines, immune response.

Resumen

La propagación pandémica del SARS-COV-2 ha representado un enorme desafío para la salud pública. A pesar de las medidas de prevención y control con base científica implementadas, no se logró el control rápido esperado de la propagación de este virus. En la etapa inicial de la pandemia, hubo una falta de evidencia científica sobre el marco temporal y la duración para que los pacientes desarrollen una respuesta inmune al SARS-CoV-2. En el período de agosto de 2021 a agosto de 2022 se realizó un estudio prospectivo entre 100 personas que fueron vacunadas con vacunas contra COVID-19. Para evaluar la dinámica de los anticuerpos IgG posvacunación y la respuesta inmune posvacunación en pacientes a partir de la recolección de muestras de sangre de 100 personas, se realizó una evaluación de tres puntos para monitorear la dinámica de la respuesta humoral de los anticuerpos IgG: en la segunda semana, en la octava semana y en el octavo mes después de la primera dosis de la vacuna.

Los valores de anticuerpos en todo el grupo muestran la dinámica conocida de las inmunoglobulinas de clase Ig G después de la infección o la vacunación. Los datos mostraron un ligero aumento, retención o disminución significativos ya en la semana ocho si se analizaron los cambios entre los tres puntos temporales para los grupos formados.

La mayor influencia fue el tipo y el tipo de vacunas anti-COVID-19. A lo largo del período de seguimiento, hubo una diferencia significativa entre los dos tipos de vacunas a favor de las vacunas de ARNm, con la respuesta más fuerte reportada para Pfizer en el día 14 y Moderna en los otros puntos de medición.

Palabras clave: COVID-19, anticuerpos, vacunas, respuesta inmune.

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Introduction

The pandemic spread of the Coronavirus disease (COVID-19) has put the health of people around the world in an extraordinary and difficult to control situation. Due to the global spread of SARS-CoV-2, the World Health Organization (WHO) declared a pandemic on March 11, 2020¹. The causative agent severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is highly contagious and has caused 7,012,986 million deaths since its discovery in Wuhan, China in December 2019². Globally, the incidence of COVID-19 manifests itself with intense epidemic waves - etiologically related to the new variants of the mutating corona virus. Morbidity in our country is high with 1,337,969 cases and 38,270 death cases³.

In many cases, infections caused by SARS-CoV-2 are mild or asymptomatic, but in the elderly and those with chronic health problems, they can lead to severe COVID-19 requiring invasive ventilation or death^{4,5,6}.

The pandemic spread of SARS-COV-2 has presented a huge challenge to public health in the world. Despite the implemented scientifically based prevention and control measures, which are effective in limiting the spread of other respiratory infections, the expected rapid control of the spread of this virus was not achieved.

Antiviral COVID-19 therapies have shown promise in preventing severe illness, but safe vaccinations and a vaccination campaign are the most scientifically confirmed solution⁷. In the initial stage of the COVID-19 pandemic, there was a lack of scientific evidence on the timeframe and duration for patients to build an immune response to SARS-CoV-2. This applies to both individuals who have been infected and those who have received vaccinations. Initially, investigations were done to delineate the B-lymphocyte response and ascertain the duration of B cell immunity conferred by antibody-mediated mechanisms, as well as its efficacy in providing protection against subsequent infections. Researchers discovered that antibodies produced in a patient infected with SARS-CoV-2 have potent neutralising abilities against the receptor binding domain (RBD) of the Spike (S) structural protein of the virus⁸.

SARS-CoV-2 enters human cells by attaching the receptor-binding domain (RBD) of the spike protein to the angiotensin-converting enzyme 2 (ACE2) receptor. The ACE2 receptor is found on the surface of various cell types, such as alveolar type II cells in the lungs and epithelial cells in the oral mucosa⁸. Subsequently, the inquiry shifted its focus towards examining the significance of T-cell mediated immunity in the context of COVID-19. Nevertheless, it is anticipated that COVID-19 vaccinations will elicit comparable B and T cell reactions, prompting the scientific community to investigate the potential of these vaccines in fostering

a robust and long-lasting immune response against SARS-CoV-2⁹.

The aim of the present study was analyze, evaluate and summarize the humoral/antibody response after vaccination with a COVID-19 vaccine among ambulatory patients.

Materials and methods

In the period August 2021-August 2022 a prospective study was conducted among 100 people who were vaccinated with one of the vaccines against COVID-19 authorized and available in Bulgaria. By using a semi-structured questionnaire, information was obtained about:

- Demographic data, occupational activity, comorbidities of the participants and information about previous infections with COVID-19 and adverse events after immunization in the past.
- Information about the first and second dose of the vaccine against COVID-19, i.e. the type of vaccine administered, the occurrence of adverse events after immunization - local reactions, systemic reactions, allergic reactions and reactions of interest in relation to vaccines against COVID-19 (thrombocytopenia, blood disorders, syncope, arthralgia).

The eligibility criteria for participants to be included in the study were:

- 1) age $\geq$ 18 years
- 2) vaccination with any of the available vaccines, regardless of previous infection with COVID-19
- 3) written consent for voluntary participation without financial compensation and the possibility of refusal at any time until the submission of the data.

To evaluate the the dynamics of post-vaccination IgG antibodies and post-vaccination immune response in patients from the collection of the blood samples from 100 people vaccinated with a COVID-19 vaccine was performed. This collection was done on three separate occasions. To monitor the dynamics of the humoral response of the IgG antibodies the a three-point assessment was done: at the second week, at the eighth week and at the eighth month after the first dose of the vaccine. The highly sensitive chemiluminescent test SARS-CoV-2 IgG II Quant (Abbott) was used to quantify neutralizing antibodies against the RBD receptor that binds the S1 subunit of the spike protein of SARS-CoV-2. In order to establish the initial level of anti-SARS-CoV-2 antibodies, a control group consisting of 20 individuals who had neither been infected with COVID-19 nor received a vaccination against SARS-CoV-2 was incorporated. The blood samples from the 20 subjects were analysed using a single test.

Statistics

Descriptive statistics was used to inform about: 1) quantitative variables, presented as mean (standard deviation), and median (25th percentile; 75th percentile) when variables lack normal distribution and 2) qualitative variables, presented as frequencies and percentages (n and %). Comparisons between two groups medians were analyzed with Mann-Whitney test for independent samples and between two groups proportions with z-test. Statistical tests were considered to have statistical significance if the p-value was less than 0.05. The systematization, processing, and analysis of the data were performed using SPSS v.26 for Windows (IBM Corp. Released 2019. Armonk, NY: IBM Corp).

Ethics

The study received approval from the Ethical Committee of the Medical University of Plovdiv, Bulgaria (Protocol 4 / 08.06.2022). The research was conducted in full accordance with the principles of the Declaration of Helsinki.

Results

A total of 120 individuals were examined and analysed. The participants were categorised into two groups for characterization and follow-up: healthy controls (non-diseased and unvaccinated, n=20) and vaccinated volunteers (n=100). Basic information about the participants is presented in **table I**. The data reveals a nearly equal representation of both genders in the groups, with an average age of roughly 51 years for the vaccinated individuals and 47 years for the healthy controls. The vaccinated participants were categorised into four age groups: 7 people aged under 30, 36 participants aged between 30 and 49, 47 participants aged between 50 and 69, and 10 participants aged above 69. Out of the overall group, 17% comprise healthcare personnel (HCP). None

of the COVID-19 vaccinated participants had experienced an adverse event following vaccination in the past. Among the COVID-19 vaccinated, 16% had co-morbidities, and 30% had previously recovered from COVID-19 before the immunisation began or were unsure about their previous infection status (4%).

The subjects were vaccinated using two types of vaccinations that are now available: mRNA and vector vaccines (**Table II**). The vaccines produced by Pfizer and Moderna belong to the first category, whereas the vaccine developed by Janssen falls into the second category. The majority of individuals received the Pfizer vaccine in both the initial and subsequent immunisation cycles, with rates of 72% and 95% respectively. Moderna, another mRNA vaccine, was chosen by 4% and 5% of participants in both stages. The Janssen vector vaccine is administered as a single dose, making it unsuitable for a subsequent immunisation. A total of 24 individuals received immunisation with it.

During the study, the researchers evaluated the incidence of potential adverse events (AEs) following immunisation. After the first dose of a COVID-19 vaccine, 78% of individuals reported AEs whereas 85.5% reported AEs after the second dose of the vaccine. These included pain and/or swelling at the injection spot, and elevated body temperature. The reported AEs did not affect the overall well-being and daily activities of vaccinated individuals.

In order to assess the humoral response and track its changes over time, the levels of IgG antibodies (measured in BAU/ml) were quantified at three specific time intervals: the second week, eighth week, and eighth month following the initial vaccine dose administration. The antibody levels of the immunised participants and the control group are presented in **table III**.

Table I: Demographic characteristics of the participants (n=120).

Groups	n	Gender		Age		
		female	male	Median age	Min	Max
COVID-19 vaccinated	100	60	40	51	18	77
Healthy controls	20	13	7	47	22	81

Table II: Distribution of participants regarding the vaccine received.

		Percentage of vaccinees studied after the first dose	Percentage of vaccinees studied after the second dose
Vaccine type			
mRNA- based		76	100
Viral-vector based		24	0

Table III: Antibody values in the immunised participants and in the control group.

Groups	IgG(BAU/ml)					
		Median (p5-p95)			Interquartile Range IQR (p25-p75)	
	2 nd week	8 th week	8 th month	2 nd week	8 th week	8 th month
Vaccinated	4146	5322	1762	9233	8084	3204
Healthy controls	Single measurement 0,142 BAU			Single measurement		

The data indicate that there is a predicted highest point of IgG class antibodies at week eight compared to the levels measured on day 14 after the start of immunisation. The third measurement taken at the eighth month had the lowest value compared to the previous measurements, but it still exceeded the protective limit established by this test, which is 150 BAU. The level of antibodies recorded in the control group was lower than this limit.

In order to establish possible relationships between the obtained values of IgG antibodies in the three measured points and statistically significant differences between them, the data were grouped according to: whether they were medical persons, presence of accompanying diseases, re-illness of COVID-19 before vaccination, type and type of the vaccine and the presence of post-vaccination reactions. The obtained values were processed with the statistical package SPSS 26, and the significant difference was determined with the non-parametric tests Mann-Whitney U Test, Friedman's Two-way analysis and Kruskal-Wallis Test. Differences at $p < 0.05$ were considered statistically significant.

Another relationship sought was between the amount of antibodies and the following factors that could have an impact on this amount, namely: whether the vaccinated were medical persons, the presence of accompanying diseases or a relapse of COVID-19 before vaccination.

We also tested whether pre-vaccination recovery from COVID-19 and the presence of co-morbidities affected antibody levels (**Table IV**). No significant difference was found between the groups at a given time point, with the exception of the antibodies measured on the second week in the previously infected and non-infected individuals - $p = 0.005$. Again, a significant difference in the amount of IgG was found between the three time

point analysis based on the presence of a comorbidity. An expected exception is the group of individuals who do not know whether they have had COVID-19 before vaccination, and in which there is likely a mixture of those who have had the disease and those who have not.

The type of vaccines also influence the humoral response. Vaccination was carried out with both types of vaccines - mRNA and vector-based, with mRNA from the companies Pfizer and Moderna, and vector-based from the Janssen company.

The antibodies obtained after the first immunization with the three types of vaccines were compared at the second week, the eighth week and the eighth month. At all three time points measured, there was a significant difference between the mean IgG antibodies with a predominance of the level of antibodies elicited after vaccination with the two mRNA vaccines (**Figure 1**).

Because the vector-based vaccine was administered as a single dose, only the effects of the two mRNA vaccines were examined and compared after the second dose. Despite the high values reported, especially at the second and eighth weeks, no statistically significant differences were found in the specific humoral response between the Pfizer and Moderna vaccines (**Figure 2**).

Our assumption about the influence of the type of vaccine – mRNA-based or vector-based on the measured amount of antibodies was confirmed by the non-parametric analysis. Regardless of the type of vaccine, immunization with the mRNA preparations elicited an excellent response against COVID-19, which, although declining by the eighth month, was significantly higher compared to antibodies generated after immunization with the vector vaccine (**Figure 3**).

Table IV: Follow up dependency on prevaccination COVID-19 recovery and presence of comorbidities affect antibody levels.

Have you had COVID-19 before receiving the vaccine?	InterquartileRangeIQR (p25-p75) IgG(BAU/ml)			Difference between the three time points for a given group	
	2 nd week	8 th week	8 th month		
No	6848,85	8756,75	2905,25	→	* 0.000
Yes	8147,50	7897,75	5225,50	→	* 0.000
Don't know	13636,95	11152,25	2343,13	→	0.174
Difference between groups at a given time point	↓ 0.005	↓ 0.338	↓ 0.354		
Comorbidities				Difference between the three time points for a given group	
No	8503,43	7897,75	3736,50	→	* 0.000
Yes	8882,75	10273,25	3036,00	→	* 0.001
Difference between groups at a given time point	↓ 0.165	↓ 0.936	↓ 0.487		

Legend: * - significant difference ($p < 0.05$) Friedman's Two-way analysis.

A probable reason is the single administration of this vaccine, which necessitated the inclusion of the booster dose with the other type of vaccine in the immunization scheme. Many studies concerning other types of vaccines are also underway, with the aim of building recommended immunization schedules based on the wide variety of established and future vaccines.

Figure 1: Level of antibody titres depending on the vaccine after the first dose.

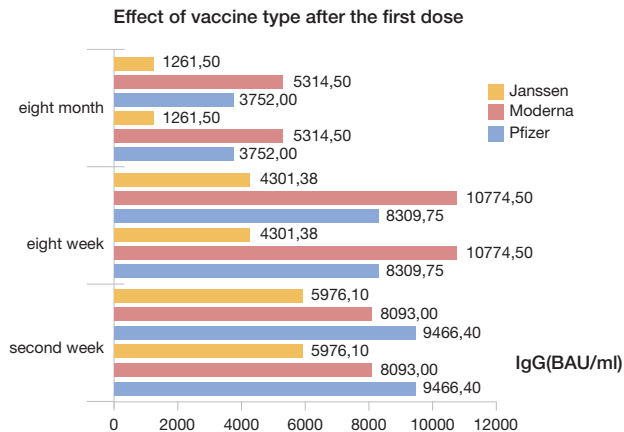


Figure 2: Level of antibody titres depending on the vaccine after the second dose.

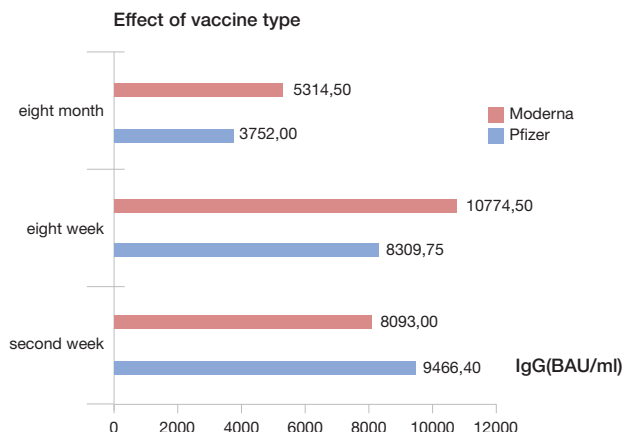
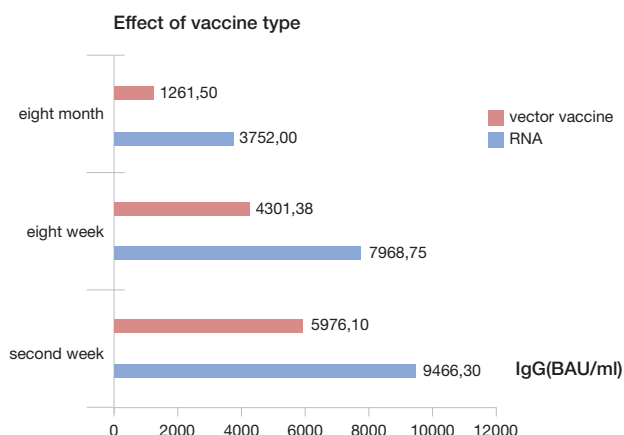


Figure 3: The effect of the type of vaccine - mRNA or vector - on the measured amount of antibodies.



Correlation relationships were also sought between the amount of antibodies measured at the three time points and various indicators related to and possibly influencing humoral immunity against COVID-19 such as gender, age, type and type of vaccine, presence of accompanying diseases and adverse reactions. As a result of the analysis, it was found that there is no moderate to strong significant correlation between the listed parameters (Spearman, $p > 0.05$).

Discussion

Public confidence in vaccination is critical to a successful immunization program, but on the other hand, the increasing number of available vaccines against COVID-19 may cause hesitation towards the decision to vaccinate. Thus, collecting reliable information about post-immunization adverse events, their severity, and their impact on an individual's life can educate the population about the issue and encourage immunization with a COVID-19 vaccine.

Understanding immune memory to SARS-CoV-2 is critical for improving disease diagnosis and vaccine efficacy, as well as for assessment of the likely future course of the COVID-19 pandemic. The values of antibodies in the whole group studied by us show the known dynamics of class Ig immunoglobulins after infection or vaccination. In our study the participants had detectable antibodies 2 weeks after vaccination and they persisted through the whole period of surveillance although declining with time. The peak of antibodies production was detected 8 weeks after vaccination which corresponds to other similar reports in the literature¹⁰. Recent studies suggest that the humoral response continues to develop long after vaccination, with memory B cells at late time points after vaccination showing improved quality and scope compared with early time points^{11,12}.

In our study the participant vaccinated with an mRNA vaccine produced significantly higher level of antibodies compared to those vaccinated with a viral-vector based vaccine throughout the whole period of surveillance. Although we did not measure antibody levels after administering two vaccine doses, our findings support the findings of Aldridge et al.¹³. They discovered that two initial doses of mRNA vaccine generated significantly higher levels of anti-SARS-CoV-2 antibodies compared to two initial doses of viral-vector based vaccine. This difference was observed at both 21 days (with antibody levels more than nine times higher) and 3 months (with antibody levels more than five times higher) after vaccination. Additionally, several researchers have documented that Pfizer/BioNTech induced a more robust humoral immune response compared to AstraZeneca at equivalent time points following immunization^{14,15}.

The humoral immune response can also be affected by other factors, including age, gender, or history of COVID-19. The existing vaccines for coronavirus disease 2019 (COVID-19) have successfully decreased both the overall incidence of illness and death rates, and they play a crucial role in managing the pandemic. Individuals who have previously recovered from COVID-19 exhibit augmented immune responses following immunisation, resulting in hybrid immunity, which surpasses the immunological responses of those who have only been vaccinated. The results from our study indicate a significantly better immune response in the previously infected individuals two weeks after vaccination although this difference proves to be insignificant in the other time periods. A team from Lahore, Pakistan performed an interesting prospective study to determine antibody levels at month 6 in SARS-CoV-2 vaccinated individuals in COVID-infected versus uninfected groups to determine the need for a COVID-19 booster vaccine in each group. At 6 months post-vaccination, in both groups, 100% of vaccine recipients had a positive or detectable antibody response, i.e. >0.8 U/ml. The mean levels of anti-SARS-CoV-2 S IgG among the recovered from COVID group was $1342 \text{ U/ml} \pm 100.67$, while among the uninfected group was $828 \text{ U/ml} \pm 82.28$ (p value: 0.000)¹⁶. It is well established that only natural infection provides short-term protection from infection¹⁷, indicating the importance of vaccination regardless of infection history. Because vaccination protects against severe disease and death¹⁸ it is safer for people to be vaccinated before than after natural infection.

Conclusions

The primary factor that had the most significant impact was the specific category of anti-COVID-19 vaccinations. During the whole observation period, there was a notable disparity between the two types of vaccinations, with the mRNA vaccines (specifically Pfizer) showing the most robust response at day 14, while Moderna performed better at other time points.

This outcome validates several prior evaluations that served as the foundation for the development of recommended immunisation systems, particularly in relation to booster doses. We anticipate a shift in attitudes about vaccinations, with a growing inclination towards favouring vaccines, due to the proven safety and efficacy of COVID-19 vaccines.

Additional Information

Disclosures

Human subjects

Consent was obtained or waived by all participants in this study. Ethical Committee of the Medical University of Plovdiv, Bulgaria issued approval Protocol 4/08.06.2022. The study received approval from the Ethical Committee of the Medical University of Plovdiv, Bulgaria (Protocol 4/08.06.2022). The research was conducted in full accordance with the principles of the Declaration of Helsinki.

Conflicts of interest

In compliance with the ICMJE uniform disclosure form, all authors declare the following:

Payment/services info:

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No potential conflict of interest was reported by the authors.

Financial relationships

All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.

Other relationships

All authors have declared that there is no other relationships or activities that could appear to have influenced the submitted work.

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The Relationship Between Postoperative Atrial Fibrillation and The Level of Preoperatively Measured Macrovesicular Fat Liver

Relación entre la fibrilación auricular postoperatoria y el nivel de hígado graso macrovesicular medido en el preoperatorio

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Abstract

Background: Postoperative atrial fibrillation (PoAF) is a common complication after coronary artery bypass grafting (CABG).

Objectives: This study aims to shed light on the potential relationship between the development of atrial fibrillation in patients undergoing isolated CABG and the levels of macrovesicular hepatic steatosis measured preoperatively.

Methods: The study included patients aged between 18 and 80 who underwent coronary bypass surgery and had thorax computed tomography performed before surgery. After exclusion criteria, 100 patients who developed PoAF and 100 patients who did not develop PoAF were included in the study. Hounsfield Unit (HU) was measured in the non-contrast CT images obtained, and mean hepatic attenuation (MHA), mean splenic attenuation (MSA), liver attenuation index (LAI), and hepatosteatosi values were recorded.

Results: There was no difference between the groups in terms of MHA, MSA, LAI, and hepatosteatosi. Additionally, no correlation was found between PoAF and MHA, MSA, LAI, and hepatosteatosi. ROC curve analysis demonstrated that LAI cut-off values of 10,5 or above could predict the development of PoAF with 47% sensitivity and 56% specificity (AUC: 0.529, log-rank P = 0.473).

Conclusion: In this study, we did not detect any relationship between PoAF and macrovesicular hepatic steatosis. However, we think that more comprehensive studies are needed because non-alcoholic fatty liver disease is associated with diseases that are risk factors for cardiovascular diseases.

Key words: Postoperative atrial fibrillation, liver attenuation index, hepatosteatosi, coronary artery bypass grafting.

Resumen

Antecedentes: La fibrilación auricular postoperatoria (FAP) es una complicación frecuente después del injerto de derivación arterial coronaria (CABG).

Objetivos: Este estudio pretende arrojar luz sobre la posible relación entre el desarrollo de fibrilación auricular en pacientes sometidos a CABG aislado y los niveles de esteatosis hepática macrovesicular medidos en el preoperatorio.

Métodos: El estudio incluyó a pacientes de entre 18 y 80 años sometidos a cirugía de bypass coronario a los que se realizó una tomografía computarizada de tórax antes de la cirugía. Tras aplicar criterios de exclusión, se incluyeron en el estudio 100 pacientes que desarrollaron FOP y 100 pacientes que no desarrollaron FOP. Se midió la unidad Hounsfield (UH) en las imágenes de TC sin contraste obtenidas, y se registraron los valores de atenuación hepática media (AHM), atenuación esplénica media (ASM), índice de atenuación hepática (IHA) y hepatosteatosi.

Resultados: No hubo diferencias entre los grupos en cuanto a MHA, MSA, LAI y hepatosteatosi. Además, no se encontró correlación entre la PoAF y la MHA, la MSA, el LAI y la hepatosteatosi. El análisis de la curva ROC demostró que los valores de corte del LAI iguales o superiores a 10,5 podían predecir el desarrollo de PoAF con una sensibilidad del 47% y una especificidad del 56% (AUC: 0,529, log-rank P = 0,473).

Conclusiones: En este estudio, no detectamos ninguna relación entre la PoAF y la esteatosis hepática macrovesicular. Sin embargo, creemos que se necesitan estudios más exhaustivos porque la enfermedad del hígado graso no alcohólico está asociada a enfermedades que son factores de riesgo de enfermedades cardiovasculares.

Palabras clave: Fibrilación auricular postoperatoria, índice de atenuación hepática, hepatosteatosi, bypass aortocoronario.

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Introduction

Postoperative atrial fibrillation (PoAF) is a common complication after coronary artery bypass grafting (CABG). PoAF has a high prevalence, affecting 20 to 45% of patients undergoing CABG¹. Advanced age, obesity, hypertension, previous atrial fibrillation (AF), and congestive heart failure are associated with a higher risk of developing AF after cardiac surgery².

Although various interventions have been used to prevent PoAF and other complications after CABG, the role of predisposing factors and the precautions taken against them to prevent the occurrence of PoAF are more remarkable³. PoAF has been associated with hemodynamic instability, increased early and late mortality, in-hospital adverse events, thromboembolic events, and progression of heart failure⁴. At this point, it is critical to understand the potential risk factors that can be detected in the preoperative period and to investigate the relationship of these factors with PoAF. In this context, macrovesicular fatty liver has recently attracted attention as a factor that plays an important role in the pathogenesis of cardiovascular diseases, and it has also been shown that it can trigger AF⁵. The most accepted theory explaining the pathogenesis of non-alcoholic fatty liver disease is the "two-hit hypothesis". According to this hypothesis, the first hit in the disease process resulting in steatosis is insulin resistance, which is responsible for the accumulation of triglycerides in hepatocytes. Oxidative stress, mitochondrial dysfunction, cytokines such as tumor necrosis factor- α (TNF α), and hormones such as adiponectin and leptin are responsible for the second hit that causes inflammation and fibrosis^{6,7}. As it is known, non-alcoholic fatty liver disease is often accompanied by the disease defined as metabolic syndrome; obesity, type II diabetes, hyperlipidemia (or dyslipidemia), and hypertension³. Hyperglycemia, which develops as a result of insulin resistance, may play a role in the development of AF through inflammation and oxidative stress mechanisms⁸. A study revealed that high HbA1c levels may be responsible for the development of PoAF⁹. The level of macrovesicular fat in the liver may be an important parameter in indicating end organ damage provoked by these risk factors.

The present study aims to elucidate the potential relationship between the development of AF and the level of macrovesicular fatty liver measured in the preoperative period in patients undergoing isolated on-pump CABG. In this context, it provides a comprehensive analysis to evaluate whether pre-CABG fatty liver is a potential predictor of PoAF. The results of our study may contribute to developing a more effective personalized approach in CABG planning, processes, and postsurgical care strategies.

Methods

Patients

This study was conducted on patients who underwent coronary bypass surgery between January 2020 and December 2021 at the Cardiovascular Surgery Clinic after receiving ethics committee approval. The data of the patients were retrospectively examined and recorded. Patients between the ages of 18 and 80 who underwent on-pump isolated CABG due to coronary artery disease and who underwent preoperative chest CT for any reason were included in the study. Patients with concomitant valvular heart disease, patients with advanced chronic obstructive pulmonary disease (COPD), patients with preoperative atrial fibrillation, patients who underwent emergency CABG, patients with chronic renal failure, and patients undergoing postoperative revision were excluded from the study. After the exclusion criteria, 100 consecutive patients who developed PoAF in the first 72 hours postoperatively were included in the study. Among the patients who did not develop PoAF, 100 patients were randomly selected as the control group using a computer program.

Surgery

The patients were subjected to routine coronary artery bypass surgery preparation in our clinic. All patients underwent general anesthesia using the intravenous narcotic anesthesia technique. After the median sternotomy, the left internal mammary artery and saphenous vein grafts were prepared simultaneously. All patients were operated under cardiopulmonary bypass. Aortic arterial and uni-caval venous cannulation were performed, and an antegrade cardioplegia cannula was placed in the aortic root. Myocardial protection was provided by applying antegrade, hyperkalemic blood cardioplegia, and systemic hypothermia after aortic cross-clamping. While distal anastomoses were performed under a cross-clamp, proximal anastomoses were performed under a side clamp placed on the aorta after all distal anastomoses were completed and the cross-clamp was removed. Following decannulation after cross-clamp removal, bleeding control was achieved, the sternum was closed and the patients were taken to the intensive care unit. The patients were extubated on the operation's day and followed in the intensive care unit for two postoperative days.

Diagnosis of PoAF

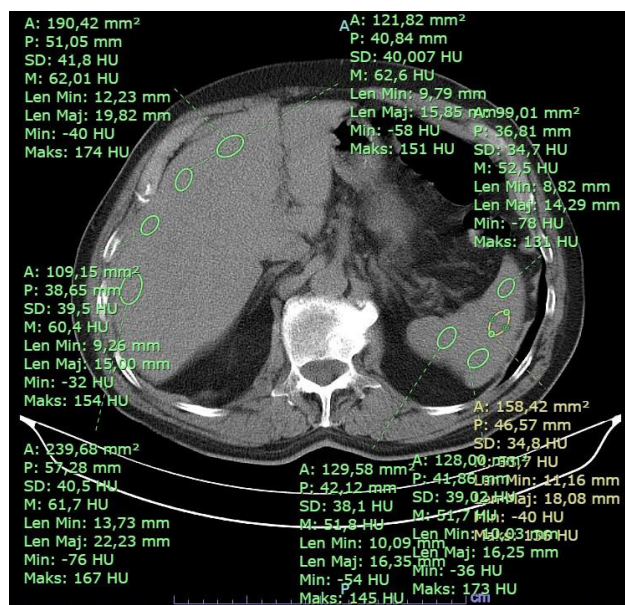
Patients were monitored with continuous electrocardiography (ECG) and invasive blood pressure monitoring in the intensive care unit. Additionally, 12-lead ECG recordings were taken daily. During the intensive care unit follow-up, required electrolyte replacements were accomplished according to blood gas controls. After two days of follow-up in the intensive care unit, the patients who were uneventful were taken to the cardiovascular surgery clinic and their pulse and arterial blood pressure were monitored at maximum 4-hour

intervals. Patients were continuously monitored by five-lead telemetry in the regular ward. A 12-lead ECG was taken after the patients complained of palpitations, shortness of breath and angina. AF was confirmed by 12-lead ECG. AF was diagnosed according to the European Society of Cardiology guidelines¹⁰. It was defined as irregular, rapid oscillations or fibrillation waves instead of regular p waves on the ECG, and AF episodes longer than 5 minutes were considered PoAF. Standard medical cardioversion therapy was administered with amiodarone (5 mg/kg) for 30 minutes followed by 900 mg/day. Patients with AF were recorded in both the intensive care follow-up files and the ward follow-up files, and patients with AF detected using this method were included in the study.

Liver attenuation index measurement technique

In the obtained non-contrast CT images, Hounsfield Unit (HU) values were measured using 10 mm diameter sample areas (Region of interest; ROI) in four different sections. For the liver, 20 different ROIs were placed in areas devoid of major vascular structures, 12 in the right lobe and 8 in the left lobe. The mean hepatic attenuation (MHA) value was found by averaging the HU values measured from these areas. On the same sections, ten different ROIs with a diameter of 10 mm were placed in areas of the spleen devoid of major splenic vascular structures. The mean splenic attenuation (MSA) value was calculated by taking the average of the HU values measured from the ROIs placed on the spleen, and the liver attenuation index (LAI) was calculated by subtracting the MSA value from the MHA value ($LAI = MHA - MSA$) (Figure 1).

Figure 1: Non-contrast CT images.



Degrees of hepatosteatosis determined according to the liver attenuation index (LAI)¹¹;

- LAI ≥ 5 , means $\leq 5\%$ steatosis,
- $5 > LAI > -10$, means $6\% - 30\%$ steatosis,
- LAI ≤ -10 means $\geq 30\%$ steatosis.

Statistical Analysis

In the present study, SPSS 26.0 program was used for the statistical analysis of the data. The Kolmogorov-Smirnov test was used to analyze the normality of the distribution of data in groups. Continuous variables that comply with normal distribution are expressed as mean $\pm$ standard deviation, continuous variables that do not comply with normal distribution are expressed as median-IQR (Interquartile range), while nominal variables are expressed as frequency and percentage. Student's t-test was used for normally distributed data in two independent groups, Mann-Whitney U tests were used for non-normally distributed data, and nominal data were compared with the Chi-square test.

Spearman correlation coefficient test was used to investigate the relationship between liver density, spleen density, liver-spleen attenuation index, and hepatosteatosis percentage values and the relationships between these parameters and the development of PoAF. ROC (Receiver Operating Characteristic) curve was applied to estimate the effect of liver-spleen attenuation index and hepatosteatosis percentage levels on the development of PoAF. To analyze the diagnostic value of LAI levels, predictive values measured by the sensitivity and specificity of the area under the ROC curve were calculated. In all tests, a p-value of less than 0.05 was considered statistically significant.

Results

This retrospective study was conducted with a total of 200 patients. Patients included in the study were divided into two groups, 100 patients who developed AF, and 100 patients who did not develop AF. Participants' demographic characteristics and laboratory findings and calculations are summarized in table I. There was no statistical difference between the groups for these parameters.

According to spearman's correlation analysis, no correlation was found between MHA, MSA, LAI, hepatosteatosis, and PoAF ($p > 0.05$). In addition, correlation analyses of hepatic and splenic density/index values measured on non-contrast CT images were statistically significant, and this result showed us that our measurements were accurate (Table II).

In ROC curve analysis, the cut-off level for the LAI to predict the development of PoAF was determined as 10.5 (AUC: 0.529, log-rank $p = 0.473$). For measurements above the measured cut-off value, the sensitivity for the LAI was 47% and the specificity was 56% (Figure 2).

Table I: Demographic and laboratory data of the patients.

	With AF n=100	Without AF n=100	p value
Demographic Data			
Age, (year)	64,4±8,4	63,4±8,4	0,397 ^a
Sex			0,599 ^c
Male, n (%)	78 (78%)	81 (81%)	
Female, n (%)	22 (22%)	19 (19%)	
Hypertension, n (%)	64 (64%)	59 (59%)	0,467 ^c
Diabetes Mellitus, n (%)	59 (59%)	62 (62%)	0,664 ^c
BMI, (kg/m ²)	28 (26,1-30,5)	27,7 (24,2-30,4)	0,703 ^b
COPD, n (%)	13 (13%)	7 (7%)	0,157 ^c
Ejection Fraction, (%)	50,1 (45-60)	51,4 (45-60)	0,794 ^b
Hepatosteatosi, (%)	1,4 (1-2)	1,4 (1-2)	0,547 ^b
MHA, (HU)	52,1 (46-59)	49 (41,2-59)	0,105 ^b
MSA, (HU)	43,7 (40-48)	42,4 (39-47)	0,079 ^b
LAI, (HU)	8,4 (2,2-15)	6,6 (0,2-15)	0,472 ^b
Laboratory datas			
Triglyceride, (mg/dL)	188,3 (115-231)	172,6 (109-210,7)	0,375 ^b
Total Cholesterol, (mg/dL)	183,1±47	170,7±47,8	0,066 ^a

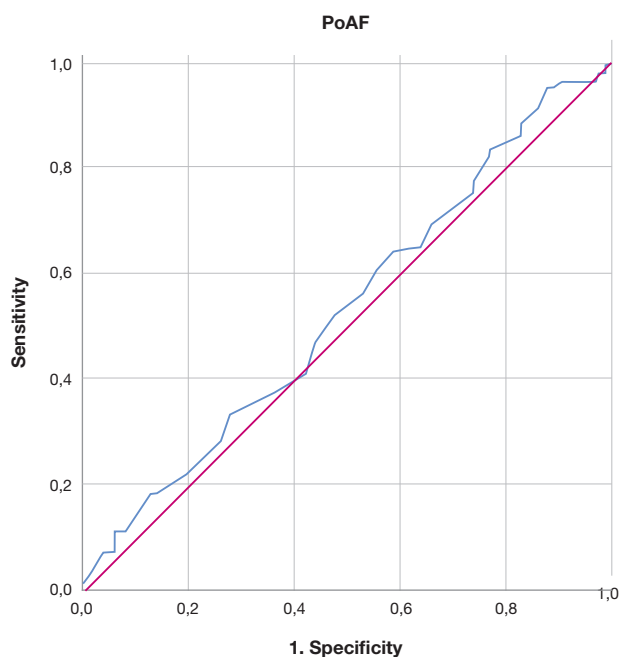
AF: Atrial fibrillation, BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, MHA: Mean hepatic attenuation, MSA: Mean splenic attenuation, HU: Hounsfield unit, LAI: Liver attenuation index.

a: Student-t Test, b: Mann-Whitney U Test, c: Chi-Square Test.

Table II: Spearman correlation test.

	LAI	MHA	MSA	Hepatosteatosi	PoAF
LAI	-	r: 0.803 / p: 0.000	r: -0.365 / p: 0.000	r: -0.805 / p: 0.000	r: 0.051 / p: 0.474
MHA	r: 0.803 / p: 0.000	-	r: 0.176 / p: 0.013	r: -0.688 / p: 0.000	r: 0.115 / p: 0.105
MSA	r: -0.365 / p: 0.000	r: 0.176 / p: 0.013	-	r: 0.240 / p: 0.001	r: 0.124 / p: 0.079
Hepatosteatosi	r: -0.805 / p: 0.000	r: -0.688 / p: 0.000	r: 0.240 / p: 0.001	-	r: -0.043 / p: 0.548
PoAF	r: 0.051 / p: 0.474	r: 0.115 / p: 0.105	r: 0.124 / p: 0.079	r: -0.043 / p: 0.548	-

MHA: Mean hepatic attenuation, MSA: Mean Splenic attenuation, LAI: Liver attenuation index, PoAF: Postoperative atrial fibrillation, r: Correlation coefficient

Figure 2: ROC Curve Plot for PoAF Development of Liver Attenuation Index (AUC: 0.529, log rank p:0.473).

Diagonal segments are produced by ties.

Discussion

This retrospective study was conducted on 200 patients who underwent isolated on-pump CABG due to coronary artery disease, no significant relationship was found between preoperatively measured macrovesicular fatty liver and PoAF. However, some important studies and epidemiological data in the literature, highlight the complexity of the potential relationship between Non-Alcoholic Fatty Liver Disease (NAFLD) and AF and suggest the requirement for further research on this subject¹².

PoAF and NAFLD are two separate pathologies that are quite common and are also associated with high complication rates. There are very inadequate studies in the literature examining the relationship between these pathologies. Although NAFLD and AF share similar risk factors and comorbid conditions (such as obesity, DM, hypertension, and hyperthyroidism, which we shared in the introduction section), the pathophysiological mechanisms of the relationship between them are still not fully elucidated¹².

However, many studies provide evidence supporting the study's hypothesis. For example, in a retrospective cohort study conducted on a large population, serum ALT over 40 U/L was considered sufficient instead of NAFLD, and

the prevalence of elevated ALT in patients with AF was reported as 27.6%¹³. In the present study, the diagnosis of NAFLD was determined according to the LAI measured on non-contrast thorax CT, and values above 30% were considered significant. However, in our study, no significant difference was found in the rate of hepatosteatosi between patients who developed AF and those who did not.

In another study, 3,744 patients were examined, based on data from the Framingham Heart Study, which has the largest AF data available today and moderately elevated serum transaminase levels (ALT and AST >40 U/L) have been shown to be independently associated with increased incidence of AF over an 8-year follow-up period¹⁴. Similarly, in a population-based prospective study, high levels of liver enzymes, especially GGT, were associated with an increased risk of AF¹⁵. The fact that patients with normal liver enzyme levels were included in our study explains why no significant results were obtained in terms of AF.

In the study conducted by Targher et al. on type 2 DM patients, the frequency of persistent and permanent AF was found to be higher in the group with NAFLD than in the group without liver disease¹⁶. The patients included in our study were not required to be diabetic, and the patients with AF in the study were not grouped as persistent or permanent. LAI values, which we associate with NAFLD, were found to be higher in the group with AF than in the group without AF. In this context, it can be said that the results of the study conducted by Targher et al. are similar to our findings.

According to the results of the study conducted by Rijzewijk et al., a positive significant relationship was found between intramyocardial and intrahepatic triglyceride ratios calculated by magnetic resonance spectroscopy (MRS). It has also been reported that increased pericardial fat volume is associated with an increased prevalence of AF, independent of multiple established risk factors¹⁷. Szczepaniak et al. conducted studies on the prevalence of hepatic steatosis by measuring hepatic triglyceride content in the general population using MRS¹⁸. MRS is expensive and can be performed in a few centers. In the present study, liver attenuation value measurement, which is the best method for estimating the degree of liver fatness, was used to diagnose NAFLD¹¹.

Shin et al. reported that the interatrial epicardial fat tissue thickness in AF patients was greater than in the control group, and that this was independently associated with left atrial remodeling in patients with AF and the chronicity of AF¹⁹. In our study, we investigated the relationship between NAFLD and new postoperative AF. However, as with pericardial fat tissue, no significant relationship could be obtained.

Experimental evidence suggests that adipocytes originating from epicardial or retrosternal fat tissues may

directly modulate electrophysiological characteristics and ion currents in isolated rabbit left atrial myocytes, resulting in high rates of arrhythmogenesis²⁰. This pathophysiological mechanism theory can be used to explain the relationship between NAFLD and AF, which we determined as the starting point in our study. In this context, we suggest that larger patient-based studies are needed.

The present study's greatest strengths include its systematic follow-up procedures and detailed outcome ascertainment. The fact that tomographic measurements are made meticulously and reliably by a single radiologist makes this study valuable. In addition, there are also some limitations. First of all, non-contrast CT examination used in the detection of NAFLD is a sensitive and specific method for moderate-severe fatty liver. However, it is not as sensitive for more severe forms of NAFLD, including mild fatty liver, steatohepatitis, or liver fibrosis, and may prevent accurate assessment of the relationship between fatty liver and PoAF in these cases. Furthermore, since the sample consisted of middle-aged and older adults and the patients were largely of the same origin, it is not possible to provide information about the generalizability of the findings to different races or ethnicities or to older or younger individuals. Additionally, the power of the study is limited because the prevalence of PoAF in the study group was low.

In conclusion, risk factors for the development of AF such as obesity, DM, HT, and hyperlipidemia are also associated with Non-Alcoholic Fatty Liver. There are not many studies investigating the relationship between AF and Non-Alcoholic Fatty Liver. In this study, we did not find a relationship between PoAF and MHA, MSA, LAI, and hepatosteatosi. However, we think that more comprehensive studies are needed because non-alcoholic fatty liver disease is associated with diseases that are risk factors for cardiovascular diseases.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author

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Ethical approval

This study was approved by the local institutional Ethical Committee of the University of Health Sciences - Turkey (Approval number: 2011- KAEK-25 2022/06-02)

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ORIGINAL

Sintomatología y transmisión del SARS-CoV-2 a contactos estrechos

Symptomatology and transmission of SARS-CoV-2 to close contacts

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Resumen

Fundamentos: La pandemia de COVID-19 evidenció la necesidad de estudiar los mecanismos de transmisión del SARS-CoV-2, particularmente el impacto de la sintomatología del paciente índice en la infección a sus contactos estrechos. La evidencia sobre la contribución de cada síntoma en la transmisión es limitada y controvertida. Este estudio tiene como objetivo analizar la asociación entre los diferentes signos y síntomas del paciente índice y el riesgo de transmisión del SARS-CoV-2 a sus contactos estrechos.

Métodos: Estudio observacional longitudinal prospectivo. Desde febrero a junio del 2021, se identificaron pacientes índices diagnosticados de SARS-CoV-2 y se realizó el rastreo de contactos estrechos. Se utilizó un cuestionario ad hoc para recopilar la sintomatología presentada por el paciente índice. Los contactos estrechos identificados se realizaron las pruebas diagnósticas pertinentes según el protocolo. A los 10 días de cuarentena se revisaron las historias clínicas de los contactos estrechos para confirmar la posible infección por SARS-CoV-2.

Resultados: Se incluyeron un total de 1.778 contactos estrechos de 463 pacientes índice (media de edad: 39,8±15,1 años; 47% mujeres; media de 4,43 contactos estrechos). El 53% de los casos índices transmitieron la infección a al menos a uno de sus contactos estrechos. El 5,8% de los pacientes índice fueron asintomáticos. No se observaron diferencias significativas en la transmisión del SARS-CoV2 entre sintomáticos o asintomáticos ($p=0,054$). Solo la tos fue asociada significativamente con la transmisión ($p<0,05$).

Conclusión: La transmisión de SARS-CoV-2 no difiere entre individuos sintomáticos y asintomáticos, lo que refuerza la necesidad de implementar medidas preventivas independientemente de la sintomatología. Estos hallazgos tienen implicaciones importantes para el control de otros virus respiratorios con patrones de transmisión similares, permitiendo optimizar protocolos de actuación.

Palabras clave: COVID-19, SAR-CoV-2, sintomatología, rastreo de contactos, prevención de enfermedades, enfermedades respiratorias, vigilancia en salud pública.

Abstract

Background: The COVID-19 pandemic highlighted the need to study the transmission mechanisms of SARS-CoV-2, particularly the impact of index patient symptomatology on infecting close contacts. However, evidence on the contribution of specific symptoms to transmission remains limited and controversial. This study aims to analyse the association between the signs and symptoms of index patients and the risk of SARS-CoV-2 transmission to their close contacts.

Methods: A prospective longitudinal observational study was conducted between February and June 2021. Index patients diagnosed with SARS-CoV-2 were identified, and routine contact tracing was performed to identify their close contacts. An ad hoc questionnaire was used to collect data on the symptoms reported by index patients. Identified close contacts underwent diagnostic testing according to established protocols. After 10 days of quarantine, the medical records of close contacts were reviewed to confirm potential SARS-CoV-2 infection.

Results: A total of 1,778 close contacts of 463 index patients were included (mean age: 39.8±15.1 years; 47% women; an average of 4.43 close contacts per patient). Fifty-three per cent of index patients transmitted the infection to at least one close contact. A total of 5.8% of index patients were asymptomatic. No significant differences in SARS-CoV-2 transmission were observed between symptomatic and asymptomatic individuals ($p=0.054$). Only cough was significantly associated with transmission ($p<0.05$).

Conclusion: SARS-CoV-2 transmission does not differ between symptomatic and asymptomatic individuals, emphasizing the importance of implementing preventive measures regardless of symptomatology. These findings have important implications for controlling other respiratory viruses with similar transmission patterns, optimizing response protocols, and managing seasonal respiratory illnesses.

Key words: COVID-19, SARS-CoV-2, symptomatology, contact tracing, disease prevention, respiratory diseases, public health surveillance.

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Introducción

La pandemia COVID-19 puso de manifiesto la necesidad urgente de comprender los mecanismos de transmisión del SARS-CoV-2, una brecha que planteaba un desafío considerable para la contención del virus¹. El conocimiento sobre estos mecanismos era importante no solo para resolver este reto, sino también como contribución a futuros brotes por virus de características similares. El SARS-CoV-2, al igual que otros virus respiratorios, se transmite principalmente a través de secreciones generadas al estornudar, toser o hablar, que entran en contacto con personas mediante microgotas respiratorias^{2,3}. Sin embargo, a pesar de compartir mecanismos de transmisión similares a otros virus respiratorios, el SARS-CoV-2 ha mostrado tasas de ataque secundario más elevadas, resaltando la influencia de factores adicionales, tanto endógenos como exógenos, en su mayor capacidad de propagación^{4,5}. La elevada tasa de transmisión viral contribuyó significativamente a la sobrecarga y colapso de los sistemas sanitarios durante la pandemia, debido en gran parte a las dificultades para identificar y aislar a individuos infectados en etapas tempranas⁶.

Una de las barreras en la identificación del virus es la amplia variabilidad de síntomas⁷. La fisiopatología de la COVID-19 manifiesta un amplio espectro de síntomas –como fiebre, tos, disnea, fatiga, entre otros⁷–, muchos de los cuales también aparecen en otras enfermedades respiratorias comunes, como la gripe estacional⁸. Esta diversidad sintomática, complicó no solo la identificación de personas infectadas, sino también la implementación efectiva de medidas de control, como el rastreo de contactos.

Además, la presencia de casos asintomáticos (personas infectadas sin síntomas pero que podían infectar a sus contactos)^{9,10} contribuyó a la transmisión comunitaria. Esta particularidad supuso un obstáculo para el rastreo y contención de la enfermedad, ya que los protocolos para la identificación de casos positivos se centraron en la detección de síntomas^{10,11}. Aunque algunos estudios indicaron que los casos asintomáticos eran más frecuentes en ciertos grupos demográficos, como niños y adultos jóvenes¹², se identificaron casos asintomáticos en todos los grupos de edad a medida que la pandemia avanzaba, lo que incrementó la complejidad del rastreo y la contención de la propagación comunitaria^{13,14}.

Estos factores limitaron la efectividad de las medidas de prevención y control, como el rastreo de contactos de riesgo, dificultando así los esfuerzos para contener la transmisión comunitaria. Ante el colapso sanitario y la falta de evidencia sobre la asociación entre sintomatología con la transmisión de SARS-CoV-2, se decidió priorizar el rastreo en individuos infectados con síntomas frente a aquellos asintomáticos¹⁵⁻¹⁷.

Si bien los estudios previos abordaron la relación entre sintomatología y transmisión del SARS-CoV-2, la mayoría de estos enfoques clasificaron la transmisión de manera dicotómica (sintomáticos vs. asintomáticos), sin analizar la contribución de cada síntoma en el riesgo de contagio^{16,18}. El objetivo principal de este estudio fue evaluar el efecto de los diferentes signos y síntomas de la COVID-19 sobre el riesgo de transmisión del SARS-CoV-2 a sus contactos estrechos.

Material y método

Diseño del estudio

Se llevó a cabo un estudio de seguimiento de contactos estrechos de casos índice diagnosticados con SARS-CoV-2 de origen desconocido en Mallorca, durante los meses de febrero a junio del 2021. El estudio se realizó en la Central de Coordinación de la COVID-19 (CC-COVID-19) en Mallorca (Islas Baleares, España), encargada del rastreo, seguimiento y control de casos positivos y de contactos estrechos, y siguiendo directrices de rastreo de contactos estrechos, realizándose de forma sistemática en todos los casos con diagnóstico de infección por SARS-CoV-2¹⁹.

El rastreo de contactos estrechos de casos diagnosticados con SARS-CoV-2 fue establecido como una medida de control y prevención epidemiológica obligatoria por el Ministerio de Sanidad del Gobierno de España, bajo las directrices de la 'Estrategia de detección precoz, vigilancia y control de COVID-19'. Según estas directrices, un contacto estrecho se define como²⁰: "Cualquier persona que haya estado en el mismo lugar que un caso positivo de COVID-19, a una distancia menor de 2 metros y durante un tiempo total acumulado de más de 15 minutos en 24 horas. El período a considerar será desde 2 días antes del inicio de síntomas del caso o, si por defecto el caso es asintomático, desde el día de la prueba diagnóstica hasta el momento en el que el caso es aislado."

Los contactos estrechos debían cumplir una cuarentena domiciliar de 10 días y someterse a las pruebas diagnósticas de SARS-CoV-2 necesarias. Estas medidas de restricción y control epidemiológico fueron implementadas bajo el marco legal establecido en la Ley Orgánica 3/1986 y el Real Decreto-Ley 6/2020, que permitieron a las autoridades sanitarias de Baleares (Consejo de Salud) adoptar acciones específicas para el control de brotes durante la pandemia²¹⁻²³.

Se incluyeron a pacientes índice diagnosticados con SARS-CoV-2 cuya fuente de infección fuese desconocida y que estos fuesen mayores de 18 años. Para la selección de los contactos estrechos, se incluyeron aquellos que fuesen asintomáticos y mayores de 18 años.

Se excluyeron los pacientes índices que habían tenido contacto previo con otro individuo identificado antes de recibir su propio diagnóstico. Esta selección se hizo con el propósito de evitar incluir pacientes que hubieran realizado medidas de protección más estrictas, debido al conocimiento del posible riesgo de infección.

Se excluyeron los contactos estrechos que residían en instituciones, aquellos que habían estado en contacto con entornos médicos, como hospitales o clínicas dado que las medidas de prevención eran distintas al entorno comunitario. Finalmente se excluyeron aquellos con dificultades en la comunicación telefónica.

Recogida de datos

Los métodos de recopilación de datos se describen en detalle en un artículo previo²⁴. Brevemente, se seleccionaron los pacientes índices a partir del listado de positivos de la CC COVID-19 de Mallorca. Posteriormente, se llevó a cabo el rastreo habitual de contactos estrechos, seleccionando a aquellos que cumplieran con los criterios de inclusión y exclusión. Finalmente, se administró un cuestionario diseñado ad hoc, en el que se recopilaban datos sociodemográficos y de sintomatología previa a la prueba diagnóstica. Los síntomas considerados en el estudio fueron aquellos definidos en el protocolo de la aplicación de notificación de nuevos casos positivos, de acuerdo con los criterios establecidos para el rastreo de contactos. La recopilación de estos datos se realizó en el marco del procedimiento rutinario de rastreo y notificación, mediante entrevista telefónica, en la cual los contactos estrechos autorreportaban su sintomatología siguiendo dicho protocolo. Se incluyeron en el estudio a todos los contactos estrechos, reportados por el paciente índice, que cumplieran los criterios de inclusión y exclusión. Transcurridos los 10 días de cuarentena impuesta por protocolo, se revisaron las historias clínicas de los contactos estrechos para identificar el resultado de las pruebas diagnósticas. Se consideró que hubo transmisión de SARS-CoV-2 desde el paciente índice hacia un contacto estrecho cuando este obtuvo un resultado positivo en la prueba diagnóstica durante los 10 días de cuarentena.

Contexto epidemiológico

Durante la recogida de datos, el Gobierno de las Islas Baleares implementó niveles de alerta sanitaria que implicaban diferentes restricciones según la incidencia acumulada (**Tabla I**). El 12 de enero de 2021, se declaró una alerta sanitaria de nivel 4 (incidencia acumulada >250 positivos) en Mallorca²⁵. Durante este período, se aplicaron restricciones severas en el ámbito social, como la prohibición de reuniones. Posteriormente, debido a la disminución de la transmisión del SARS-CoV-2, Mallorca pasó al nivel 2 de alerta sanitaria (incidencia acumulada entre 50 y 150 positivos). Esto se tradujo en el levantamiento de algunas restricciones sociales y deportivas, como permitir reuniones de hasta 6 personas, la reapertura de bares y restaurantes con aforo limitado y la posibilidad de ocupar un 50% de la capacidad en actividades deportivas colectivas²⁶. En cuanto al uso de mascarillas, se mantuvo la obligatoriedad de uso en todos los ámbitos, ya fuesen interiores o exteriores, a lo largo de todo el estudio²⁷.

Análisis estadístico

Se realizó un análisis descriptivo de las variables sociodemográficas y de la sintomatología de los pacientes índice. Las variables numéricas se presentaron mediante la media y su desviación estándar, mientras que las variables categóricas se describieron a través de frecuencias absolutas y relativas. Para evaluar la asociación entre la sintomatología y el riesgo de transmitir la infección a los contactos estrechos, se calcularon las Odds Ratio (OR) con sus respectivos intervalos de confianza al 95% (IC95%).

Todas las pruebas estadísticas fueron bilaterales, considerando como significativo un valor de $p < 0,05$. Para llevar a cabo el análisis estadístico, se empleó el paquete de software Statistical Package for the Social Sciences (SPSS), en su versión 26.0 (IBM SPSS Statistics para Windows, versión 26.0, Armonk, NY: IBM Corp.).

Aspectos éticos

El estudio se llevó a cabo en estricto cumplimiento de los principios éticos establecidos en la Declaración de

Tabla I: Niveles medidas de salud pública por la COVID-19 en las Islas Baleares.

	SITUACIÓN PREVENTIVA (NIVEL 0)	SITUACIÓN CONTROL (NIVEL 1)	RIESGO MEDIO (NIVEL 2)	RIESGO ALTO (NIVEL 3)	RIESGO EXTREMO (NIVEL 4)
Incidencia acumulada*	1-24	25-50	50-150	150-250	>250
Reuniones	15 p**	10p	6 p	6 p	0 p
Movilidad	Sin restricción	Toque de queda 00h-06h	Toque de queda 00h-06h	Toque de queda 00h-06h	Toque de queda 22h-06h
Restaurantes	10 p/mesa	10p/mesa	6p/mesa	10p/mesa	Cerrado
Ceremonias	75 p	50 p	30 p	20 p	15 p
Tiendas	75% ocupación	75% ocupación	75% ocupación	50% ocupación	50% ocupación
Deportes	30 p	30 p	15 p	15 p	6p

*Casos nuevos en 14 días por cada 100.000 habitantes ** personas

Helsinki y de la normativa legal vigente en materia de protección de datos y ética en investigación con seres humanos. El protocolo fue aprobado por el Comité de Ética de la Investigación de las Islas Baleares (CEI-IB, Ref. no: IB 4444/21). Todos los participantes recibieron información detallada sobre la finalidad y los procedimientos del estudio, y dieron su consentimiento informado antes de participar.

Resultados

Durante el período de estudio, se identificaron 2.050 contactos estrechos derivados de 463 pacientes índice diagnosticados con SARS-CoV-2. Tras aplicar los criterios de inclusión y exclusión, se incluyeron finalmente 1.778 contactos estrechos en el análisis.

Características descriptivas del paciente índice

Como se detalla en la **tabla II**, la edad media de los pacientes índice fue de $39,71 \pm 15,3$ años, y el 46,9% eran mujeres. En promedio, cada paciente índice generó $4,43 \pm 3,38$ contactos estrechos. En cuanto a la transmisión de la enfermedad, el 53% de los pacientes índices transmitieron la enfermedad a al menos a uno

de sus contactos estrechos. La media de contactos estrechos infectados por paciente índice fue de $0,92 \pm 1,23$ y la tasa de ataque secundario fue del 24%.

En cuanto al nivel educativo, el 29,4% de los pacientes índice tenían estudios universitarios, seguido de aquellos con educación secundaria (23,1%), formación profesional (22,2%) bachillerato (15,5%), y educación primaria (9,4%). Respecto a la ocupación, el 20,5% de los pacientes índice trabajaban en oficinas, el 17,4% en el sector industrial, y el 11,5% en restauración. Por otro lado, el 59,5% de los pacientes índice se encontraban en situación laboral activa, el 33,4% estaban desempleados y el 7,1% eran jubilados.

Descriptivo de sintomatología

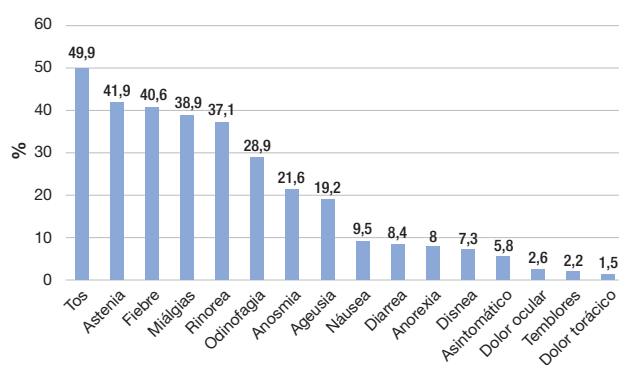
El 94,4% de los pacientes índice presentaron algún síntoma antes o en el momento del diagnóstico. Los síntomas más frecuentes fueron cefalea (51,4%) y tos (49,9%), seguidos de astenia (41,9%) y fiebre (40,6%). Síntomas como la anosmia (pérdida del olfato) y la ageusia (pérdida del gusto) también se reportaron con relativa frecuencia (21,6% y 19,2% de los casos, respectivamente). En contraste, algunos síntomas como disnea (7,3%) y dolor torácico (1,5%) fueron menos comunes (**Figura 1**).

Tabla II: Características descriptivas de los pacientes índices.

N=463	N (%)
Edad M (Desviación Estándar)	39,71 (15,3)
Sexo	
Masculino	246 (53,1)
Femenino	217 (46,9)
Nivel de estudios	N=457
Primarios	43 (9,4)
Secundarios	106 (23,1)
Bachillerato	71 (15,5)
Formación profesional	102 (22,2)
Universitarios	135 (29,4)
Profesión	N=419
Oficinas	86 (20,5)
Sector industrial	73 (17,4)
Restauración	48 (11,5)
Estudiante	37 (8,8)
Profesor	23 (5,5)
Sector turístico	13 (3,1)
Cuidados informales	13 (3,1)
Personal limpieza	13 (3,1)
Profesional sanitario	9 (2,1)
Profesional sociosanitario	8 (1,9)
Conductor	7 (1,7)
Otros	89 (21,3)
Estatus laboral	N=435
Activo	259 (59,5)
Situación de desempleo	145 (33,4)
Jubilación	31 (7,1)
Sintomatología (n=457)	
No	27 (5,8)
Si	436 (94,2)
Transmisión (n=457)	
No	215 (47,0)
Si	242 (53,0)
Contactos por paciente índice	
M (Desviación Estándar)*	
Contacto infectado por paciente índice	
M (Desviación Estándar)	4,43 (3,38)
	0,92 (1,23)

*La media de contactos estrecho por caso índice incluye los contactos generados totales, incluyendo los contactos que no pudieron participar (n=2050).

Figura 1: Sintomatología del paciente índice antes del diagnóstico (%). El paciente índice podía reportar más de un síntoma.



Factores asociados a la infección entre paciente índice y sus contactos estrechos

No hubo diferencias significativas en la transmisión del SARS-CoV-2 entre hombres y mujeres ($p=0,429$). Un 45,6% de los pacientes índice de 18 a 26 años contagiaron al menos a uno de sus contactos estrechos y entre la franja de edad de 40 a 50 años fue del 60,5%, estas diferencias no fueron estadísticamente significativas ($p=0,163$). En cuanto al nivel educativo, el 65,1% de los pacientes índice con estudios primarios y el 51,9% de aquellos con estudios universitarios transmitieron el SARS-CoV-2 a al menos a uno de sus contactos estrechos, sin diferencias significativas ($p=0,554$). De manera similar, el estatus laboral no mostró asociación significativa con la transmisión ($p=0,251$).

Como se muestra en la **tabla III**, el 54,1% de los pacientes índice sintomáticos transmitieron la infección, mientras que entre los asintomáticos fue un 34,6%. Esta diferencia no fue estadísticamente significativa ($p=0,054$). Para evaluar la posible interacción de otras variables en los resultados obtenidos son la sintomatología y el contagio, se realizó un análisis de sensibilidad estratificando las variables sociodemográficas de sexo y edad. En este análisis, se observó que, en el grupo de edad entre 27 y 39 años, la comparación entre sintomáticos y asintomáticos resultó ser estadísticamente significativa ($p=0,015$). No se encontraron cambios estadísticamente significativos en las demás variables analizadas.

Al analizar los síntomas específicos, como fiebre, cefalea, rinorrea, odinofagia, astenia, anosmia y ageusia, ninguno de ellos se asoció significativamente con un mayor riesgo de transmisión del SARS-CoV-2. Salvo la tos ($p=0,004$) que se asoció significativamente con la transmisión del SARS-CoV-2 de los pacientes índice a al menos uno de sus contactos estrechos. Con el objetivo de evaluar posibles interacciones entre la tos y otros síntomas en relación con el riesgo de transmisión, se realizó un análisis de interacción considerando fiebre, cefalea, ageusia, anosmia, rinorrea, odinofagia y astenia. No se encontraron interacciones estadísticamente significativas entre la tos

y ninguno de los síntomas analizados. Estos resultados sugieren que la asociación observada entre la tos y un mayor riesgo de transmisión no parece estar modulada por la presencia de otros síntomas.

Discusión

Este estudio caracteriza la sintomatología de los casos positivos de SARS-CoV-2 identificados en Mallorca entre febrero y junio de 2021 y explora la asociación entre dicha sintomatología con el riesgo de transmisión a sus contactos estrechos. En nuestros resultados, solo la tos como síntoma en el caso índice se relacionó con un mayor riesgo de contagio. Por el contrario, otras variables sociodemográficas como el sexo, la edad, el nivel educativo o el estatus laboral, así como otros síntomas clínicos en el paciente índice, no se asociaron con riesgo de transmisión del SARS-CoV-2.

La baja proporción de pacientes índice asintomáticos en nuestro estudio coincide con datos reportados en estudios previos^{28,29}. En cuanto a la sintomatología, los síntomas más frecuentes como tos, fiebre, mialgias y cefaleas coinciden con los reportados en otros estudios^{30,31}. Pocos estudios concuerdan con nuestros resultados, mostrando que no hay diferencia en las tasas de transmisión del coronavirus entre pacientes sintomáticos y asintomáticos³². Sin embargo, en el mayor riesgo de transmisión del SARS-CoV-2 en pacientes con sintomatología, los resultados de algunos estudios previos mostraban que la sintomatología era un factor de riesgo en la transmisión del SARS-CoV-2¹⁵⁻¹⁷. Una revisión sistemática con metaanálisis reciente reportó que el riesgo relativo de transmisión en hogares era 3,23 veces mayor cuando el caso índice presentaba sintomatología en comparación con aquellos asintomáticos¹⁵. En dicho estudio, la tasa de ataque secundario en hogares con casos índice sintomáticos fue del 20,0%, mientras que en casos asintomáticos se redujo al 4,7%¹⁵. Estos hallazgos sugieren que, si bien la transmisión asociada a individuos asintomáticos es menor, no es despreciable. De hecho, estudios de modelado epidemiológico sugieren que la transmisión del SARS-CoV-2 puede ocurrir tanto en la fase presintomática como en individuos que permanecen asintomáticos durante todo el curso de la infección^{16,17}. Estos hallazgos refuerzan la importancia de considerar la sintomatología al evaluar el riesgo de transmisión, al tiempo que destacan el papel potencial de los individuos asintomáticos en la dinámica de propagación del virus.

En nuestro estudio, al analizar la sintomatología por separado, destacamos que ninguno de los síntomas principales (fiebre, cefalea, rinorrea, odinofagia, astenia, anosmia y ageusia) se asoció con una mayor transmisión, excepto la tos, que mostró una asociación estadísticamente significativa. Estos resultados sugieren que, aunque tiene sentido centrar los recursos materiales

Tabla III: Table III. Factores de riesgo del paciente índice asociados a la transmisión del SARS-CoV-2 a sus contactos estrechos.

N=457	No transmisión de la infección N (%)	Transmisión de la infección N (%)	p-valor
Sexo			
Femenino	96 (48,8)	117 (51,2)	0,429
Masculino	119 (45,1)	125 (54,9)	
Grupos de edad			
18-26	62 (54,4)	52 (45,6)	0,163
27-39	54 (46,6)	62 (53,4)	
40-50	45 (39,5)	69 (60,5)	
>50	54 (47,8)	59 (52,2)	
Nivel de estudios (n=451)			
Primarios	15 (34,9)	28 (65,1)	0,554
Secundarios	48 (46,6)	55 (53,4)	
Bachillerato	35 (50,0)	35 (50,0)	
Formación profesional	49 (49,0)	51 (51,0)	
Universitarios	65 (48,1)	70 (51,9)	
Estatus laboral (n=430)			
Situación de desempleo	60 (41,4)	85 (58,6)	0,251
Activo	127 (49,8)	128 (50,2)	
Jubilado	13 (43,3)	17 (56,7)	
Sintomatología			
No	17 (65, 4)	9 (34,6)	0,054
Sí	198 (45,9)	233 (54,1)	
Tos			
No	124 (53,7)	107 (46,3)	0,004
Sí	91 (40,3)	135 (59,7)	
Fiebre			
No	133 (49,1)	138 (50,9)	0,294
Sí	82 (44,1)	104 (55,9)	
Cefalea			
No	103 (46,6)	118 (53,4)	0,855
Sí	112 (47,5)	124 (52,5)	
Rinorrea			
No	136 (47,2)	152 (52,8)	0,921
Sí	79 (46,7)	90 (53,3)	
Odinofagia			
No	161 (49,4)	165 (50,6)	0,114
Sí	54 (41,2)	77 (58,8)	
Astenia			
No	134 (50,4)	132 (49,6)	0,092
Sí	81 (42,4)	110 (57,6)	
Anosmia			
No	171 (47,6)	188 (52,4)	0,631
Sí	44 (44,9)	54 (55,1)	
Ageusia			
No	178 (48,2)	191 (51,8)	0,296
Sí	37 (42,0)	51 (58,0)	

y humanos en los grupos de población sintomáticos, más propensos a contribuir significativamente a la importancia de seguir refinando las características clínicas y epidemiológicas de las infecciones emergentes. En este contexto, la continua investigación sobre la sintomatología y sus implicaciones en la transmisión es importante para optimizar los programas de cribado y maximizar su eficacia.

La relación entre la tos y transmisión puede explicarse por los mecanismos propios de propagación del SARS-CoV-2, las microgotas generadas al toser, estornudar o hablar^{2,3}. Esto sugiere que la sintomatología general puede no ser un factor determinante para la transmisión de la COVID-19 de manera dicotómica; en cambio, la presencia específica de tos parece representar un riesgo más elevado.

Aunque observamos un mayor porcentaje de transmisión entre adultos jóvenes, esta diferencia no fue estadísticamente significativa. Esto coincide con estudios previos que indican que la COVID-19 afecta a personas de todas las edades, con una mayor incidencia en adultos jóvenes y de mediana edad^{29,33}. De manera similar, nuestros hallazgos respaldan investigaciones previas que tampoco observaron diferencias estadísticamente significativas en la transmisión según el sexo^{35,35}, ni el nivel educativo³⁶, lo que refuerza la idea de que estos factores no son determinantes en la propagación del virus.

En cuanto a las limitaciones de este estudio, una de las principales es la imposibilidad de establecer relaciones causales entre la sintomatología y la transmisión del SARS-CoV-2 debido a su diseño observacional. Además, aunque se identificaron síntomas comunes

entre los contactos estrechos, no se tuvo en cuenta la intensidad ni la duración de los síntomas, lo cual podría haber influido en el riesgo de transmisión. Por otro lado, se registraron los síntomas presentados desde dos días antes de la prueba diagnóstica hasta el momento de la entrevista, sin distinguir qué síntomas estaban presentes en cada momento del encuentro con sus contactos estrechos. Además, debido a que los datos se recopilaban de forma rutinaria en la central COVID durante la pandemia, no fue posible registrar variables como el tiempo de exposición o el uso de mascarillas, las cuales podrían haber influido en los resultados. Por último, el estudio se basó en autoinformes de sintomatología, lo que introduce el riesgo de sesgo interpretación subjetiva de los síntomas.

En cuanto a las fortalezas, este estudio se llevó a cabo dentro de un sistema de rastreo de contactos estrechos bien establecido, lo que permitió una identificación sistemática y precisa de los contactos y una recopilación confiable de datos. La definición estandarizada de "contacto estrecho" y el protocolo de seguimiento riguroso de pruebas diagnósticas "aseguraron que la transmisión fuera evaluada de manera controlada y detallada. Otra de las fortalezas fue realizar el cuestionario en personas que eran potenciales contactos estrechos pero que en ese momento no sabían que la persona con la que mantuvieron ese contacto era positiva, así pudiendo saber que no modificaron su conducta habitual. Además, la muestra de contactos estrechos fue representativa de la población general, lo que aumenta la validez externa de los resultados. Finalmente, el diseño prospectivo y la recolección de datos en tiempo real mejoraron la precisión y la fiabilidad de los hallazgos, permitiendo un análisis más detallado de la relación entre síntomas y transmisión en un contexto de seguimiento cercano.

En conclusión, este estudio muestra que la probabilidad de transmisión entre individuos asintomáticos es similar a la de los sintomáticos, lo que respalda la necesidad de implementar medidas preventivas universales, independientemente de la presencia de síntomas. No obstante, se recomienda un monitoreo riguroso de los

pacientes que presentan tos, ya que estos podrían representar un mayor riesgo de contagio y, por lo tanto, requieren una atención especial para la identificación y control de sus contactos estrechos.

Nuestros hallazgos ofrecen una comprensión más detallada de la variedad de síntomas asociados con la infección por SARS-CoV-2, lo cual es relevante para el diagnóstico y manejo clínico, incluso en un contexto postpandémico. En relación con las implicaciones para futuras estrategias de rastreo y control epidemiológico, nuestros resultados sugieren que la optimización del rastreo de contactos puede lograrse mediante la priorización de los casos índices con mayor probabilidad de transmisión. La focalización de estos esfuerzos permitiría implementar intervenciones más eficaces y oportunas, mejorando la capacidad de respuesta ante brotes y crisis sanitarias. Asimismo, en contextos de alta demanda de recursos, la priorización del rastreo en función del riesgo de transmisión podría contribuir a una asignación más efectiva del personal y de las intervenciones de control, minimizando la propagación del virus de manera estratégica.

Por otro lado, los resultados de este estudio aportan información relevante sobre la dinámica de transmisión del SARS-CoV-2 y pueden ser extrapolados al control de otras enfermedades respiratorias con mecanismos de transmisión similares. La integración de estos hallazgos en las estrategias de salud pública podría fortalecer la preparación y la respuesta ante futuras epidemias, incluyendo aquellas causadas por virus emergentes o por la reemergencia de patógenos estacionales como la gripe. Un enfoque basado en la identificación de los factores que modulan la transmisibilidad de los casos índice permitiría un rastreo de contactos más dirigido y efectivo, optimizando los recursos disponibles y reduciendo el impacto epidemiológico de futuras crisis sanitarias.

Conflictos de interés

Los autores declaran no tener conflictos de intereses

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The COVID-19 Pandemic and Its Role on the Lifestyle of University Students According to Gender

La pandemia por COVID-19 y su rol en el estilo de vida de la población estudiantil universitaria con una perspectiva de género

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Abstract

The advent of the global pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus led to sudden disruptions in the routines and habits of people across the globe. The enforced lockdowns may have significantly altered lifestyles, with work and study schedules, opportunities for leisure, social contact, and outdoor physical activity being disrupted. Given that university students are a target group for health promotion and prevention initiatives, as they are in a period of lifestyle consolidation, it becomes necessary to analyze in detail how the Coronavirus Disease 2019 (COVID-19) pandemic has affected their lifestyles and the development of anxiety-depressive symptoms, fear, or concern about this coronavirus. The pandemic was found to have had a negative effect on the health status and perceived quality of life of university students, as well as on their sleep quality, tobacco use, and other substance use. Furthermore, a considerable proportion of the sample exhibited elevated levels of anxiety and depressive symptoms, along with notable distress. Conversely, they also engaged in greater physical activity, adopted a somewhat healthier diet, and consumed less alcohol during this period. It is therefore evident that the impact of the pandemic on the lifestyles of this population is significant.

Key words: Healthy lifestyle, students, sleeping, alcohol drinking, tobacco consumption, illicit drugs, Mediterranean diet, exercise, anxiety, depression, psychological distress.

Resumen

Con la promulgación de la pandemia por el virus SARS-CoV-2, todas las personas alrededor del mundo vieron interrumpidas sus rutinas y hábitos de forma abrupta. El confinamiento decretado a raíz de esta también ha podido alterar de forma significativa los estilos de vida de la población, que vio interrumpidas sus jornadas laborales, de estudio, oportunidades de ocio y contacto social, actividad física en el exterior, etc. Considerando que la población universitaria representa un grupo clave para las intervenciones en promoción de la salud y prevención, debido a que se encuentran en una etapa crítica de consolidación de sus hábitos y estilos de vida, resulta indispensable analizar a profundidad cómo la pandemia por Coronavirus Disease 2019 (COVID-19) ha impactado en sus dinámicas cotidianas. Este grupo no solo enfrentó cambios significativos en sus rutinas académicas, sino también en su interacción social, un aspecto fundamental para su desarrollo emocional y psicológico. Se comprobó que la pandemia ha ocasionado efectos negativos en el estado de salud y la calidad de vida que percibe el alumnado universitario, al igual que en su calidad del sueño, consumo de tabaco y otras sustancias. Asimismo, se comprobó una alta sintomatología ansiosa-depresiva y gran preocupación en gran parte de la muestra estudiada. Por otro lado, también realizaron más actividad física, llevaron una dieta algo más saludable y consumieron menos alcohol desde este período. Por tanto, es innegable el efecto que ha tenido la pandemia para los estilos de vida de esta población.

Palabras clave: Estilo de vida saludable, estudiantes, sueño, consumo de alcohol, consumo de tabaco, drogas ilícitas, dieta Mediterránea, ejercicio, ansiedad, depresión, angustia psicológica.

Introduction

The profound impact of the global pandemic and its associated restrictions on individuals' health and lifestyle choices is undeniable. Additionally, ongoing social and economic transformations continue to generate significant concerns within society. According to the World Health Organization (WHO; OMS for its acronym in Spanish), lifestyles are defined in its 1998 Health Promotion Glossary as discernible patterns of behavior that are dynamic rather than static, constantly evolving through modifications, assessments, and social interpretations¹. These patterns significantly influence not only individuals' health but also the well-being of their immediate environment.

In line with the WHO's Social Determinants of Health model, as outlined by the Commission established for this purpose, psychosocial, behavioral, and biological factors are classified as intermediate determinants that shape inequalities in health and well-being². While a range of other determinants—such as education, income, gender, socioeconomic conditions, and political contexts—are also influential, this discussion focuses on psychosocial and behavioral factors, given their direct relevance to health promotion programs targeting university students.

One behavior under close examination is sleep, which is strongly associated with positive mental health and a lower prevalence of depressive symptoms³. Adequate sleep also plays a crucial role in physical health (e.g., impacting weight management, preventing diabetes, hypertension, or heart disease) and psychological health, mitigating issues such as irritability and difficulties in social interactions^{4,5}.

Additionally, the consumption of alcohol, tobacco, and other substances is recognized as a major risk factor for adverse health outcomes. According to the WHO⁶, harmful alcohol consumption is causally linked to more than 200 diseases, increasing the risk of mental and behavioral disorders, noncommunicable diseases (NCDs), injuries, and traumas. Tobacco, a highly addictive substance, is linked to an increased risk of certain types of cancer and a host of other diseases, with nearly half of all smokers who die if they do not quit⁷. Moreover, the global burden of disease and mortality is significantly exacerbated by the consumption of alcohol, tobacco, and illicit drugs⁸. Cannabis, for instance, remains the most consumed illicit drug, with approximately 200 million users worldwide in 2019—4% of the global population aged 15-64, as noted

in a United Nations Office on Drugs and Crime (UNODC) report⁹. Among adolescents and young adults, cannabis is the most commonly used illicit substance.

Conversely, nutrition is a cornerstone of a healthy lifestyle. Imbalances between caloric intake and expenditure, which directly contribute to obesity, also promote the development of various NCDs, including respiratory diseases, cardiovascular conditions, type II diabetes, certain cancers, and musculoskeletal disorders¹⁰.

Furthermore, there is a strong correlation between overweight and obesity and physical activity in terms of energy expenditure. Nevertheless, physical exercise has been demonstrated to prevent a range of other conditions, including cardiovascular disease, hypertension, diabetes, certain types of cancer, anxiety, and depression. Additionally, it has been linked to improved mental and social health¹¹.

The deterioration of psychological well-being, including heightened anxiety, depression, and stress, has been attributed to lifestyle disruptions caused by factors such as isolation, online learning, and social distancing¹².

The prevalence of mental health issues has increased notably among young people during the pandemic^{13,14}. This underscores the urgent need to implement programs and campaigns within universities to promote healthy lifestyle habits and provide accessible mental health care and preventive services.

Importantly, habits formed during university years often become deeply ingrained and persist throughout adulthood. This makes university students a key target population for the promotion of healthy lifestyle behaviors¹⁵. Conducting research into their lifestyles, interpersonal relationships, and the social phenomena they engage with is therefore of paramount importance.

Objective

The primary objective of this study was to assess the role of the COVID-19 pandemic on lifestyle and psychological well-being among university students, with a focus on gender differences.

Specific objectives:

- To evaluate how the pandemic affected the nutritional profile and physical activity levels of university students, gender differences were considered.
- To analyze changes in sleep quality during the pandemic and identify gender-specific variations.
- To investigate the impact of the pandemic on addictive behaviors, differences between genders were compared.
- To examine anxiety, depressive symptoms, and fear experienced during the pandemic from a gender-based perspective.

Methods

This study was funded by Fundación MAPFRE, which enables the collection of data on lifestyle and health variables relevant to university students.

The design was observational, cross-sectional, and descriptive, targeting students enrolled in official degree programs with sufficient Spanish proficiency to understand the questionnaire.

A 95% confidence level, $\pm 2\%$ precision, and a 15% replacement rate were assumed. Stratified random sampling was conducted across 18 Spanish universities by field of knowledge, excluding master's and doctoral students, who were categorized as "postgraduates".

The fields of knowledge included the following:

- Arts and Humanities
- Sciences
- Health Sciences
- Social and Legal Sciences
- Engineering and Architecture

Data were collected from June 2021 to October 2022 via an online, pilot-validated questionnaire. Statistical analyses were performed via statistical software SPSS 24.0, employing contingency tables, Pearson's χ^2 test, Student's t test, one-way analysis of variance (ANOVA), and nonparametric tests where applicable. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for dichotomous variable comparisons. The study received approval from the University of the Balearic Islands ethics committee.

The questions used to assess the impact of the pandemic on various variables were developed primarily by the research team, as detailed below:

- Sociodemographic variables: Self-designed questions addressing age, field of study, gender, occupation, mode of residence, weight and height.
- General health indicators: Two questions from the 2006 Barcelona Health Survey¹⁶ were employed to evaluate perceived general health and quality of life:
 1. Perceived general health status: "In general, how would you rate your current health status?" Responses were recorded on a five-point scale ranging from "very good" to "very bad".
 2. Perceived quality of life: "In general, how would you rate your current quality of life?" Responses were recorded on another five-point scale ranging from "very good" to "very bad".
- Sleep patterns: Students were asked, "How do you think the pandemic has affected your sleep quality?" They were required to indicate whether it had improved, worsened, or remained unchanged.

- Alcohol consumption: The research team posed the following question: "How do you think the pandemic has influenced your alcohol consumption?". The students were asked to indicate whether they drank less, more, or not at all.
- Tobacco consumption: Initial questions were used to determine the prevalence of smokers, ex-smokers, and nonsmokers within the sample. Students were then asked, "How do you think the pandemic has influenced your tobacco consumption?". They indicated whether they smoked less, more, or not at all.
- Other substance use: Students were asked, "Do you use any other substances (e.g., cannabis, ecstasy, amphetamines, psychedelics, cocaine, heroin)?". Students were required to specify if they had never used, previously used, or currently used substances either occasionally or frequently. An open-ended question allowed the students to specify the type of substance. They were then asked how the pandemic influenced their consumption, following the format of prior questions.
- Eating habits: Students responded to the following question: "How do you think the pandemic has influenced your diet?". They indicated whether their eating habits had improved, worsened, or remained unchanged.
- Physical activity: Students were asked if they engaged in physical activity at home during confinement. The response options included no activity, 1-2 times per week, 3-4 times per week, or 5 or more times per week. They were subsequently asked how the pandemic had affected their physical activity and whether physical activity contributed to their physical and emotional well-being during this time. To this question, the students could specify whether it had contributed nothing, or if, on the contrary, it had contributed a little, a lot, or quite a lot.
- Anxiety, depressive symptoms, and fear related to the pandemic: Questions from the Center for Sociological Research (CIS, for its Spanish acronym) Survey on the Mental Health of Spaniards during the COVID-19 Pandemic were used alongside self-developed questions to explore the pandemic's influence on these variables¹⁷.

Results

The total sample consists of 20,138 valid surveys. The sociodemographic profile can be seen in **table I**.

General health indicators:

People who rated their health as poor or very poor constituted 3.2%, compared with 59.0% who rated it as good and 15.9% who rated it as very good.

However, the pandemic had a negative influence on 49.1% of the respondents, whereas 15.1% considered their health to be better.

On the other hand, the percentage of university students who rated their quality of life as poor or very poor was 2.3%, whereas 61.0% considered it good and 16.5% rated it very good.

In this case, the pandemic worsened the situation for 44.9% of the respondents, whereas 13.7% reported improvement.

When analyzed by gender, women reported a worse health status (3.4%) than men did (2.8%). Additionally, men had a greater proportion of good/very good health (79.9%) than women did (72.7%), with statistically significant differences (Pearson $\chi^2 = 212.725$; $p < 0.001$).

The same was observed with perceived quality of life. Fewer women reported good/very good quality of life compared to men (76.9% vs. 79.0%, respectively). However, men reported poor/very poor quality of life in a greater proportion than women did (2.7% vs. 2.2% of women), with statistically significant differences (Pearson $\chi^2 = 46.051$; $p < 0.001$).

The pandemic had a more negative impact on women's health (51.9%) and quality of life (46.2%) than on men's health (43.3% and 42.1%, respectively), with statistically

Table I: Sociodemographic data of the sample.

Sociodemographic Variables	Women	Men	Total (n)
Sample	13,439 (66,7%)	6458 (32,1%)	20,138
Age	22.33 (SD 6.356)	23.16 (SD 7.454)	22.6 (SD 6.761)
Arts and Humanities	72.4%	25.1%	2625
Sciences	61.2%	37.0%	1963
Health Sciences	76.7%	22.6%	5626
Social and Legal Sciences	73.4%	25.9%	5966
Engineering and Architecture	35.8%	62.9%	2938
Living with parents	47.6%	52.4%	9636
Living with roommates	31.9%	27.1%	5936
Living in university dorms	69.4%	30.6%	1111
Living with a partner	67.8%	32.2%	1381
Occupation	22.8%	24.9%	23.5%
Weight	60.53 kg (SD 11.166)	74.91 kg (SD 12.537)	65.19 kg (SD 13.465)
Height	164.46 cm (SD .063)	178.09 cm (SD .071)	168.86 cm (SD 9.214)
Underweight	11.0%	4.9%	9.0%
Normal weight	71.1%	68.4%	70.2%
Overweight	17.9%	26.8%	20.8%
Academic profile	88.3% graduate	11.7% postgraduate	
Nationality	92.8% Spanish	7.1% foreign	0.1% dual nationality

significant results (Pearson $\chi^2 = 131.618$; $p < 0.001$ for health; Pearson $\chi^2 = 36.742$; $p = 0.000$ for quality of life).

Sleep quality:

The pandemic negatively affected sleep quality in 32.9% of the patients. Only 5.0% reported that it had improved since then. This negative impact was also greater in women (35.8%) than in men (26.7%) (Pearson $\chi^2 = 147.700$; $p < 0.001$).

Alcohol consumption:

The pandemic negatively affected alcohol consumption in 8.8% of the sample (drinking more or having started drinking), whereas 16.0% had drunk less alcohol or stopped drinking since then.

When gender was considered, women consumed less alcohol than men did since the pandemic (16.8% vs. 14.5%) (Pearson $\chi^2 = 15.018$; $p = 0.001$).

Tobacco Consumption:

In the present sample, 73.8% of the participants were nonsmokers, 12.4% were former smokers, and 13.9% were current smokers.

Conversely, 87.0% of the respondents indicated that the pandemic had not influenced their smoking habits, either positively or negatively. In contrast, 7.9% of the respondents reported an increase in their smoking frequency or initiation of smoking. A mere 5.1% of the respondents indicated that they had either quit smoking or smoked less during this period.

With respect to gender, the proportion of smokers and ex-smokers was highest among females (14.3% of females were smokers, compared with 13.0% of the total population; 13.1% of females were ex-smokers, compared with 10.9% of the total population) (Pearson's $\chi^2 = 26.650$; $p < 0.001$).

Furthermore, women also started smoking or smoked more since the pandemic than men did (8.3% vs. 7.0%, respectively) (Pearson $\chi^2 = 28.040$; $p < 0.001$).

Substance use:

The prevalence of substance use in the sample is shown in the following figure (Figure 1).

Cannabis and its derivatives were the most consumed substances (83.6%). A total of 8.5% reported using two or more different substances.

Moreover, in the period after the pandemic, 2.6% of the respondents indicated a reduction in substance consumption, whereas 3.0% reported an increase in or initiation of substance use.

With respect to gender, the data revealed that men used substances occasionally or frequently in 9.5% of the cases, compared with 6.0% of the women (Pearson $\chi^2 = 124.633$; $p < 0.001$). No significant differences were observed regarding the substance used.

The impact of the pandemic was found to be different in women, with 2.3% of cases indicating cessation or reduction in consumption, whereas 3.4% of men did. However, 2.7% of women and 3.4% of men had initiated substance consumption or augmented their intake since the onset of the pandemic (Pearson $\chi^2 = 24.619$; $p < 0.001$).

Eating Habits:

The pandemic had a positive impact on the dietary habits of 27.4% of the students, who reported an increase in the consumption of healthier foods, whereas 13.3% reported a decrease in healthy eating.

Furthermore, a greater proportion of women than men reported improvements in their eating habits

Figure 1: Prevalence of Substance Use.

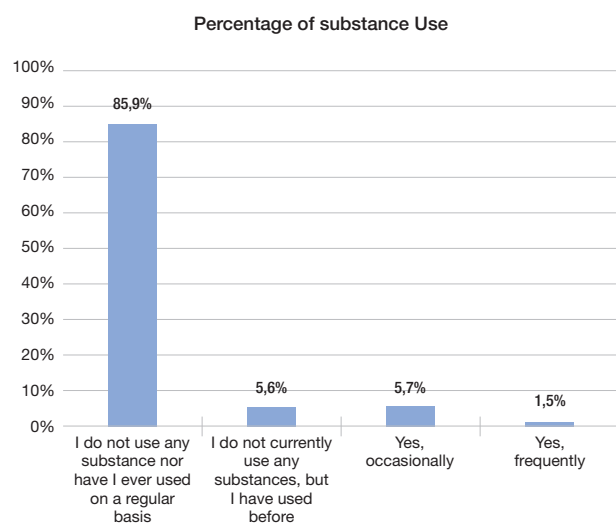
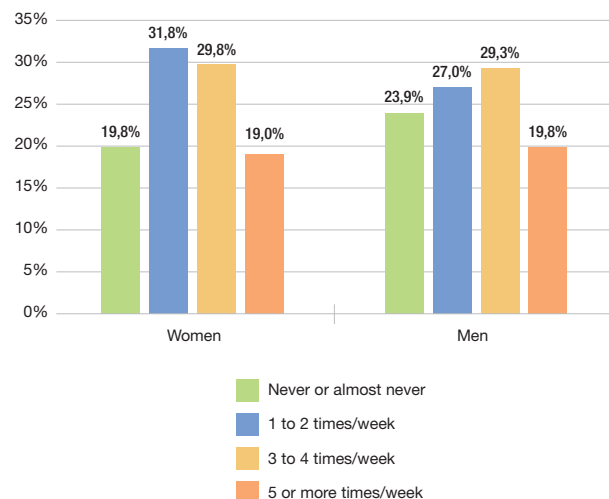


Figure 2: Physical Activity During Lockdown by Gender.



since the pandemic (28.6% vs. 24.9%, respectively), whereas a greater proportion of men than women reported deterioration (14.7% vs. 10.4%) (Pearson $\chi^2 = 110.614$; $p < 0.001$).

Physical activity:

When the physical activity performed during confinement was analyzed, the largest group was the one that performed physical activity 1 or 2 times per week (30.3%), closely followed by those who did it 3 to 4 times per week (29.3%). Those who did not engage in any physical activity constituted 21.2%, whereas those who engaged 5 or more times per week constituted 19.2%.

A total of 39.3% of the respondents reported that the pandemic did not affect their exercise habits; 37.6% increased their exercise hours, and 23.1% decreased them.

These latter data are significant because 24.3% of the respondents stated that physical activity had a substantial impact on their physical and emotional well-being; 32.9% reported a considerable impact; 33.7% reported a slight impact; and 9.1% reported no impact.

Physical activity during the lockdown by gender is shown in **figure 2**.

Moreover, women have increased their weekly hours of physical activity more since the pandemic (39.0% compared with 35.0% of men). Among the total percentage of individuals who decreased their physical activity during this period, women also slightly stood out (23.5% compared with 22.5% of men) (Pearson $\chi^2 = 47.012$; $p = 0.000$).

However, men reported greater physical and emotional benefits from physical activity during the pandemic: 27.3% of men compared with 23.0% of women (Pearson $\chi^2 = 54.577$; $p < 0.001$).

Pandemic-related variables:

Anxiety-depression symptomatology due to the pandemic:

The mean obtained was 36.58 (range 17-68), with a standard deviation of 12.413. According to the median, 52.5% of individuals exhibited low levels of symptomatology, whereas 47.5% reported high levels.

Regarding gender, differences are shown in **table II**.

Women have experienced, with statistically significant differences, generally twice as many anxiety and/or depressive symptoms in most items. In fact, they are up to 1.906 times more likely to experience high symptomatology, as evidenced by the comparison of their means: 38.16 (standard deviation [SD] = 12.429) for women and 33.21 (SD = 11.644) for men (Welch's $t = 23.297$; $p < 0.001$).

In terms of the median score, 52.6% of the women presented high symptomatology compared to only 36.8% of the men presented high symptoms (Pearson $\chi^2 = 313.979$; $p < 0.001$).

Fear/concern experienced due to the pandemic:

In this instance, the mean value (range 11-55) was 36.74 (SD = 9.212). The 51.5% of the sample, as determined by the median, indicated a low or negligible level of fear, in contrast to the 48.5%, which indicated a considerable level of fear.

Finally, based on gender, **table III** is presented:

The results demonstrated that women exhibited twice as much fear as men across a range of items. The median revealed that 57.2% of women experienced a significant or high level of fear, whereas 31.1% of men experienced a significant or high level of fear (Pearson $\chi^2 = 857.207$; $p < 0.001$). This was further corroborated by the comparison of their means (Welch's $t = 34.528$; $p < 0.001$), with a mean score of 38.58 for women (SD = 8.661) and 33.04 for men (SD = 9.141).

This finding indicates that women are 2.961 times more likely to experience a significant or high level of fear than men are.

Discussion

General health indicators:

The pandemic has undeniably negatively impacted both health status and perceived quality of life among students. Comparative data from studies conducted before and during the pandemic highlights this deterioration. For example, Bennasar's study, which used the same questions, reported that 91.0% of students perceived their health as "very good", compared to 74.9% did so in the present study¹⁸. This aligns with findings from Amengual¹⁹ (82.7%) and the 2020 Annual Report of the Spanish National Health System (75.5%)²⁰.

Similarly, quality of life metrics reflect this decline. Bennasar's study revealed that 88.9% of students rated their quality of life as high, compared with 77.5% in this study and 82.4% in Amengual's study^{18,19}. Notably, the pandemic appears to have had a greater impact on women, who reported significantly lower scores for both health status and quality of life, a pattern not observed in Bennasar's study¹⁸. This gender disparity aligns with findings at both the national and European levels¹¹.

The elevated prevalence of anxiety, depressive symptoms, and fear among women further supports these findings, as detailed in the section on pandemic-related variables.

Sleep habits:

The pandemic has significantly disrupted sleep quality, as reported by 32.9% of the current sample. This aligns with previous studies^{12,21}. Moreover, Diz-Ferreira et al. reported that the prevalence of insomnia increased in Spain from 23.1% before the pandemic to 36.3% after its onset²².

Alcohol consumption:

Postlockdown studies indicate a reduction in alcohol consumption during the pandemic^{12,23,24}, with 7.1% of the population ceasing alcohol use altogether. In this study, 16.0% of the respondents reduced or stopped

alcohol consumption, whereas 8.8% reported increased intake or initiation.

However, it is important to note that elevated alcohol consumption in households may have normalized during this period because of the temporary closure of bars and restaurants, especially among women, which may serve as a risk predictor for other health issues^{25,24}. This study revealed that women were more likely to consume alcohol occasionally, with some reporting up to four instances per month.

Table II: Anxiety and depression symptomatology because of the Coronavirus Disease 2019 according to gender.

During the pandemic...	Categories	Women	Men
You have felt little interest or pleasure in doing things ^a	Never or almost never	10.8%	15.4%
	Some days	35.4%	38.3%
	Several or many days	53.8%	46.4%
You have been feeling down, depressed or hopeless ^a	Never or almost never	14.1%	25.4%
	Some days	34.5%	37.6%
	Several or many days	51.4%	37.0%
You have been feeling nervous, anxious or very upset ^a	Never or almost never	15.6%	27.0%
	Some days	34.2%	39.3%
	Several or many days	50.1%	33.7%
You have felt unable to stop or control worries ^a	Never or almost never	20.5%	33.3%
	Some days	33.0%	35.4%
	Several or many days	46.5%	31.3%
You have had unwanted unpleasant thoughts or memories about coronavirus and its consequences ^a	Never or almost never	33.4%	45.9%
	Some days	34.3%	31.9%
	Several or many days	32.3%	22.1%
You have had nightmares or images related to coronavirus ^a	Never or almost never	69.3%	75.9%
	Some days	18.5%	15.4%
	Several or many days	12.2%	8.6%
You have had sleep problems ^a	Never or almost never	28.1%	38.5%
	Some days	32.1%	33.2%
	Several or many days	39.8%	28.2%
You have had thoughts or memories that have produced physical reactions ^a	Never or almost never	53.0%	61.2%
	Some days	23.6%	23.0%
	Several or many days	23.5%	15.9%
You have felt overwhelmed or distressed by thoughts or memories about coronavirus ^a	Never or almost never	49.6%	61.5%
	Some days	29.4%	24.2%
	Several or many days	21.1%	14.3%
You have tried to avoid upsetting thoughts or memories about the coronavirus ^a	Never or almost never	46.4%	57.5%
	Some days	28.4%	24.1%
	Several or many days	25.2%	18.4%
Thoughts about the coronavirus have disrupted your social life, work or daily tasks ^a	Never or almost never	51.5%	59.4%
	Some days	26.2%	23.2%
	Several or many days	22.2%	17.4%
You have felt a lot of anxiety or fear ^a	Never or almost never	34.0%	54.0%
	Some days	32.0%	27.4%
	Several or many days	34.1%	18.7%
You have felt isolated or alone ^a	Never or almost never	28.9%	36.9%
	Some days	32.0%	34.0%
	Several or many days	39.1%	29.2%
You have felt hopeless about the future ^a	Never or almost never	19.4%	29.9%
	Some days	32.1%	33.6%
	Several or many days	48.5%	36.5%
You have felt irritable, angry, angry or aggressive ^a	Never or almost never	27.6%	37.2%
	Some days	35.2%	36.1%
	Several or many days	37.2%	26.8%
You have felt overwhelmed or stressed ^a	Never or almost never	11.8%	25.5%
	Some days	32.3%	35.9%
	Several or many days	56.0%	38.5%
You have felt uneasy or restless ^a	Never or almost never	16.5%	28.3%
	Some days	35.3%	37.3%
	Several or many days	48.2%	34.4%

^aStatistically significant ($p < 0.05$).

Tobacco Consumption:

Furthermore, the pandemic has had an impact on tobacco consumption among the population. In general, there has been an increase in consumption, with some reports indicating that up to 49.9% of respondents have experienced an increase in their use of tobacco products¹². Individuals who consumed more alcohol and tobacco products prior to the pandemic reduced their consumption the least during this period²⁶. This is evidenced by the findings of this study, which indicate that only 5.3% of the respondents had ceased smoking or reduced their consumption, whereas 7.9% smoked more or initiated smoking.

The prevalence of tobacco use was greater among women than among men, a finding that is consistent with the results of Amengual's research but contrasts with the EDADES (Encuesta Sobre Alcohol y Otras Drogas en España) national report^{19,27}. Furthermore, the present study revealed that women were more likely to smoke during the pandemic (8.3% vs. 7.0%, respectively), which may be associated with a higher prevalence of anxious and depressive symptoms and elevated levels of fear related to the ongoing pandemic.

Substance Use:

The pandemic is anticipated to have resulted in a decline in substance use due to the restricted accessibility of these substances. In this study, 2.6% of the participants reduced or ceased substance use, whereas 3.0% initiated or increased substance use. In countries such as the Netherlands, where cannabis is legally available, higher increases in use were reported (49.4%)²⁸.

In this case, despite men being the primary consumers, they are also the group that discontinued use at a higher rate than women did, as evidenced by the present study. Similarly, a greater percentage of men than women initiated substance use or increased their consumption.

Eating Habits:

Hospitality closures prompted changes in dietary habits, with some studies reporting increased food and sweet consumption (34.0% and 33.0%, respectively), which has led to a slight weight gain of up to 40.3%^{29,26}.

Nevertheless, an improvement of 16.7% in adherence to the Mediterranean diet was observed, particularly among the 18-30 years of age group studied by Di Renzo et al.²⁶. In the present study, 27.4% of the participants reported

Table III: Fear of the coronavirus in the sample and its consequences by gender.

Fear of...	Categories	Women	Men
To catch the coronavirus ^a	None or little	32.2%	51.5%
	Some	29.4%	25.8%
	Quite a lot or a lot	38.5%	22.7%
To die due to coronavirus ^a	None or little	56.9%	72.8%
	Some	17.5%	13.8%
	Quite a lot or a lot	25.6%	13.4%
A family member or loved one may become infected ^a	None or little	7.1%	16.1%
	Some	14.6%	23.0%
	Quite a lot or a lot	78.2%	60.9%
The death of a family member or loved one ^a	None or little	7.8%	16.8%
	Some	11.2%	19.3%
	Quite a lot or a lot	81.0%	64.0%
To the further spread of the coronavirus ^a	None or little	17.2%	33.1%
	Some	26.1%	30.1%
	Quite a lot or a lot	56.7%	36.8%
You may infect a family member or loved one ^a	None or little	7.0%	16.4%
	Some	11.3%	18.7%
	Quite a lot or a lot	81.6%	64.9%
You could lose your income ^a	None or little	43.0%	54.1%
	Some	20.4%	18.4%
	Quite a lot or a lot	36.5%	27.5%
To a family member or loved one losing a job ^a	None or little	33.5%	34.9%
	Some	17.9%	21.6%
	Quite a lot or a lot	58.4%	43.5%
To be alone or socially isolated ^a	None or little	33.1%	47.4%
	Some	22.9%	21.6%
	Quite a lot or a lot	43.9%	31.0%
To society never being the same as it was before ^a	None or little	20.0%	37.3%
	Some	21.0%	22.1%
	Quite a lot or a lot	59.0%	40.5%
To pandemics becoming a part of our lives ^a	None or little	18.6%	35.8%
	Some	20.3%	22.4%
	Quite a lot or a lot	61.0%	41.8%

^aStatistically significant ($p < .05$).

an increase in the consumption of healthier foods and diets since the onset of the pandemic.

In this context, women have exhibited the greatest improvement since the pandemic.

Physical Activity:

The percentages achieved in this study are noteworthy, as more than 75% of the sample engaged in physical exercise during the lockdown period, with 37.6% of the students increasing the time dedicated to it after the onset of the pandemic. These figures differ from those reported in other studies^{12,26,29}, in which, for instance, the prevalence of vigorous physical activity declined in more than half of the subjects, whereas the lowest level increased by 111.1%³⁰.

In this study, women were found to engage in the greatest amount of physical exercise after the pandemic. This finding is consistent with those reported by Romero-Blanco et al.³¹. However, the Annual Report of the National Health System indicates that women exhibited higher levels of sedentary behavior in 2020²⁰.

Pandemic-Related Variables:

Anxiety-Depressive Symptoms Due to the Pandemic:

A comparison of the anxiety-depressive symptoms reported by the CIS¹⁷ with those reported in the current study revealed a greater percentage in the present sample across nearly all items. These findings are consistent with those reported by Romero-Blanco et al., who reported the prevalence of anxiety and/or depressive disorders among students, with a reported incidence of up to 26.6%³¹. However, when evaluated specifically in the context of the pandemic, the percentage increased to 47.5%, as observed in the current study.

Fear/Concern Experienced Due to the Pandemic:

With respect to the presence of fear or concern experienced as a result of the pandemic, the findings

in the sample are more aligned with those reported by the CIS¹⁷. However, some items, in contrast to the CIS sample, indicate lower levels of fear or concern among the surveyed students¹⁷. For example, items such as "Fear of catching the coronavirus" or "Fear of the further spread of the coronavirus" suggest that, over time since the onset of the pandemic, students may have adapted to the presence of the coronavirus and its daily impacts.

Conclusion

The pandemic seems to have significantly impacted the lifestyles of university students, leading to adverse effects on perceived health status, quality of life, sleep quality, tobacco consumption, substance use, and increased anxiety-depressive symptoms. Additionally, approximately half of the sample reported experiencing heightened levels of apprehension and unease.

On a more positive note, there have been slight reductions in alcohol consumption (with reduced intake), physical activity, and adherence to the Mediterranean diet within this population. However, these changes require further investigation to ascertain whether they represent a long-term shift in lifestyle or, conversely, whether they are behavioral patterns that may diminish over time.

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Ethical approval

The study was approved by the ethics committee of the Universitat de les Illes Balears, Spain (approved with expedient number 197CER21, on May 12th, 2021).

Conflict of interests

The author(s) declared no potential conflicts of interest.

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Prevención de trastornos musculoesqueléticos, autocuidado y planificación del estudio en estudiantes de música.

Análisis descriptivo y correlacional

*Prevention of musculoskeletal disorders, self-care and study planning in music students.
Descriptive and correlational analysis*

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Resumen

Introducción: La práctica musical está sometida a riesgos por carga física, movimientos repetidos, posturas forzadas y riesgos psicosociales, favoreciendo así la aparición de lesiones. Las estrategias de conocimiento y el cuidado de la salud son fundamentales para poder actuar en prevención desde fases tempranas.

Objetivo: Conocer en estudiantes de música el impacto del dolor por lesiones musculoesqueléticas, su localización, estrategias de prevención, actividad física realizada, planificación del tiempo de estudio, autopercepción profesional y variables relacionadas.

Material y métodos: Estudio observacional multicéntrico en estudiantes de música de conservatorios de España, mediante entrevista con la plataforma Google Forms desde noviembre de 2021 hasta febrero de 2022. Incluye: dolor musculoesquelético y actividad física; planificación del estudio y autopercepción de su nivel como intérprete.

Resultados: El dolor cervical es más frecuente en estudiantes de instrumentos de cuerda y el de hombro en los de viento. El dolor es más frecuente y de mayor duración en mujeres. Las mujeres se consideran con un nivel de intérprete más bajo que los hombres. La práctica de ejercicio y técnicas de relajación o calentamiento es poco frecuente en ambos sexos, con mayor práctica por los hombres y guarda relación con la intensidad del dolor y su localización.

Conclusiones: Aunque la prevalencia de dolor por lesiones musculoesqueléticas en los músicos es alta, las estrategias de estudio en cuanto a su prevención parecen estar poco consolidadas, al igual que la planificación del tiempo de estudio. Estos aspectos deben ser incluidos en la etapa de estudiantes en los conservatorios de música.

Palabras clave: músicos, dolor muscular, ejercicio físico, autocuidado, autopercepción.

Abstract

Introduction: Musical practice is associated with risks due to physical strain, repetitive movements, forced postures, and psychosocial factors, all of which contribute to the development of injuries. Knowledge and health care strategies are essential for implementing preventive measures from early stages.

Objective: To assess the impact of musculoskeletal pain on music students, including its localization, prevention strategies, physical activity, study time planning, self-perception as performers, and related variables.

Materials and methods: A multicenter observational study conducted among music students from conservatories in Spain through interviews using the Google Forms platform from November 2021 to February 2022. The study includes assessments of musculoskeletal pain and physical activity, study planning, and self-perceived performance level.

Results: Cervical pain is more frequent among string instrument students, while shoulder pain is more prevalent among wind instrument players. Pain occurs more frequently and lasts longer in women. Female students tend to rate their performance level lower than male students. Both sexes engage infrequently in exercise, relaxation techniques, or warm-up routines, although men participate more than women. These practices are associated with pain intensity and localization.

Conclusions: Despite the high prevalence of musculoskeletal pain among musicians, preventive study strategies remain insufficiently established, as does the planning of study time. These aspects should be incorporated into the curriculum of music conservatories during students' training.

Key words: musicians, muscle pain, physical exercise, self-care, self-perception.

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Introducción

La carrera del músico se inicia mayoritariamente en la infancia y conlleva una elevada autoexigencia¹, así como importantes demandas físico-ergonómicas y psicosociales que pueden entrañar riesgo para su salud^{2,3}. Destacan los trastornos musculoesqueléticos (TME) y la sintomatología dolorosa^{4,5}, especialmente en columna y miembros superiores (MMSS)⁶.

Entre el 38 y 89% de los músicos sufren estas patologías por movimientos repetitivos, posturas forzadas y manejo del instrumento, entre otros factores. Estas lesiones pueden interferir o incapacitar al músico para tocar. Pese a ello, es escasa la formación en cuanto a prevención y tratamiento de estas afecciones, siendo realizados básicamente ejercicios de calentamiento previos a la actividad para conseguir la mejor calidad del sonido, pero no se actualizan durante el ejercicio profesional posterior.

Los estudios realizados muestran la relación entre los TME y estos factores de riesgo que se incrementan con el peso del instrumento y el número de horas de práctica semanal⁷, lo que convierte a este colectivo en personas de alto riesgo en TME⁸ y, a las estrategias de autocuidado en una herramienta preventiva fundamental que contribuye a mejorar la calidad y bienestar del profesional⁹.

Estudios realizados indican que, el estilo de vida del músico predispone a riesgo cardiovascular incrementado asociado al sedentarismo de su actividad y malos hábitos en alimentación y ritmo de sueño. Se destaca la alta prevalencia de obesidad y dislipemia, por lo que es relevante implementar programas de promoción de la salud en este colectivo profesional ya desde la etapa de estudiantes¹⁰. Así lo recomiendan las organizaciones internacionales, como la ONU en su agenda 2030 de desarrollo sostenible¹¹, resaltando la importancia de modificar los comportamientos de actividad física en jóvenes y adolescentes¹².

Los TME en los músicos se deben a tensiones físicas, movimientos repetitivos, posturas incorrectas y peso del instrumento. Los síntomas van desde dolor leve hasta crónico, pudiendo incapacitar al profesional o estudiante de música¹³. Pese a su elevada prevalencia, hay poca formación en prevención, control y seguimiento. En los centros formativos o conservatorios se enseña a calentar antes de comenzar a tocar, pero no para prevenir trastornos o lesiones, sino con el objetivo de mejorar la calidad del sonido¹⁴.

Intervenir desde el inicio de los estudios con buenas prácticas y estrategias preventivas podría conducir a una mejor perspectiva en salud física y mental. Resulta necesario conocer aspectos relativos a los TME, su autocuidado, motivación de los estudiantes y estrategias de estudio, para poder plantear mejoras

en su práctica musical y evitar lesiones futuras y sintomatología dolorosa.

De otro lado, una práctica eficaz en la técnica de estudio requiere tres fases de aprendizaje: planificación y preparación de la práctica, ejecución y evaluación¹⁵. Este aspecto puede tener relación con el concepto de identidad que, en el ámbito musical ha captado la atención de los investigadores, ya que comienza a desarrollarse desde una edad temprana y puede cambiar a lo largo de la vida del músico profesional. Destacan aspectos como la autopercepción y la autoeficacia, consideradas fundamentales para el éxito, destacando cinco variables como más significativas: capacidad, esfuerzo, confianza, suerte y el apoyo de otros¹⁶.

Se propone en la planificación de estrategias de estudio: establecer objetivos a corto, medio y largo plazo; llevar un diario; analizar la partitura y tener un horario preestablecido¹⁷. Estas estrategias están relacionadas con la identidad musical, que se desarrolla desde una edad temprana y afecta el desarrollo en práctica y rendimiento. La autoeficacia, o creencia en la propia capacidad es clave para el éxito académico y musical, al igual que la responsabilidad personal y el locus de control. La teoría del control percibido, que combina elementos de modelos anteriores, sugiere que las creencias sobre la capacidad y las citadas estrategias son fundamentales para alcanzar las mayores cotas profesionales, destacando como variables: capacidad, esfuerzo, confianza, suerte y el apoyo de otros.

Pese a lo anteriormente mencionado, se detecta una carencia de estudios más completos que incluyan estos aspectos y, que podrían ser claves para actuar en prevención tanto del riesgo en el desarrollo de TME como en salud mental.

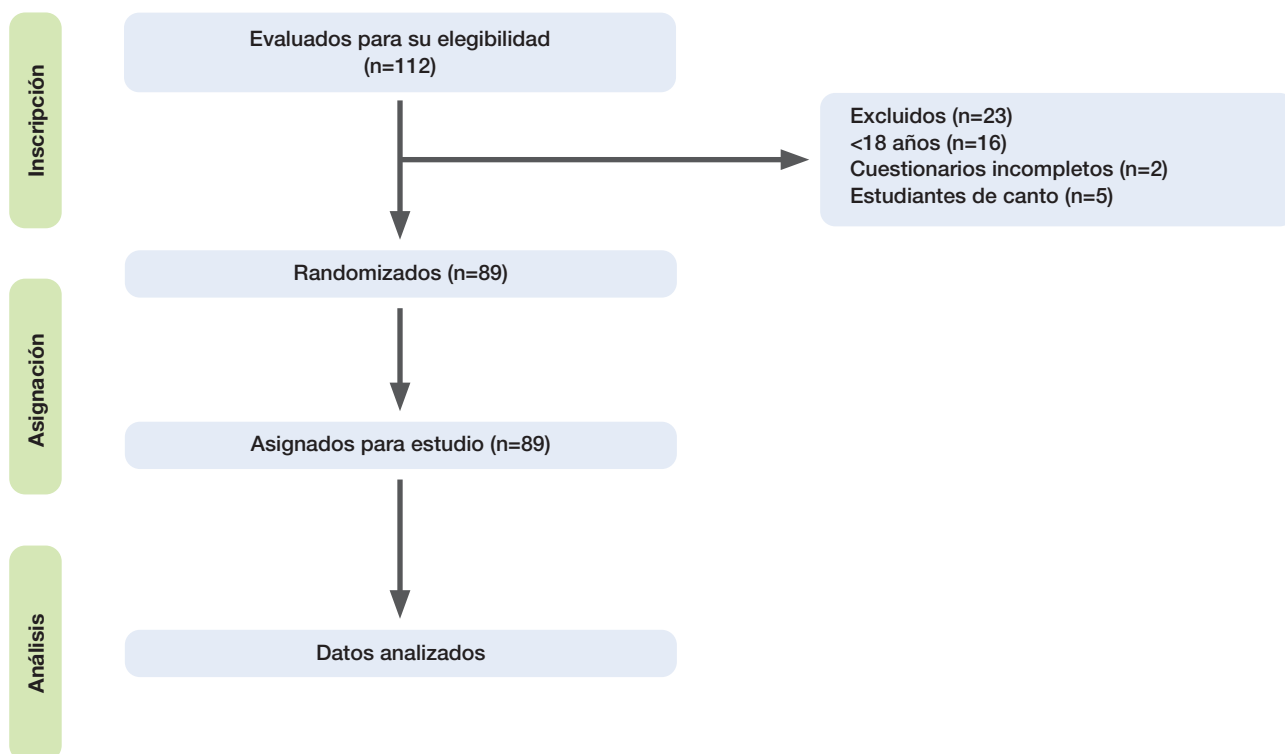
Es objetivo del presente estudio conocer los TME del estudiantado de música, las características del dolor asociado, la actividad física realizada, la planificación del tiempo de estudio y su autopercepción como intérprete.

Material y métodos

Se realiza estudio descriptivo transversal y de correlación en la Universitat de València (España) desde noviembre de 2021 hasta febrero de 2022 a 112 estudiantes del conservatorio superior de música o de máster, mayores de 18 años. Quedaron excluidos 23 por cursar otros estudios oficiales, ser músicos profesionales o estudiantes de canto, completando finalmente el estudio 89 músicos (**Figura 1**).

La recogida de datos fue telemática, mediante cuestionario online diseñado ad hoc para el presente

Figura 1: Esquema del estudio.



estudio utilizando la plataforma de formularios de Google incluyendo datos antropométricos y sociodemográficos: sexo, edad, curso actual, e instrumento que practica. El cuestionario consta de 19 preguntas con cuatro secciones: a) 14 preguntas de factores musculoesqueléticos y autocuidado, técnicas de prevención utilizadas, zonas del cuerpo afectadas, y práctica de actividad física; b) 3 preguntas sobre planificación del estudio y c) 2 preguntas sobre su percepción como intérprete y calificación académica.

Consideraciones éticas

Los sujetos han participado de forma voluntaria, garantizando la confidencialidad y su anonimato, y el de sus respuestas, de acuerdo con la Ley española de protección de datos de carácter personal (LOPD)¹⁸ y los criterios de la declaración de Helsinki, siendo informados del propósito y la finalidad del estudio y otorgando su consentimiento. El protocolo de estudio fue aprobado por el Comité de Ética en Humanos de la Universitat de València (blinded) (UV-INV_ETICA-2014207) y registrado previamente en el ClinicalTrials.gov (NCT05503472).

Análisis estadístico

Los datos obtenidos fueron codificados y analizados con el programa estadístico SPSS para Windows, versión 26.0. Todas las variables fueron analizadas por sexo, edad y grupo de instrumento, para valorar diferencias entre grupos.

Para facilitar los análisis por tipo de instrumento se procedió a realizar una agrupación de los mismos: a) cuerda pulsada (guitarra, mandurria, arpa, piano, clavecín); b) viento-metal (trompeta, trompa, trombón); c) cuerda frotada (cello, violín, viola); d) viento-madera (clarinete, flautín, saxo, oboe, flauta travesera). No se incluyeron por falta de suficiente muestra: en viento-metal: tuba, bombardino y fliscorno; en cuerda frotada: contrabajo; en viento-madera: fagot. Se clasificó el tipo de ejercicio en: moderado (correr, ciclismo, natación, resistencia, gimnasio, etc.) y suave (caminar y yoga).

Dado que la mayoría de las variables son categóricas, se realizó test chi-cuadrado de grupos independientes para analizar la relación entre ellas. El tamaño del efecto fue medido, en este caso, con la V de Cramer (0.10 bajo, 0.30 medio, 0.50 grande).

La variable nivel de intérprete fue tratada como variable cuantitativa, con lo que se realizaron pruebas t de grupos independientes o ANOVA entresujetos según la variable relacionada tuviera 2 o más categorías. El tamaño del efecto en este caso fue medido con la d de Cohen (0.20 bajo, 0.50 medio, 0.80 grande) o eta cuadrado parcial (<0.1 despreciable, entre 0.1 y 0.06 bajo, entre 0.06 y 0.15 medio, >0.15 grande). La prueba de homogeneidad de varianzas de Levene se cumplió en todos los análisis t de grupos independientes.

Resultados

Los resultados del descriptivo se muestran en la **tabla I** y, en ellos se destaca mayor participación de hombres, con una edad media en ambos sexos de $21,2 \pm 5$ años. La mayoría de los participantes son de grado superior y, el grupo instrumental mayoritario corresponde a viento-metal. Destaca el dolor cervical en cuerda pulsada, cuerda frotada y viento-madera (**Figura 2**), aunque los resultados no tienen significación estadística.

Las diferencias significativas entre las variables de estudio y el sexo se muestran en la **tabla II** y muestran diferencias en función del grupo de instrumento, siendo las más notables las obtenidas en viento-metal, especialmente entre los hombres. En cuanto al dolor, la mayor prevalencia se obtiene en mujeres, especialmente en MMSS. Un mayor porcentaje de hombres que de mujeres realiza ejercicio físico continuo (4 o más días de ejercicio por semana), siendo principalmente de nivel moderado en ambos sexos.

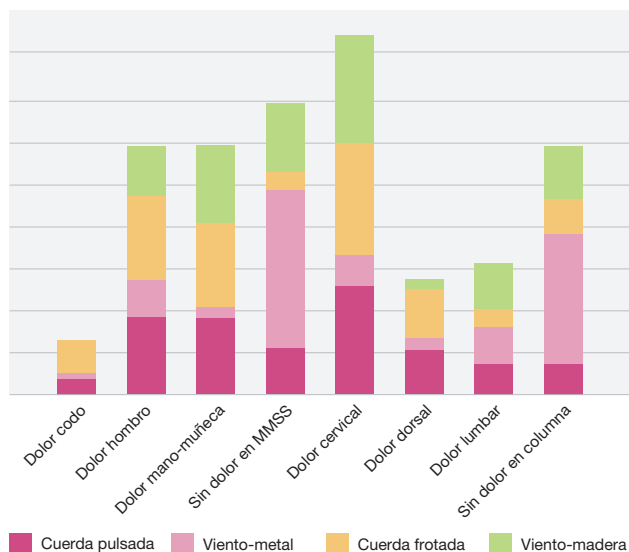
Tabla I: Descriptivo de la población.

Variable	n (%)					
NIVEL DE ESTUDIOS						
1º Grado Superior	23 (25.8)					
2º Grado Superior	24 (27.0)					
3º Grado Superior	9 (10.1)					
4º Grado Superior	3 (3.4)					
Grado medio (profesional)	17 (19.1)					
Máster	13 (14.6)					
GRUPO INSTRUMENTAL						
Cuerda pulsada	14 (15.7)					
Viento-metal	39 (43.8)					
Cuerda frotada	13 (14.6)					
Viento-madera	23 (25.8)					
AUTOCUIDADO MUSCULOESQUELÉTICO (DOLOR Y ACTIVIDAD FÍSICA)						
Cuestiones planteadas en la encuesta	Sí		No			
1. ¿Haces ejercicios de calentamiento antes de comenzar la sesión de estudio?	60 (67.4)		29 (32.6)			
2. ¿Haces ejercicios de estiramientos o relajación muscular al finalizar la sesión?	32 (36.0)		57 (64.0)			
3. ¿Sufres algún tipo de dolor muscular?	60 (67.4)		29 (32.6)			
4. ¿La zona de dolor es en el miembro superior?	48 (53.9)		41 (46.1)			
5. ¿La zona de dolor es en la espalda?	55 (61.8)		34 (38.2)			
6. ¿La zona de dolor es en el miembro inferior?	5 (5.6)		84 (94.4)			
7. ¿Tienes miedo a realizar deporte por si sufres una lesión que te impida continuar tocando?	30 (33.7)		59 (66.3)			
8. ¿Realizas ejercicio continuo más de 30 minutos al día?	37 (1.6)		52 (58.4)			
9. ¿Te sientes mejor tocando si estás en buena forma física?	72 (80.9)		17 (19.1)			
10. Cuando sientes alguna molestia muscular en el estudio, ¿qué haces?	Parar de inmediato	Tocar menos	No parar			
	45 (50.6)	32 (36.0)	12 (13.5)			
11. Zona de dolor de miembros superiores	Hombro	Codo	Mano/muñeca			
	23 (25.8)	4 (4.5)	21(23.6)			
12. Zona de dolor en la espalda	Cervical	Dorsal	Lumbar			
	31 (34.8)	9 (10.1)	15 (16.9)			
13. ¿Cuántos días a la semana realizas ejercicios?	Ninguno	1-3 días	4 días o más			
	21 (23.6)	34 (38.2)	22 (24.7)			
14. ¿Qué tipo de ejercicio realizas?	Ninguno	Suave	Moderado			
	19 (21.3)	10 (11.2)	60 (67.4)			
NIVEL DE PERCEPCIÓN COMO INTÉRPRETE Y CALIFICACIÓN						
15. Consideras que tu nivel como intérprete es...	Bajo	Medio -bajo	Medio	Medio -alto	Alto	Muy alto
	1 (1.1)	7 (7.9)	21 (23.6)	43 (48.3)	17 (19.1)	0
16. ¿Cuál fue tu puntuación final en instrumento el curso anterior?	Bien		Notable		Sobresaliente	
	7 (7.9)		24 (27.0)		49 (55.1)	
PLANIFICACIÓN						
17. ¿Planificas el tiempo y el contenido del estudio?	Sí			No		
	68 (76.4)			21 (23.6)		
18. ¿Planteas objetivos a cumplir en cada sesión de estudio?	Sí			No		
	55 (61,8)			34 (38,2)		
19. ¿Cómo planificas el estudio?	Dependiendo al reto que me enfrente		Siempre, diariamente		Siempre, semanalmente o más	
	49 (55,1)		20 (22,5)		20 (22,5)	

n= Frecuencias absolutas. %= Frecuencias relativas.

Las mujeres se consideran con un nivel de intérprete más bajo que los hombres, aunque se observan diferencias por niveles: en el nivel medio-bajo y medio hay mayor porcentaje de mujeres; en el nivel medio-alto y alto mayor porcentaje de hombres.

Figura 2: Localización del dolor según instrumento utilizado.



Las diferencias significativas entre las variables de estudio y el grupo de instrumento se muestran en la **tabla III**. Destaca la presencia de dolor en MMSS en instrumentos de cuerda frotada, cuerda pulsada y viento madera. Respecto al dolor de raquis/espalda, se observa principalmente entre los estudiantes de cuerda pulsada, cuerda frotada, viento madera y, en menor porcentaje en los de viento-metal. Realizan más ejercicio físico continuo los estudiantes de viento metal y, en menor porcentaje los de cuerda frotada, viento madera y cuerda pulsada. Las variables de planificación del estudio no ofrecieron ningún resultado significativo ni con relación al sexo, ni al grupo de instrumento.

Los resultados de las relaciones significativas entre áreas de autocuidado de TME y planificación de la actividad musical se muestran en la diagonal inferior de la **tabla IV**. El 72.1% de los participantes que se planifican, se plantean objetivos en cada sesión de estudio ($\chi^2(1)=12.85$, $p<.001^*$, $v=.380$). De los que se planifican, solo un 41.2% hace ejercicios de relajación. Un 81.0% de los que no se planifican, tampoco realiza ejercicios de relajación.

Tabla II: Relación de las variables del estudio con el sexo.

Cuestiones planteadas en la encuesta*	Hombre n (%)	Mujer n (%)	Total n (%)	p (tamaño)
1. ¿Haces ejercicios de calentamiento antes de comenzar la sesión de estudio?	37 (75.5)	23 (57.5)	60 (67.4)	-
2. ¿Haces ejercicios de estiramientos o relajación muscular al finalizar la sesión?	19 (38.8)	13 (32.5)	32 (36.0)	-
3. ¿Sufres algún tipo de dolor muscular?	22 (44.9)	38 (95.0)	60 (67.4)	.001* (.532)
4. ¿La zona de dolor es en el miembro superior?	15 (36.6)	33 (82.5)	48 (53.9)	.001* (.518)
5. ¿La zona de dolor es en la espalda?	21 (42.9)	34 (85.0)	55 (61.8)	.001* (.431)
6. ¿La zona de dolor es en el miembro inferior?	3 (6.1)	2 (5.0)	5 (5.6)	-
7. ¿Tienes miedo a realizar deporte por si sufres una lesión que te impida continuar tocando?	14 (28.6)	16 (40.0)	30 (33.7)	-
8. ¿Realizas ejercicio continuo más de 30 minutos al día?	29 (59.2)	8 (20.0)	37 (41.6)	.001* (.395)
9. ¿Te sientes mejor tocando si estás en buena forma física?	44 (89.8)	28 (70.0)	72 (80.9)	.018* (.251)
11. Zona de dolor de MMSS	Mano M 5 (33.3) Codo 3 (20.0) Hombro 7 (46.7)	Mano M 16 (48.5) Codo 1 (3.0) Hombro 16 (48.5)	Mano M 21 (43.8) Codo 23 (47.9) Hombro 4 (8.3)	-
12. Zona de dolor en la espalda	Cervical 7(33.3) Dorsal 2 (9.5) Lumbar 12 (57.1)	Cervical 24 (70.6) Dorsal 7 (20.6) Lumbar 3 (8.8)	Cervical 31 (56.4) Dorsal 9 (16.4) Lumbar 15 (27.3)	.001* (.527)
13. ¿Cuántos días a la semana realizas ejercicios?	0: 7 (17.5) 1-3: 15 (37.5) >4: 18 (45.0)	0: 14 (37.8) 1-3: 19 (51.4) >4: 4 (10.8)	0: 21 (27.3) 1-3: 34 (44.2) >4: 22 (28.6)	.003* (.388)
14. ¿Qué tipo de ejercicio realizas?	Ninguno: 7 (14.3) Suave: 2 (4.1) Moderado: 40 (81.6)	Ninguno: 12 (30.0) Suave: 8 (20.0) Moderado: 20 (50.0)	Ninguno: 19 (21.3) Suave: 10 (11.2) Moderado: 60 (67.4)	.005* (.348)
15. Consideras que tu nivel como intérprete es...	1: 1 (2.0) 2: 1 (2.0) 3: 6 (12.2) 4: 27 (55.1) 5: 14 (28.6) Media=4.06	1: 0 (0) 2: 6 (15.0) 3: 15 (37.5) 4: 16 (40.0) 5: 3 (7.5) Media=3.40	1: 1 (1.1) 2: 7 (7.9) 3: 21 (23.6) 4: 43 (48.3) 5: 17 (19.1) Media=3.76	.001* (.793)
16. ¿Cuál fue tu puntuación final en instrumento el curso anterior?	Bien: 3 (7.0) Notable: 12 (27.9) Sobres: 28 (65.1)	Bien: 4 (10.8) Notable: 12 (32.4) Sobres: 21 (56.8)	Bien: 7 (8.8) Notable: 24 (30.0) Sobres: 49 (61.3)	-

*En las preguntas 1-9, se incluyen los valores y porcentajes de las respuestas afirmativas (Sí). En las preguntas 11-16 se incluyen los resultados para cada categoría de la variable. n= Frecuencias absolutas. %= Frecuencias relativas. Se considera significativo un valor de $p<0,05$

Los que no hacen ejercicios de calentamiento tienen más dolor muscular en MMSS, que disminuye cuando comienzan a realizarlos de forma previa a la actividad musical. Incluso en aquellos que hacen estos ejercicios de calentamiento, existe dolor en el codo, hombro, mano-muñeca y espalda, aunque con menor intensidad y frecuencia que en el resto.

La mayoría de estudiantes realizan ejercicio físico continuo, calentamiento previo y, más de la mitad practica ejercicios de relajación y autorregulan el esfuerzo, tocando menos cuando sienten dolor muscular.

Respecto a la autopercepción de su nivel como intérprete, existen diferencias significativas en los grupos de viento-metal (media 4.05) y cuerda pulsada (media 3.21) siendo estas diferencias significativas ($p < 0,05$), también entre viento-metal y cuerda frotada (media 3.31) ($p < 0,05$).

La autopercepción como intérprete es mayor en los que no tienen dolor muscular. El dolor de espalda es menor en personas con calificación académica alta, de sobresaliente (71.4%) frente a los que obtienen una calificación de notable (79.2%), siendo estas diferencias significativas ($p < 0,05$). Cuando los sentimientos son positivos la autopercepción es mayor.

Existe relación directa entre el dolor del MMSS y el dolor raquídeo. La mayoría de los estudiantes no tienen miedo a sufrir lesiones si estas no se acompañan de dolor. Cuando tienen molestias o dolor, la mayoría evita el ejercicio continuo. Los que no hacen ejercicio intenso de forma habitual sienten dolor en MMSS más que los que hacen ejercicio suave (73.7% frente a 90.0%) y, que los que hacen ejercicio moderado (41.7%). El dolor muscular, dolor en MMSS y dolor raquídeo están relacionados con la frecuencia de la actividad física realizada ($p = .001$; $p = .001$; $p = .003$) y con el nivel de dicha actividad ($p = .008$; $p = .003$ $p = .061$).

Tabla III: Relación de las variables del estudio con el instrumento utilizado.

Cuestiones planteadas en la encuesta*	Cuerda pulsada n (%)	Viento-metal n (%)	Cuerda frotada n (%)	Viento-madera n (%)	Total n (%)	P (tamaño del efecto)
1. ¿Haces ejercicios de calentamiento antes de comenzar la sesión de estudio?	8 (57.1)	34 (87.2)	6 (46.2)	12 (52.2)	60 (67.4)	.005* (.378)
2. ¿Haces ejercicios de estiramientos o relajación muscular al finalizar la sesión?	3 (21.4)	16 (41.0)	6 (46.2)	7 (30.4)	32 (36.0)	-
3. ¿Sufres algún tipo de dolor muscular?	12 (85.7)	16 (41.0)	13 (100)	19 (82.6)	60 (67.4)	.001* (.511)
4. ¿La zona de dolor es en el miembro superior?	11 (78.6)	10 (25.6)	12 (92.3)	15 (65.2)	48 (53.9)	.001* (.529)
5. ¿La zona de dolor es en la espalda?	12 (85.7)	15 (38.5)	11 (84.6)	17 (73.9)	55 (61.8)	.001* (.433)
6. ¿La zona de dolor es en el miembro inferior?	3 (21.4)	2 (5.1)	0 (0)	0 (0)	5 (5.6)	-
7. ¿Tienes miedo a realizar deporte por si sufres una lesión que te impida continuar tocando?	4 (28.6)	11 (28.2)	8 (61.5)	7 (30.4)	30 (33.7)	-
8. ¿Realizas ejercicio continuo más de 30 minutos al día?	2 (14.3)	24 (61.5)	4 (30.8)	7 (30.4)	37 (41.6)	.006* (.375)
9. ¿Te sientes mejor tocando si estás en buena forma física?	10 (71.4)	36 (92.3)	8 (61.5)	18 (78.3)	72 (80.9)	-
11. Zona de dolor de MMSS	Mano M 5 (35.7) Codo 1 (7.1) Hombro 5 (35.7) Sin dolor 3 (21.4)	Mano M 2 (5.1) Codo 1 (2.6) Hombro 7 (17.9) Sin dolor 29 (74.4)	Mano M 5 (38.5) Codo 2 (15.4) Hombro 5 (38.5) Sin dolor 1 (7.7)	Mano M 9 (39.1) Codo 0 (-) Hombro 6 (26.1) Sin dolor 8 (34.8)	Mano M 21 (23.6) Codo 4 (4.5) Hombro 23 (25.8) Sin dolor 41 (46.1)	-
12. Zona de dolor en la espalda	Cervical 7 (50.0) Dorsal 3 (21.4) Lumbar 2 (14.3) Sin dolor 2 (14.3)	Cervical 6 (15.4) Dorsal 2 (5.1) Lumbar 7 (17.9) Sin dolor 24 (61.5)	Cervical 7 (53.8) Dorsal 3 (23.1) Lumbar 1 (7.7) Sin dolor 2 (15.4)	Cervical 11 (47.8) Dorsal 1 (4.3) Lumbar 5 (21.7) Sin dolor 6 (26.1)	Cervical 31 (34.8) Dorsal 9 (10.1) Lumbar 15 (16.9) Sin dolor 34 (38.2)	-
13. ¿Cuántos días a la semana realizas ejercicios?	0: 6 (46.2) 1-3: 6 (46.2) >4: 1 (7.7)	0: 4 (12.9) 1-3: 11 (35.5) >4: 16 (51.6)	0: 2 (16.7) 1-3: 7 (58.3) >4: 3 (25.0)	0: 9 (42.9) 1-3: 10 (47.6) >4: 2 (9.5)	0: 21 (27.3) 1-3: 34 (44.2) >4: 22 (28.6)	.006* (.342)
14. ¿Qué tipo de ejercicio realizas?	Ninguno: 5 (37.5) Suave: 1 (7.1) Moderado: 8 (57.1)	Ninguno: 4 (10.3) Suave: 4 (10.3) Moderado: 31 (79.5)	Ninguno: 2 (15.4) Suave: 2 (15.4) Moderado: 9 (69.2)	Ninguno: 8 (34.8) Suave: 3 (13) Moderado: 12 (52.2)	Ninguno: 19 (21.3) Suave: 10 (11.2) Moderado: 60 (67.4)	-
15. Consideras que tu nivel como intérprete es...	Media=3.21 Con viento metal díf=-.837, p=.011, IC (-1.54,-.13)	Media=4.05 Con cuerda frotada díf=.744, p=.041, IC (.02,1.47)	Media=3.31	Media=3.87	Media=3.76	.003* (.149)
16. ¿Cuál fue tu puntuación final en instrumento el curso anterior?	Bien: 2 (15.4) Notable: 5 (38.5) Sobres: 6 (46.2)	Bien: 2 (5.6) Notable: 8 (22.2) Sobres: 26 (72.2)	Bien: 2 (18.2) Notable: 4 (36.4) Sobres: 5 (45.5)	Bien: 1 (5.0) Notable: 7 (35.0) Sobres: 12 (60.0)	Bien: 7 (8.8) Notable: 24 (30.0) Sobres: 49 (61.3)	-

*En las preguntas 1-9, se incluyen los valores y porcentajes de las respuestas afirmativas (Si). En las preguntas 11-16 se incluyen los resultados para cada categoría de la variable. n= Frecuencias absolutas. %= Frecuencias relativas. Se considera significativo un valor de $p < 0,05$

Tabla IV: Estudio multivariante.

Cuestionario. Preguntas numeradas	1	2	3	4	5	7	8	13	14	9	15	16
1. ¿Haces ejercicios de calentamiento antes de comenzar la sesión de estudio?												
2. ¿Haces ejercicios de estiramientos o relajación muscular al finalizar la sesión?	-											
3. ¿Sufres algún tipo de dolor muscular?	$\chi^2(1)=9.68$.002* (.330)	-										
4. ¿La zona de dolor es en el miembro superior?	$\chi^2(1)=8.33$.004* (.306)	-	$\chi^2(1)=50.36$.001* (.752)									
5. ¿La zona de dolor es en la espalda?	$\chi^2(1)=5.59$.018* (.251)	-	$\chi^2(1)=69.59$.001* (.884)	$\chi^2(1)=34.07$.001* (.619)								
7. ¿Tienes miedo a realizar deporte por si sufres una lesión que te impida continuar tocando?	-	-	-	$\chi^2(1)=4.70$.030* (.230)	-							
8. ¿Realizas ejercicio continuo más de 30 minutos al día?	$\chi^2(1)=5.38$.020* (.246)	$\chi^2(1)=4.43$.035* (.223)	$\chi^2(1)=16.85$.001* (.435)	$\chi^2(1)=9.01$.003* (.318)	$\chi^2(1)=12.12$.001* (.369)	-						
13. ¿Cuántos días a la semana realizas ejercicios?	$\chi^2(2)=8.44$.015* (.331)	$\chi^2(1)=10.08$.006* (.362)	$\chi^2(1)=16.32$.001* (.460)	$\chi^2(1)=13.67$.001* (.421)	$\chi^2(1)=9.83$.007* (.357)	-	$\chi^2(2)=43.68$.001* (.753)					
14. ¿Qué tipo de ejercicio realizas?	$\chi^2(2)=10.38$.006* (.341)	$\chi^2(1)=8.27$.016* (.305)	$\chi^2(1)=9.69$.008* (.330)	$\chi^2(1)=11.85$.003* (.365)	$\chi^2(2)=5.59$.061 (.251)	-	$\chi^2(2)=19.70$.001* (.470)	$\chi^2(4)=69.58$.001** (.672)				
9. ¿Te sientes mejor tocando si estás en buena forma física?	$\chi^2(1)=3.96$.046* (.211)	-	$\chi^2(1)=4.15$.042* (.216)	$\chi^2(1)=6.83$.009* (.277)	-	-	$\chi^2(1)=4.95$.026* (.236)	$\chi^2(2)=12.28$.002* (.399)	$\chi^2(2)=18.33$.001* (.454)			
15. Consideras que tu nivel como intérprete es...	-	-	$t(87)=3.15$.001* (.713)	$t(87)=4.05$.001* (.861)	$t(87)=2.26$.013* (.492)	-	-	-	-	$t(87)=-2.16$.017* (.581)		
16. ¿Cuál fue tu puntuación final en instrumento el curso anterior?	-	-	$\chi^2(1)=5.78$.055* (.269)	-	$\chi^2(1)=7.41$.025* (.304)	-	-	-	-	-	-	-

χ^2 (Chi cuadrado). (gl. grados de libertad). T= t de student. p (tamaño del efecto). (-) No se incluyen los resultados no significativos o marginalmente significativos; o bien cuando no se cumplen los supuestos para realizar la prueba estadística.

Discusión

El presente estudio realizado en estudiantes de conservatorios de música muestra que, más de la mitad de ellos ya presentan dolor en esta etapa, especialmente en raquis y MMSS. La mayor prevalencia de dolor se localiza en raquis cervical, seguido de dolor de hombro y de muñeca-mano. No todos los estudiantes tienen una actitud adecuada frente al autocuidado, ni acostumbran a regular la intensidad de la práctica musical cuando comienzan las molestias.

Se observa relación entre el dolor muscular, práctica de ejercicio y nivel de intérprete, con diferencias significativas hombre/mujer y en función del instrumento que practica. Se constata que la realización de más de 30 minutos de ejercicio diarios tiene un efecto positivo, especialmente entre los hombres que son los que realizan mayor actividad física. Existe cierta sensación de miedo a realizar ejercicio cuando sienten dolor y se constata una relación positiva entre la práctica de actividad física moderada, más de 30 minutos/día, con parámetros relativos al autocuidado.

Las mujeres sufren más dolor que los hombres, siendo también más prevalente el dolor en MMSS, especialmente en el hombro. Estos resultados coinciden con lo reflejado en la bibliografía que destaca esta mayor prevalencia en mujeres, especialmente en localizaciones como raquis

dorso-lumbar y cervical y en MMSS, especialmente mano y brazo¹⁹, siendo independiente de la actividad desarrollada, por lo que constituye un problema de salud pública que debería tenerse en cuenta en estrategias preventivas futuras y en el manejo del dolor.

Las diferencias de género en el dolor y su manejo derivan de una interacción compleja de factores genéticos, anatómicos, fisiológicos, neuronales, hormonales, psicológicos y sociales que modulan el dolor de manera específica en cada sexo²⁰, determinando una mayor o menor predisposición a la cronificación del mismo²¹. Es esencial incorporar análisis de género/sexo en la investigación de esta problemática para poder avanzar hacia abordajes personalizados más efectivos²².

En nuestro trabajo se constata que las mujeres refieren sufrir más dolor muscular, probablemente debido a una combinación de factores sociales, culturales, económicos y de género existentes en este ámbito profesional²³, aunque en la práctica musical no se han perfilado claramente los factores que pueden influir de forma más destacada²⁴. El dolor referido a MMSS es claramente más prevalente en mujeres, hecho que ya se había constatado en estudios previos, al igual que el localizado en columna cervical²⁵ coincidiendo con lo detectado también entre nuestros estudiantes.

Nuestro estudio concuerda con otros realizados entre estudiantes de conservatorio en cuanto a la alta prevalencia de dolor de la columna cervical en ambos sexos^{26,27}, destacando la necesidad de tratamiento fisioterapéutico integral. Los estudiantes relacionan sus dolencias con el trabajo y con los instrumentos utilizados²⁸. En nuestro estudio, solo la mitad de los participantes realizaban ejercicio físico habitual de moderada intensidad. Un 67.4% realiza ejercicios de calentamiento previo y sólo un 36.0% estiramientos o relajación al final de la práctica musical con su instrumento. Los que realizaban calentamiento previo y estiramientos tenían menos dolor muscular y eran más conscientes de la importancia del autocuidado. Este es un tema que se debe abordar ya desde los centros educativos y formar parte de investigaciones futuras, con una visión de género dadas las diferencias observadas entre hombres y mujeres^{29,30}.

Aspectos como la autoexigencia, la tensión psicológica y las horas de práctica y estudio que requieren los músicos hace que permanezcan en la misma posición durante mucho tiempo y son factores a considerar, no sólo durante la formación académica, sino también a lo largo de la posterior vida profesional. La bibliografía muestra que, los hombres son sistemáticamente más activos físicamente que las mujeres, independientemente de la edad o de su actividad profesional³¹ decantándose por actividades deportivas³², coincidiendo también con los resultados obtenidos en este trabajo que hemos realizado entre estudiantes de música.

Los resultados de nuestro estudio permiten confirmar que el ejercicio minimiza las consecuencias de las posturas forzadas, necesarias en la práctica musical aunque, sería preciso comprobar estos resultados en poblaciones más amplias tanto de estudiantes como de músicos profesionales.

La relación dolor y ejercicio muestra que los estudiantes sufren más dolor cuando realizan menos ejercicio y que, el dolor, a su vez limita la propia actividad física. El ejercicio moderado y frecuente parece tener una relación más positiva en lo relativo a la disminución del dolor que el ejercicio suave. El no sentir dolor hace que el estudiante tenga menos miedo a lesionarse con la actividad física.

Un dato relevante en este estudio es que, los que no tienen sentimientos positivos como músicos, esto es, no se sienten bien tocando, tienen más sensación de dolor. Los que no hacen ejercicio continuo tienen menos sentimientos positivos como profesionales y, de forma contraria van aumentando según se incrementa la frecuencia e intensidad de la actividad física.

En nuestro trabajo se observa una relación significativa entre el dolor derivado de la actividad musical y el instrumento utilizado. Esto se había constatado ya en otros trabajos que relacionaban el dolor de espalda, cuello y hombros con los músicos de viento y cuerda frotada³³.

Nuestros resultados orientan a establecer como prioritario en el abordaje de la formación de los músicos y, desde los propios centros académicos, la implementación de contenidos que orienten hacia la prevención de lesiones y al dolor que conllevan, limitante de su actividad.

La experiencia de otros autores muestra que, la adaptación de un programa de ejercicios hecho a medida para cada músico, según el instrumento que utilice es capaz de reducir las lesiones inducidas por la práctica musical, disminuyendo así la tensión y el estrés muscular³⁴. Las diferencias observadas por instrumento se deben probablemente a la postura asimétrica adoptada³⁵ por lo que, en el proceso de aprendizaje se deben considerar medidas tendentes a mejorar la simetría y estabilidad como factores de riesgo³⁶ que inducen la aparición de lesiones³⁷.

Las conclusiones de nuestro trabajo, en concordancia con lo recogido en la bibliografía previamente, muestran la necesidad de realizar intervenciones educativas en los músicos para que sean capaces de reconocer los primeros signos de una lesión, y no retrasar la búsqueda de atención médica o fisioterapéutica, de manera que se puedan tomar las medidas necesarias de forma temprana para limitar los daños^{38,39}.

Otra cuestión que abordamos es la planificación del estudio y la prevención de lesiones. Nuestro trabajo destaca que la mayoría de los alumnos se organiza en función de los objetivos que se marcan para mejorar los resultados. Entre los estudiantes de nuestro trabajo, una parte de ellos, aunque no de forma mayoritaria hacen ejercicios de relajación. Estudios previos al nuestro han mostrado su capacidad para mejorar los resultados en cuanto al afrontamiento de la ansiedad escénica⁴⁰, tanto con ejercicios básicos con técnicas de control mediante respiración profunda⁴¹, como mediante actividades cuerpo-mente como el yoga⁴².

Realizar ejercicios de calentamiento previos al comienzo de la actividad musical reduce el dolor por sobrecarga muscular, si bien no excluye la posibilidad de tenerlo, pero en menor porcentaje, tal y como ya se ha constatado en nuestro trabajo y también afirmado por otros autores⁴³, que ratifican la relación positiva entre calentar la musculatura previamente a la práctica musical y la posibilidad de sufrir dolor de espalda.

En nuestro estudio, los que no hacen ejercicios de relajación tampoco realizan actividad física de forma continua. Los que sí que lo hacen, suelen ser más responsables de la necesidad de autocuidado y tienen una visión más preventiva de su actividad profesional. Hacer o no ejercicio parece no modificar el resultado final en cuanto a rendimiento académico, sin embargo, las condiciones musculoesqueléticas del músico en edad estudiantil pueden comenzar a verse afectadas en estas etapas tempranas y condicionar su futuro en la carrera musical.

La bibliografía muestra que la prevalencia del dolor es alta entre los músicos. Esto lleva a plantear la necesidad de políticas conjuntas, sanitarias y educativas, de modo que se investiguen los mecanismos asociados al dolor y se diseñen e implementen estrategias para su prevención⁴⁴.

Si bien se ha reconocido que la práctica e interpretación de un instrumento puede llegar a ser dolorosa y perjudicial, los estudiantes afirman no recibir instrucciones sobre técnicas de buenas prácticas, posturas adecuadas y cuidado de su cuerpo⁴⁵. Esto puede explicar la elevada prevalencia de TME en este grupo de población, con impacto y consecuencias en la capacidad de interpretación y el riesgo de posterior cronificación generando limitaciones. Algunos autores han publicado resultados esperanzadores tras realizar programas de intervención mediante ejercicios de fortalecimiento y flexibilidad con estiramientos y calentamiento/enfriamiento. Los resultados mostraron buena aptitud física y buena conexión mente-cuerpo-rendimiento⁴⁶. Sin embargo, la mayoría de los músicos en formación apenas reciben educación en salud orientada a la prevención de lesiones⁴⁷.

Vistos los resultados de este trabajo, parece claro que la formación del músico es importante, no solo a nivel de técnica musical, sino en prevención de lesiones, adopción de buenas estrategias de estudio, refuerzo mental y motivacional, junto con el complemento de actividad física para obtener el mejor estado de salud global, tanto física, como mental.

Programas de ejercicios de fuerza y resistencia realizados dos veces por semana durante un mínimo entre 35 y 40 minutos han mostrado disminuir la intensidad y el impacto de los síntomas de dolor en los músicos⁴⁸. Existen varias opciones para el manejo del dolor: desde aspectos formativos, terapia manual, fisioterapia convencional o el apoyo de fármacos⁴⁹, entre otros. La combinación de varias formas de tratamiento ha mostrado ser más eficaz que aplicarlas de forma independiente.

Una cuestión preocupante es que las mujeres tengan una percepción de su nivel como intérpretes más baja que los hombres. Esto también se observa entre músicos jóvenes⁵⁰. Esta menor valoración es mayor que la observada en otros grupos profesionales⁵¹, lo que podría influir de forma paralela en su percepción de habilidades, confianza profesional y bienestar general.

Limitaciones del Estudio

Una de las principales limitaciones en este estudio ha sido el tamaño muestral, sin embargo, parece un buen punto de partida, al mostrar tendencias que pueden orientar al manejo preventivo de los riesgos asociados a TME y de salud mental en estudiantes de música, ya desde estas etapas tan tempranas y, con ello permitir diseñar estrategias orientadas a este subgrupo profesional de estudiantes con la opción de que, los hábitos adoptados en esta etapa formativa se mantengan posteriormente en su etapa como músicos profesionales.

Considerando la alta prevalencia de TME observada entre los estudiantes de nuestra muestra y, en concordancia con lo observado en estudios similares es necesario incidir en las medidas de prevención desde la etapa de estudiantes y con programas para el cuidado de su salud física y mental que se integren en su ciclo formativo⁵².

Conclusiones

- La actividad física regular, el calentamiento previo a la práctica musical, la planificación del tiempo de estudio y las técnicas de relajación son aspectos básicos para mantener un estado físico y mental adecuado en la etapa de estudiante, así como para mantenerlas posteriormente en su ejercicio como músico profesional.
- La formación de los músicos en los conservatorios necesita incorporar aspectos de prevención de lesiones y atención a la salud mental que limiten en el futuro su actividad profesional.
- La formación preventiva ha de adaptarse al instrumento utilizado e incorporar una visión de género.
- Se necesitan investigaciones que contemplen estos aspectos y que refuercen los resultados obtenidos en este trabajo con muestras más amplias y, reforzados con valores cualitativos y cuantitativos.

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Conflictos de interés

Los autores declaran no tener conflictos de intereses.

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ORIGINAL

Effects of Botulinum Toxin on Chewing Function, Orofacial Pain, and Nutritional Status: A Follow-Up Study

Efectos de la toxina botulínica en la función masticatoria, el dolor orofacial y el estado nutricional: Un estudio de seguimiento

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Abstract

Background: Botulinum toxin (BoNT) is increasingly used to manage orofacial pain and masticatory dysfunction, though its long-term effects in different areas remain uncertain.

Objectives: This study aimed to assess BoNT's effects on masticatory performance, orofacial pain, and nutritional status in patients with orofacial pain disorders over six months.

Methods: This prospective study was conducted in the Department of Surgery from May 2022 to May 2024. Demographic data, masticatory performance, orofacial pain scores, anthropometric measurements, dietary intake, and Diet Quality Index (DKI-I) were evaluated. Masticatory performance was assessed with color-changeable chewing gum, and orofacial pain was measured using the Fonseca Anamnestic Index (FAI) and Visual Analog Scale (VAS). Dietary intake was evaluated via a 24-hour recall at baseline (T0), 7th day (T1), 1st month (T2), 2nd month (T3), 3rd month (T4), and 6th month (T5), with anthropometric measurements taken at T0 and T5.

Results: Nineteen TMD patients (84.2% female, mean age 32.2 ± 8.3 years) were included. Masticatory performance significantly decreased from T0 to T2 and T2 to T5 ($p < 0.001$). FAI and VAS scores decreased from T0 to T5 ($p < 0.05$). After T5 body fat parameters and body mass index increased significantly ($p < 0.05$). B12 and zinc intake differed significantly between T0 and T2 ($p < 0.05$), while DKI-I scores showed no significant changes ($p > 0.05$).

Conclusion: BoNT injections reduced masticatory performance and orofacial pain over six months. However, body weight increased despite unchanged food intake. Further studies with larger samples should explore causes of weight gain. The protocol of the study was registered at the website of clinical trials (<https://clinicaltrials.gov/>) with name Botulinum Toxin Administration on Masticatory Performance and identifier number NCT05562531.

Key words: Temporomandibular Joint Disorders, Botulinum Toxin, Dietary Habits, Nutritional Status, Orofacial Pain, Body Mass Index.

Resumen

Antecedentes: La toxina botulínica (BoNT) se utiliza cada vez con mayor frecuencia para el tratamiento del dolor orofacial y la disfunción masticatoria, aunque sus efectos a largo plazo en distintas áreas aún no están completamente determinados.

Objetivos: Este estudio tuvo como objetivo evaluar los efectos de la BoNT sobre el rendimiento masticatorio, el dolor orofacial y el estado nutricional en pacientes con trastornos de dolor orofacial durante un período de seis meses.

Métodos: Este estudio prospectivo se llevó a cabo en el Departamento de Cirugía desde mayo de 2022 hasta mayo de 2024. Se evaluaron datos demográficos, rendimiento masticatorio, puntuaciones de dolor orofacial, mediciones antropométricas, ingesta dietética y el Índice de Calidad de la Dieta (DQI-I). El rendimiento masticatorio se evaluó mediante goma de mascar que cambia de color, y el dolor orofacial se midió utilizando el Índice Anamnésico de Fonseca (FAI) y la Escala Visual Analógica (VAS). La ingesta dietética se analizó mediante un recordatorio de 24 horas en los siguientes momentos: línea de base (T0), día 7 (T1), mes 1 (T2), mes 2 (T3), mes 3 (T4) y mes 6 (T5); mientras que las mediciones antropométricas se realizaron en T0 y T5.

Resultados: Se incluyeron diecinueve pacientes con trastornos temporomandibulares (84.2% mujeres, edad media 32.2 ± 8.3 años). El rendimiento masticatorio disminuyó significativamente de T0 a T2 y de T2 a T5 ($p < 0.001$). Las puntuaciones FAI y VAS disminuyeron de T0 a T5 ($p < 0.05$). Al finalizar el período (T5), los parámetros de grasa corporal y el índice de masa corporal aumentaron significativamente ($p < 0.05$). La ingesta de vitamina B12 y zinc mostró diferencias significativas entre T0 y T2 ($p < 0.05$), mientras que las puntuaciones del DQI-I no mostraron cambios significativos ($p > 0.05$).

Conclusión: Las inyecciones de BoNT redujeron el rendimiento masticatorio y el dolor orofacial a lo largo de seis meses. Sin embargo, se observó un aumento del peso corporal a pesar de no registrarse cambios en la ingesta alimentaria. Se requieren estudios adicionales con muestras más amplias para explorar las posibles causas de este aumento de peso. El protocolo del estudio fue registrado en el sitio web de ensayos clínicos (<https://clinicaltrials.gov/>) bajo el nombre *Botulinum Toxin Administration on Masticatory Performance* y el número de identificación NCT05562531.

Palabras clave: Trastornos de la Articulación Temporomandibular, Toxina Botulínica, Hábitos Alimentarios, Estado Nutricional, Dolor Orofacial, Índice de Masa Corporal.

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Background

Temporomandibular disorders (TMDs) have been studied extensively since the 20th century due to their significant impact on patient health. American Association for Dental, Oral, and Craniofacial Research (AADOCR) defines TMDs as a group of musculoskeletal and neuromuscular conditions affecting the temporomandibular joint (TMJ), masticatory muscles, and associated tissues¹. These disorders are a major cause of chronic orofacial pain, ranking third after headaches and back pain². The prevalence of TMDs varies from 21.1% to 73.3%, depending on the diagnostic criteria and methodologies^{3,4}.

TMDs are characterized by pain in the masticatory muscles and/or TMJ, along with symptoms such as joint clicking, articular noise, and restricted mandibular movement⁵. Other symptoms include myofascial tenderness, headaches, and tinnitus^{6,7}. Myofascial pain is caused by parafunctional habits, postural problems, and psychological factors, involving painful trigger points in the muscles⁸.

Bruxism, a repetitive jaw-muscle activity involving clenching or grinding of the teeth, is a significant contributor to TMDs and shares a myogenic origin with these disorders¹. It leads to increased activity in the masticatory muscles, which may cause pain and functional limitations⁹. The psychogenic component of bruxism, is linked to stress and anxiety. Similarly, TMDs are frequently myogenic in origin, and this shared pathophysiology is reflected in the Research Diagnostic Criteria for TMD (RDC/TMD), which classifies both disorders under Axis I¹⁰. Despite the complexity of their pathophysiology, the common myogenic involvement in both conditions plays a central role in symptom development⁹.

In addition to pain and muscle dysfunction, TMD patients often modify their diets in response to discomfort and functional limitations. Studies have shown that they tend to avoid hard or chewy foods, which reduces fiber and nutrient intake and may lead to nutritional deficiencies⁹⁻¹¹. Deficiencies in vitamins and minerals, such as vitamin C, magnesium, and zinc, have been linked to pain and difficulty managing TMD symptoms^{9,12}. These dietary changes can worsen the chronicity of TMD by contributing to neuropathic pain, complicating the patient's overall health¹¹. It is also noted that TMD patients, particularly those with pain, often experience nutritional deficiencies, which may contribute to the condition's persistence^{9,10,13}.

Management of bruxism and TMD typically involves a combination of physical therapy, occlusal splints, and pharmacological interventions¹. Botulinum toxin (BoNT), derived from *Clostridium botulinum*, has emerged as an effective alternative for bruxism treatment¹⁴. BoNT works by inhibiting acetylcholine release at the neuromuscular junction, reducing muscle contractions and alleviating symptoms. Type A botulinum toxin (BoNT-A) has shown

promise in controlling bruxism-related muscle activity, particularly in cases where other treatments have been less effective^{14,15}.

While many studies have investigated the use of BoNT for bruxism, research on optimal injection protocols, such as dosage, dilution, and injection sites within the masticatory muscles, is still limited^{16,17}. Additionally, the effects of BoNT on chewing function, dietary habits, and nutritional status in TMD patients with bruxism have not been fully explored. This study aims to assess the impact of BoNT injections on masticatory performance, nutritional status, and related factors such as pain and anxiety in TMD patients with bruxism.

Methods

This prospective study was conducted at the Marmara University School of Dentistry, Department of Oral, Dental, and Maxillofacial Surgery, between May 2022 and May 2024.

Before their participation, written informed consent was obtained from all study participants. TMD diagnosis was confirmed using RDC/TMD criteria¹⁸, and only those with Axis I symptoms, such as myofascial pain and temporomandibular joint disorders, were included. Inclusion criteria required patients to be 18-50 years old, diagnosed with TMD, and considered candidates for botulinum toxin (BoNT) therapy, exhibiting marked masticatory muscle tension or spasticity, and having overall health compatible with study participation (e.g., absence of severe systemic disease). Further requirements included literacy, effective communication, completion of at least three months of ineffective splint therapy, a class I molar relationship, no removable prostheses, documented myofascial pain, bruxism, and informed consent. Exclusion criteria were individuals without a TMD diagnosis or significant masticatory muscle symptoms, prior BoNT treatment within six months, injection site infections, and conditions associated with systemic neuropathy (e.g., diabetes, renal disease, cardiovascular disorders, or immune conditions). Patients were also excluded if they had a malignancy history, recent radiotherapy or chemotherapy, pregnancy, lactation, or known BoNT allergies or adverse reactions. Exclusions extended to patients with inconsistent study attendance, significant psychiatric disorders, or those initiating treatments likely to affect masticatory function during the study. Additionally, patients with a Beck Anxiety Inventory (BAI) score of 8 or above were excluded¹⁹.

Instruments and Evaluation

A questionnaire form was utilized in the study, covering demographic characteristics (e.g., gender, education, profession, income, comorbidities), nutritional habits (number of meals, frequency and reasons for skipping meals), subjective chewing difficulties (foods perceived

as difficult to chew and the ability to chew listed items), the Visual Analogue Scale (VAS), the Fonseca Anamnestic Index (FAI), and a 24-hour dietary recall form. VAS and FAI scores were all recorded by the same researcher, while masticatory performance, assessed using color-changing chewing gum, was evaluated by three researchers. Anthropometric measurements were taken by experienced dietitians.

The study timeline included the day of the operation (T0), followed by assessments on the 7th day (T1), and at 1 month (T2), 2 months (T3), 3 months (T4), and 6 months (T5) post-operation. (**Supplementary table I**).

Fonseca Anamnestic Index

The Fonseca Anamnestic Index, developed by Fonseca et al., serves as a tool for assessing temporomandibular disorders (TMD) based on clinical signs and symptoms.²⁰ It offers a straightforward, rapid, user-friendly, and cost-effective method of evaluation. The Turkish version of the FAI has been validated for reliability and diagnostic accuracy by Kaynak et al.²¹. The index comprises 10 items, each with three response options (yes, sometimes, and no), scored as follows: 10 points for "yes," 5 for "sometimes," and 0 for "no." Total scores range from 0 to 100 and are categorized as follows: no TMD (0-15), mild (20-40), moderate (45-65), and severe TMD (70-100).

Visual Analog Scale

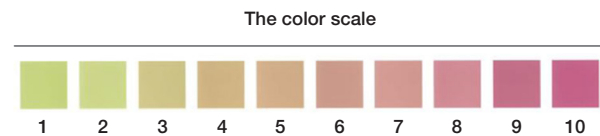
The Visual Analogue Scale (VAS) is a continuous self-report scale used to measure pain intensity. It consists of a 10 cm line, presented horizontally, with anchor points labeled as "no pain" and "worst possible pain"²². Patients are instructed to mark the point on the line that best represents their pain severity. Pain is classified as follows: 0-10 mm for "no pain", 10-30 mm for "mild pain", 30-70 mm for "moderate pain," and 70-100 mm for "severe pain."

Masticatory Performance

Masticatory performance was assessed using color-changeable gum, specifically designed for this purpose, known as "XYLITOL" (70 x 20 x 1 mm, 3 g; Masticatory Performance Evaluating Gum XYLITOL, Lotte, Tokyo, Japan)^{23,10}. This gum, which changes color as it is chewed, allows for an objective evaluation of masticatory function. Patients with TMD chewed the gum 60 times, after which its color was assessed independently by

three researchers using a standardized color scale, both visually and photographically. The color scale ranged from 1 to 10, categorizing masticatory performance as poor (scores 1-6), normal (scores 7-8), or good (scores 9-10) (**Figure 1**)²⁴.

Figure 1: The color scale The color scale ranged from 1-10, and the masticatory performance was evaluated as poor (1-6), normal (7-8), or good (9-10) with the improved color scale²⁵.



Chewing ability

Chewing ability was subjectively assessed using a modified questionnaire from the literature^{25,26}. This assessment included soft foods (bread, pasta, rice, feta cheese, meatball, boiled carrots, boiled vegetables) and hard foods (whole pieces of meat, fried chicken, peeled apple, raw carrot, almond, chocolate pieces). Participants responded to closed-ended questions, rating their ease of chewing as "Easy to chew," "Eat with some difficulty," or "Eat with extreme difficulty/could not chew at all"^{25,26}.

Assessment of Nutritional Status

Participants' food consumption status was assessed utilizing the 24-hour dietary recall method. This method involves individuals recalling and documenting the foods and beverages they consumed over a day on a form. Participants provided detailed information, including names and quantities of foods and beverages, and for packaged items, type, brand name, and quantity. The amount of nutrients included in the meals were calculated by using a photographic atlas of the food portion size²⁷.

The daily energy and nutrient intake of participants was determined using the Nutrient Database (BeBIS, BEBIS Pro for Windows, Willstaett, Germany; Turkish Version, BeBiS 9). The quality of the participants' diets was assessed using the Diet Quality Index - International (DKI-I), which was developed by Kim et al.²⁸. DKI-I contains 2 different components: General nutrient and food group diversity. The DKI-I includes eight nutrient combinations such as total fat, saturated fat, cholesterol, vegetables and fruits, cereals and legumes, protein, sodium and calcium. The variables are scored separately in four different groups: diversity, adequacy, content, and

Supplementary Table I: Timeline of the study.

T(0) Operation day	Operation Notes, Anthropometric Measurements, VAS, FAI, BAI, Masticatory Performance Test, 24-hour recall form
T(1) Postop 7th day	VAS and FAI
T(2) Postop 1st month	VAS, FAI, Masticatory Performance Test, and 24-hour recall form
T(3) Postop 2nd month	VAS and FAI
T(4) Postop 3rd month	VAS and FAI
T(5) Postop 6th month	Anthropometric Measurements, VAS, FAI, Masticatory Performance Test, 24-hour recall form

The timeline of the study was operation day (T0), 7th day (T1), 1st month (T2), 2nd month (T3), 3rd month (T4), and 6th month (T5) after the operation. VAS: Visual Analog Scale, FAI: Fonseca Anamnestic Index, BAI: Beck Anxiety Index

balance. During the evaluation, diversity is scored over 0-20 points and the diversity of food groups and protein source foods is questioned. Adequacy is assessed on a 0-40 point scale and is calculated by comparing daily consumption of vegetables and fruits, cereals, grains, fiber, and protein with the daily reference value of iron, calcium minerals and vitamin C. The amount of balanced consumption is scored over 0-30 points and when the content is analyzed, total fat, saturated fat, cholesterol, sodium, and daily consumption of empty energy sources are evaluated. Finally, the content evaluation is calculated over 0-10 points and the macronutrient and fatty acid ratio is questioned. The total value varies between 0-100. A score above 60 indicates that the diet quality is 'good'²⁸.

Anthropometric Measurements

Experienced dietitians took anthropometric measurements (body composition analysis, height, body weight) according to the standardized protocols. The height of patients was taken using a stadiometer with the nearest 0.1 cm, while each participant was standing erect against the wall with heels together touching the wall, without shoes. Body composition was analyzed by Tanita DC-360 (Accurate Technology Co., Ltd. Tianjin, China) according to the standard procedure, and the body weight, percentage of body lean mass, and fat of the participants were recorded. Body mass index (BMI) was calculated using weight (in kilograms) divided by the height squared (in square meters). BMI was categorized based on the World Health Organization's cut-offs: an underweight for adults was defined as a BMI less than 18.5 kg/m², healthy (normal) weight as a BMI from 18.5 to less than 25 kg/m², overweight as a BMI 25 to less than 30 kg/m², obese as a BMI 30 or greater²⁹.

Botulinum Toxin Application

The standard dilution ratio used was 2 mL of normal saline into 100 units of BT. The BT product used in this study was Botox® (onabotulinumtoxinA: Btx; Allergan, Dublin, Ireland), administered in doses of [30 units per side]^{30,31}. Botox® is a well-established product for therapeutic applications, and its dosing can be tailored based on clinical needs and individual patient characteristics.

Before starting the procedure, the patient was asked to clench their teeth and hold for a while to mark the anterior border and the most prominent area of the masseter muscle. A line was drawn from the tragus to the corner of the mouth to define the upper boundary, and the lower boundary was marked to be 2 cm away from the lower border of the mandible to avoid any damage to the mandibular nerve. The most prominent points of the masseter muscle were marked at three equidistant locations. Botulinum toxin was injected perpendicularly into the muscle using a 1-cc 27G syringe. This process was repeated for three points on each side. A total of 30 units of botulinum toxin were used for each muscle. An ice compress was applied for 5 minutes post-injection to control bleeding.

When patients came in for follow-up sessions, no additional doses or injections at different sites were administered.

All patients were regularly followed up for 6 months after treatment, and no negative side effects were observed. Therefore, this method is considered a safe and effective option for managing issues related to masticatory muscles³². Despite the generally positive outcomes, potential side effects of botulinum toxin treatment include muscle weakness, facial asymmetry, temporary facial changes (such as swelling or bruising), mild pain, dry mouth, difficulty swallowing, and headaches³³. These side effects are typically transient and resolve on their own within a few days³⁴.

Statistical Analysis

Study data were evaluated with the statistical program SPSS 24.0 (Statistical Package for the Social Sciences, Inc., Chicago, Illinois, United States). Categorical data were expressed as the frequency (percentage), and differences were analyzed using Fisher's exact test (when including any expected p-value ≤ .05) or the chi-square test. The Kolmogorov-Smirnov test was used to assess whether the data were normally distributed. Differences in continuous variables were analyzed using ANOVA for normally distributed data, while the Friedman test was applied to non-normally distributed data. For all statistical tests, a p-value of < 0.05 was considered statistically significant.

Results

The demographic characteristics of the 19 TMD patients who completed the study are presented in **table 1**. The cohort comprised predominantly female participants (84.2%), with a mean age of 32.2 ± 8.3 years. A substantial proportion held university degrees (78.9%) and were employed (84.2%). Additionally, 57.9% had a chronic condition, and 63.2% reported regular medication use. The majority of patients (68.4%) smoked and consumed alcohol. The mean number of main meals per day was 2.1 ± 0.6, while the average number of snacks was 0.8 ± 0.8.

Analysis between FAI and VAS pain scores indicated a moderate positive correlation at baseline (T0), with a Pearson correlation coefficient of 0.49 (p=0.027). At the T2, the correlation remained moderate (r=0.45, p=0.047). By the T3, the correlation strengthened considerably (r=0.69, p < 0.001). At the T4, the correlation diminished (r=0.38, p=0.102) and was not statistically significant. At the T5, a strong correlation was observed, indicated by a Spearman coefficient of 0.63 (p=0.004) (**Figure 2**).

The inter-observer correlation was evaluated by the Intraclass correlation coefficient (ICC). The ICC value was 0.925 (p < 0.001) for the naked-eye measurements and 0.899 (p < 0.001) for the photographic evaluations.

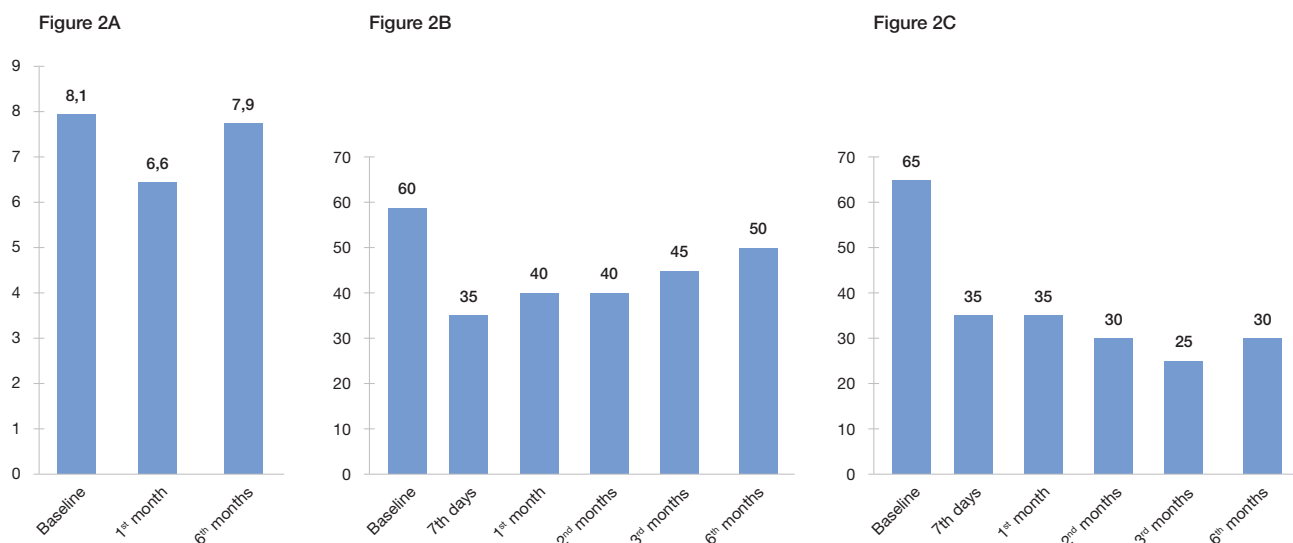
Table I: Participant characteristics (n: 19).

	Mean $\pm$ SD	
Age (year)	32.2 $\pm$ 8.3	
Height (cm)	163.2 $\pm$ 6.9	
	n	%
Gender		
Man	3	15.8
Woman	16	84.2
Marital status		
Single	10	52.6
Married	9	47.4
Education status		
College	4	21.1
University	15	78.9
Employment status		
Employee	16	84.2
Unemployed	3	15.8
Income status		
Income less than expenses	2	10.5
Income equals expense	6	31.6
Income more than expenses	11	57.9
Presence of another disease		
No	8	42.1
Yes	11	57.9
Drug use		
No	7	36.8
Yes	12	63.2
Cigarette use		
No	6	31.6
Yes	13	68.4
Alcohol use		
No	6	31.6
Yes	13	68.4
Main meals (mean $\pm$ SD)	2.1 $\pm$ 0.6	
Snacks (mean $\pm$ SD)	0.8 $\pm$ 0.8	

Table showing the socioeconomic characteristics of the participants.

Figure 2: Comparison of Masticatory Performance(A), FAI(B), and VAS(C) scores baseline to 6th months of botulinum toxin administration. (A) The masticatory performance was 8.1 at baseline and 7.9 at the 6th month (Figure 2A). There was a statistically significant difference in masticatory performance (values were given as median, $p < 0.001$, chi-square: 30.677, Friedman test was used, post hoc Wilcoxon test was used) between the baseline and 1st month and post-op 1st month and 6th month ($p < 0.001$). (B) FAI score decreased at post-op 6th months compared to baseline (Figure 2B). There is a statistical difference (values were given as median, $p = 0.004$, chi-square: 17.129, Friedman test was used, post hoc Wilcoxon test was used) between baseline and post-op 7th day, 1st month, 2nd months, 3rd months, and 6th months, and between 1st month and 6th months ($p < 0.05$). (C) VAS score decreased at post-op 6th months compared to baseline (Figure 2C). There is a statistical difference (values were given as median, $p < 0.001$, chi-square: 24.480, Friedman test was used, post hoc Wilcoxon test was used) between baseline and post-op 7th day, 1st month, 2nd month, 3rd month, and 6th month ($p < 0.05$).

Masticatory Performance, FAI, and VAS score assessment



FAI: Fonseca Anamnestic Index, VAS: Visual Analog Scale.

Anthropometric Assessment

Table II shows the anthropometric measurements of the participants at T0 and T5. Body weight ($p = 0.005$), BMI ($p=0.028$), body fat percentage ($p=0.013$), and fat mass ($p=0.022$) increased statistically significantly at the end of the T5 compared to the T0.

Energy and Nutrient Intakes and Diet Quality

Table III shows the energy and nutrient intakes of the participants T0, T2, and T5. B12 intake levels of the patients showed a statistically significant difference at T0 and T2 ($p=0.019$), whereas zinc intakes showed a significant difference at T0 and after T2 and after T2 and T5 ($p=0.028$). DKI-I scores didn't show a significant difference at time points ($p=0.223$). Those with good diet quality were 78.9% at T0, 100% at T2, and 73.7% at T5.

Table II: Anthropometric Measurements.

	T0	T5	Z value	P value
	Median (25. -75. Quarter)	Median (25. -75. Quarter)		
Body weight (kg)	58.50 (53.40-71.10)	60.20 (53.50-71.60)	-2.818	0.005*
Body mass index (kg/m ²)	22.40 (20.20-25.30)	23.20 (20.50-25.40)	-2.197	0.028*
Body fat percentage (%)	26.80 (19.20-30.90)	29.00 (20.10-32.60)	-2.476	0.013*
Fat mass (kg)	14.70 (10.90-21.20)	15.90 (10.50-22.30)	-2.295	0.022*
Lean body mass (kg)	42.70 (40.70-48.70)	43.00 (40.40-48.10)	-0.457	0.647
Muscle mass (kg)	40.90 (38.45-52.70)	40.70 (38.30-51.60)	-1.527	0.127
Total body fluid (kg)	31.00 (29.20-35.70)	31.20 (29.40-35.20)	0.000	1.000

Comparison of anthropometric measurements baseline (T0) and post-op 6 months (T5) of botulinum toxin administration. * $p<0.05$, the Wilcoxon test was used.

Table III: DKI-I scores, energy, and nutritional intakes.

	T0	T2	T5	P value
	Median (25. - 75. Quarter)	Median (25. - 75. Quarter)	Median (25. - 75. Quarter)	
DKI-I classification	n (%)	n (%)	n (%)	
Good (> 60 scores)	15 (78.9)	19 (100.0)	14 (73.7)	-
Poor (≤ 60 scores)	4 (21.1)	-	5 (26.3)	-
DKI-I score	87.04 (65.70-99.75)	83.45 (67.41-100.00)	82.80 (59.16-100.00)	0.223
Energy (kcal)	1192.08 (1022.10-1524.52)	1425.41 (1208.82-1724.65)	1438.40 (964.84-1838.46)	0.570
Protein (g)	56.97 (41.61-69.60)	57.92 (52.75-83.38)	49.79 (37.61-74.24)	0.269
Protein (E %)	18.00 (15.00-22.00)	17.00 (13.00-19.00)	15.00 (12.00-20.00)	0.164
Plant-based protein (g)	23.49 (16.04-34.33)	30.81 (19.47-34.53)	25.24 (13.62-35.59)	0.646
Animal protein (g)	27.44 (18.38-39.09)	32.27 (23.98-58.41)	27.40 (20.55-50.33)	0.368
Fat (g)	64.26 (38.57-84.98)	72.13 (65.62-114.18)	74.50 (50.11-114.19)	0.087
Fat (E %)	46.00 (37.00-51.00)	47.00 (44.00-55.00)	47.00 (40.50-59.50)	0.444
Saturated fatty acids (g)	22.29 (15.50-30.55)	24.91 (20.50-36.09)	24.55 (15.36-32.57)	0.444
MUFA (g)	23.15 (11.47-38.50)	30.51 (23.19-42.63)	29.41 (17.07-38.54)	0.087
PUFA (g)	8.57 (7.07-17.35)	17.57 (11.02-21.52)	12.67 (6.45-27.68)	0.779
Omega 3 (g)	0.97 (0.68-2.12)	1.32 (0.98-1.75)	1.16 (0.84-1.72)	0.269
Omega 6 (g)	7.05 (5.63-16.14)	14.85 (7.21-18.96)	11.45 (5.59-25.21)	0.829
Cholesterol (mg)	222.20 (128.05-358.65)	163.00 (114.75-488.35)	310.38 (225.78-377.17)	0.068
Carbohydrate (g)	96.39 (83.20-160.88)	112.05 (80.43-159.04)	128.26 (57.95-186.56)	0.939
Carbohydrate (% E)	35.00 (26.00-45.00)	33.00 (28.00-38.00)	31.00 (19.00-45.50)	0.538
Fiber (g)	13.99 (10.31-22.16)	15.72 (12.25-18.72)	16.29 (6.41-22.15)	0.939
Vitamin A (mcg)	719.55 (447.48-1435.07)	1054.70 (389.52-1482.15)	1102.37 (456.73-1647.46)	0.444
Vitamin E (mg)	8.41 (5.02-19.83)	11.55 (6.21-27.95)	14.41 (8.77-32.28)	0.444
Vitamin K (mcg)	58.54 (21.50-85.85)	66.00 (26.20-120.70)	66.45 (24.90-111.77)	0.779
Vitamin C (mg)	52.66 (24.59-73.40)	45.71 (12.86-130.53)	46.28 (23.45-130.41)	1.000
Vitamin B1 (mg)	0.61 (0.51-0.85)	0.93 (0.72-1.11)	0.63 (0.32-1.07)	0.269
Vitamin B2 (mg)	0.85 (0.49-1.32)	1.01 (0.86-1.40)	1.13 (0.63-1.59)	0.269
Vitamin B6 (mg)	0.97 (0.88-1.54)	1.14 (0.90-1.38)	1.04 (0.60-1.82)	0.939
Vitamin B12 (mcg)	2.88 (1.02-3.96)a	5.24 (2.85-5.92)a	2.84 (1.55-4.95)	0.019*
Vitamin B3 (mcg)	23.30 (15.48-30.55)	25.49 (18.88-34.79)	21.21 (13.24-37.21)	0.368
Vitamin B5 (mcg)	2.98 (2.48-5.21)	4.01 (3.05-5.16)	3.58 (2.77-5.82)	0.646
Biotin (mg)	36.93 (17.29-52.54)	35.12 (24.31-51.65)	38.29 (21.32-60.93)	0.210
Folic acid (mcg)	197.72 (143.40-291.50)	285.83 (164.95-355.05)	289.95 (113.32-436.87)	0.472
Sodium (mg)+	1544.54 (1189.62-2263.10)	1605.47 (1120.89-2845.70)	1545.50 (881.37-2225.58)	0.444
Potassium (mcg)	1742.63 (1374.34-2043.45)	2185.85 (1575.60-2840.25)	2028.30 (1253.25-2966.94)	0.174
Calcium (mg)	422.80 (314.15-580.50)	500.75 (368.30)	346.70 (217.47-659.11)	0.174
Magnesium (mg)	207.20 (145.25-250.85)	255.13 (195.80)	216.75 (111.04-330.14)	0.444
Phosphorus (mg)	842.16 (562.37-1153.70)	894.20 (727.47-1149.24)	808.55 (559.90-1013.25)	0.144
Iron (mg)	8.14 (5.52-11.02)	9.13 (5.36-12.56)	7.80 (5.56-12.36)	0.368
Zinc (mg)	7.47 (4.72-9.70)a	8.82 (7.71-13.17)a,c	8.44 (4.96-10.70)c	0.028*
Fructose (g)	7.14 (2.17-11.96)	2.46 (1.10-10.39)	8.37 (2.26-14.26)	0.939

Comparison of DKI-I scores, energy, and nutritional intakes baseline and post-op 1 and 6 months of Botulinum Toxin Administration.

* $p<0.05$, the Friedman test was used. +from foods. a Differences between baseline and 1st month, b Differences between T2 baseline and 6th month, c Differences between 1st month and 6th month, E: Energy, MUFA: Monounsaturated fatty acids, PUFA: Polyunsaturated fatty acids. DKI-I: Diet Quality Index – International

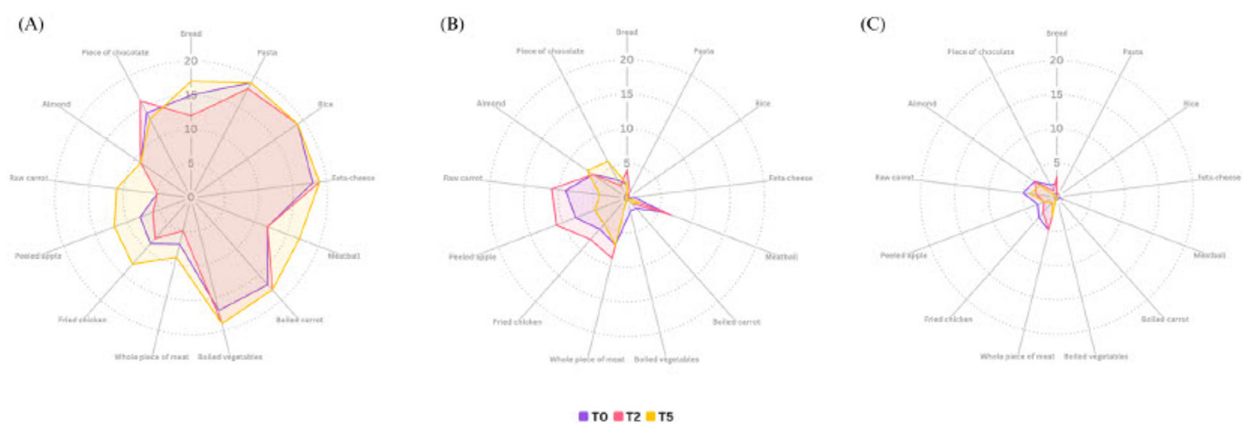
The Ability of the Patients' to Chew Soft and Hard Foods

Figure 3 shows the patients' ability to chew soft (bread, pasta, rice, feta cheese, meatball, boiled carrots, boiled vegetables) and hard foods (whole pieces of meat, fried chicken, peeled apple, raw carrot, almond, piece of chocolate). In T0, 57.9% of patients reported no difficulty chewing foods. However, 31.6% of patients experienced slight difficulty, and 5.2% reported difficulty chewing meatballs. At T2, 15.8% of patients experienced significant difficulty chewing bread. By T5, only 5.2% of patients reported slight difficulty chewing boiled carrots. When analyzing the ability to chew hard foods at T0,

47.4% of patients reported difficulty chewing raw carrots, 42.10% for peeled apples, and 36.8% for whole pieces of meat. Additionally, 31.6% of patients experienced difficulty chewing fried chicken, almonds, and hazelnuts, while 15.8% had difficulty chewing a piece of chocolate. At T2, 26.3% of patients experienced difficulty chewing whole pieces of meat, 4 patients for almonds and hazelnuts, 15.8% of patients for fried chicken and raw carrots, 10.5% patients for peeled apples, and 5.8% of patients for pieces of chocolate. By T5, 21.1% of patients indicated difficulty chewing raw carrots, 15.8% for pieces of meat, almonds, and hazelnuts, 10.5% for peeled apples, and 5.2% for fried chicken (**Figure 3**).

Figure 3: The patients' soft and hard food chewing status is given as a number. (A) Easy to chew, (B) A bit difficult, (C) Very difficult

The Ability of the Patients' to Chew Soft and Hard Food



Discussion

In this prospective observational study, we investigated the effects of BoNT injection on symptoms, masticatory performance, anthropometric measurements, and nutritional status over a 6-month follow-up period in patients with TMDs. The initial hypothesis of the study was partially accepted. Short-term decreases in pain and TMD symptoms were observed posttreatment, but these symptoms increased again toward the end of the follow-up period. Chewing performance decreased in the first month, followed by an improvement at the end of the follow-up. No significant changes were noted in muscle mass, but body weight, BMI, and body fat percentage increased, with no significant differences in nutritional habits.

Our hypothesis that symptom reduction would enhance dietary variety was not supported in this cohort. The absence of notable changes in energy, macronutrient, and micronutrient intake suggests that weight gain and alterations in body composition were not driven by dietary intake. These findings indicate that while BoNT therapy offers short-term improvements in pain relief,

masticatory performance, and body composition, its sustained efficacy appears limited and may influence metabolic processes. This study provides the first thorough assessment of anthropometric measures and nutritional status post-BoNT application, underscoring the significance of these results.

The results of this study demonstrate that BoNT application significantly reduced pain levels, with notable reductions observed at 7 days, 1 month, and 2 months post-treatment. However, pain levels rose again by the 6-month mark. These findings are consistent with the literature to some extent. For instance, previous research has shown that BoNT injections significantly improve quality of life and VAS scores in TMD patients at 1 and 3 months³⁵. Similarly, studies report that BoNT injections effectively reduce pain scores in TMD patients³⁶. A meta-analysis of fifteen randomized controlled trials with 504 participants further supports the efficacy of BoNT in alleviating pain and enhancing function at both 1 and 6 months³⁷. In contrast, another meta-analysis observed that while BoNT was effective in pain relief, it did not

improve maximum mouth opening when compared to placebo³⁸. Although our study did not assess mouth opening, this indicates that BoNT's effect on pain control does not necessarily lead to functional improvements.

At the same time, some meta-analyses have suggested that BoNT does not outperform placebo in reducing pain, improving maximum mouth opening, addressing bruxism, or increasing maximum occlusal force, highlighting the need for higher-quality randomized controlled trials³⁹. Our study, however, demonstrates that BT impacts masticatory performance by reducing masseter muscle tone and is effective in pain control, particularly in patients who show an early response to treatment. The discrepancies in the literature suggest that treatment outcomes may vary among individuals, and pain relief does not always correlate directly with TMD symptoms.

The inclusion of FAI alongside VAS provides a more comprehensive assessment of TMD⁴⁰. The multidimensional nature of FAI, which includes both pain and functional aspects, consistent well with the comprehensive evaluation required for TMD⁴¹ and may complement VAS in clinical settings. In our study, the application of BoNT resulted in significant improvement in the FAI, with substantial symptom relief observed at 7 days and 1 month post-treatment. However, symptoms worsened again at 3 and 6 months, suggesting that while BoNT offers short-term benefits for TMD dysfunction, the effects may diminish over time.

The correlation analysis between VAS and FAI showed variabilities in the relationship between TMD symptoms and pain levels throughout the treatment period. These variabilities may indicate that while BoNT provides a significant short-term improvement in TMD symptoms, the severity of symptoms is closely linked to pain levels. However, the reduction in pain at 3 months may have made symptoms less noticeable, thereby weakening this relationship. As the treatment effects decreased and symptoms recurred at 4 and 5 months, pain levels rose, and the correlation between FAI and VAS strengthened.

These findings are parallel with studies on TMJ disorders in fibromyalgia patients. Cakmakci and Demirci observed no significant correlation between FAI and VAS, suggesting that these tools may assess different aspects of TMD⁴². FAI focuses more on the presence and severity of TMD symptoms, while VAS specifically measures pain intensity. Therefore, the severity of TMD symptoms and pain levels do not always consistent. Our study reflects a similar trend, particularly the weakening of the correlation at 3 months, implying that symptoms may be perceived differently and are not always directly proportional to pain intensity.

Masticatory performance showed a significant decrease from baseline to the 1st month but improved again by the 6th month. This indicates that while BoNT may

affect muscle function in the short term, its effects diminish over time. Although BoNT reduces pain and muscle hyperactivity, it may also reduce masseter muscle density and occlusal force, potentially affecting chewing performance. Preclinical studies have shown that bilateral BoNT treatment of the masseter muscle resulted in reduced biting force and muscle size⁴³. These insights were supported by a meta-analysis of randomized controlled trials, which reported significant reductions in masseter muscle activity at 1 month and occlusal force at 3 months. The reduction in muscle activity and occlusal force was attributed to diminished chewing function³⁷. Our findings are consistent with these results, demonstrating that as the effects of the toxin wore off, masticatory performance began to improve after the 6th month.

The results regarding chewing ability are consistent with those on masticatory performance. A decrease was observed in the first month following BoNT application, but the ability improved significantly by the 6th month. This reveals that patients' chewing capacity was largely recovered by the end of the 6-month period.

Anthropometric measurements indicated an increase in body weight and BMI at 6 months following BoNT application. While significant increases were recorded in body fat percentage and fat mass, there was no significant change in muscle mass. These findings imply that BoNT may affect metabolic processes and body composition. When evaluated together with other studies, our results show that the effects of BoNT treatment on masseter muscle function are not directly related to body composition. A study by Tatli and Arslan involving 28 children found no correlation between masseter muscle thickness and BMI, illustrating that TMD symptoms and muscle function may develop independently of body composition⁴⁴. In our study, while BoNT treatment led to a temporary reduction in chewing performance, its effects on body composition were more prolonged. This signifies that alterations in masseter muscle function may occur independently of body composition changes.

The lack of variation in dietary intake despite increases in weight and BMI may indicate that reduced chewing efficiency could contribute to weight gain. A recent review suggests that improved chewing might reduce energy intake and influence hunger and satiety hormones, potentially contributing to weight gain due to insufficient chewing⁴⁵. However, to reach a definitive conclusion, long-term randomized controlled trials comparing botulinum toxin-treated individuals with placebo groups, and including variables such as food chewing time and intake, are needed.

In this study, no significant effect of BoNT treatment on food intake was observed. There were no significant differences in energy, macro nutrient intake, and no substantial changes in dietary habits were noted. As

such, weight gain and changes in body composition could not be directly linked to food intake. However, a slight increase in the consumption of animal-based proteins was observed, though not statistically significant. Animal-derived proteins are important sources of essential micronutrients such as vitamin B12 and zinc⁴⁶. Vitamin B12, found exclusively in animal products, is essential for the proper functioning of the nervous system and muscles. Adequate B12 intake supports healthy masticatory muscle function, while deficiencies may lead to muscle weakness and impairments⁴⁷. Similarly, zinc plays a crucial role in muscle repair and cellular regeneration, with its bioavailability being higher in animal-based foods⁴⁸. Zinc deficiency can impair muscle function, potentially affecting chewing performance. In this context, when evaluating the effects of BoNT on masticatory performance, it is important to consider that animal-derived proteins, by enhancing the intake of key micronutrients like B12 and zinc, could potentially improve therapeutic outcomes. Additionally, some studies have suggested that increasing fiber intake could alleviate sleep bruxism in young adults, pointing to a possible dietary intervention for managing this condition⁴⁹. Sleep bruxism has also been associated with vitamin D deficiency, low calcium intake, and increased anxiety and depression, although it remains unclear whether vitamin D and calcium supplementation can alleviate the condition⁵⁰.

Limitations

This study has several limitations. Although the power analysis indicated that the sample size was adequate, the reliance on a single patient group and the relatively small sample size limit the generalizability of the findings and restrict our capacity for more detailed subgroup analyses. Future research should include larger sample sizes and diverse populations to obtain clearer results on the long-term effects of BoNT on anthropometric changes and nutritional status.

The 6-month follow-up period also limited our ability to fully assess the long-term effects of botulinum toxin. Additionally, the reliance on subjective participant

reports for evaluating pain, symptoms, and nutritional status may have introduced variability due to individual differences. To address these limitations, future studies should incorporate more objective measurement tools to offer a more comprehensive understanding of the treatment's impact.

Conclusion

This study demonstrates that BoNT injections have a short-term positive impact on masticatory performance and pain reduction in patients with TMDs. While significant improvements were observed in pain control and muscle function during the first few months, these effects diminished over time. Additionally, although BoNT treatment led to some changes in body composition, particularly an increase in body fat, there was no direct correlation with dietary intake. The results suggest that BoNT may influence muscle function independently of body composition changes. Future studies with larger sample sizes and longer follow-up periods are needed to further investigate the long-term effects of BoNT on TMD, muscle function, and nutritional status. Furthermore, incorporating more objective measurement tools would help enhance the accuracy and depth of the findings.

Ethical Statement

The ethical protocol of the study was approved by the Non-Interventional Clinical Studies Ethics Committee of Marmara University Faculty of Health Sciences with protocol number 44 on 31.03.2022, and Helsinki guidelines were followed during the study.

Conflict of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Sistema de anotación de imágenes radiológicas 2D de periodontitis apical para su estudio mediante Deep Learning

2D Radiological Image Annotation System for the Study of Apical Periodontitis Using Deep Learning

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Resumen

Introducción: La inteligencia artificial (IA) es una herramienta que ayuda en el diagnóstico de patologías que requieren para su detección imágenes radiográficas. En odontología la periodontitis apical (PA) es una de estas patologías, pues es la presencia de radiolucidez periapical lo que nos indica el diagnóstico de periodontitis apical.

Objetivo: Exponer como la IA, concretamente el deep learning (DL) ayuda al odontólogo en el diagnóstico de la PA y de esta forma favorecer la integración de la IA en el campo odontológico.

Metodología: Se creó una base de datos, con imágenes radiográficas de distintos dientes con lesiones apicales, a los que se les realizó tratamiento endodóntico con la misma técnica de instrumentación y obturación. Para el análisis de las imágenes se ha utilizado el software de AnotIA que permite anotar y segmentar con precisión las radiografías y que ofrece además una serie de herramientas que permiten agregar notas, etiquetas y comentarios detallados. Se han utilizado dos etiquetas, una para indicar que la lesión se ha curado (0) y la otra que no ha curado (1), que se utilizan para contrastar la información proporcionada por el especialista con los resultados obtenidos por DL.

Discusión-Conclusiones: Muchos profesionales presentan unos conocimientos muy limitados para evaluar las aplicaciones de la IA a la odontología. Estos profesionales para conseguir una alta cualidad en cualquier aplicación de la IA en la odontología necesitan un básico conocimiento y unas habilidades para evaluar la IA dental. Es necesaria la formación tanto en pregrado como en el postgrado con el fin de establecer un conjunto mínimo de resultados que los estudiantes deben adquirir cuando se les enseña sobre inteligencia artificial en el terreno bucal y dental. En nuestra investigación, si bien hemos empleado una pequeña muestra de imágenes radiográficas, hemos podido exponer como es nuestra sistemática para poder acceder a realizar un estudio de DL.

Palabras clave: machine learning, deep learning, periodontitis apical.

Abstract

Introduction: Artificial intelligence (AI) is a powerful tool that assists in the diagnosis of pathologies that require radiographic imaging for detection. In dentistry, apical periodontitis (AP) is one such condition, as the presence of periapical radiolucency serves as a key diagnostic indicator.

Objective: To demonstrate how AI, particularly deep learning (DL), supports dental professionals in diagnosing AP, thereby promoting the integration of AI in the dental field.

Methodology: A database was created using radiographic images of various teeth with apical lesions, all of which underwent endodontic treatment using the same instrumentation and obturation technique. For image analysis, the AnotIA software was employed, which enables precise annotation and segmentation of radiographs and offers a range of tools for adding notes, labels, and detailed comments. Two labels were used: one indicating that the lesion had healed (0), and the other indicating that it had not healed (1). These labels were used to compare the specialist's assessment with the results obtained through DL.

Discussion-Conclusions: Many professionals have limited knowledge regarding the application of AI in dentistry. To ensure high-quality implementation of AI in dental practice, these professionals require foundational knowledge and skills to evaluate dental AI systems. Training at both undergraduate and postgraduate levels is essential in order to establish a minimum set of learning outcomes that students must achieve when being taught about AI in the oral and dental domains. In our study, although we worked with a small sample of radiographic images, we were able to present our systematic approach to conducting a DL-based investigation.

Key words: Machine learning, deep learning, apical periodontitis.

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Introducción

La periodontitis apical (PA) es una respuesta inflamatoria causada por la presencia de microorganismos en el canal radicular de un diente infectado afectando a los tejidos periapicales produciendo una pérdida ósea apical¹.

Su oportuno tratamiento es el tratamiento de conductos teniendo como alternativa la indeseada pérdida del diente.

El dentista toma la decisión de realizar uno u otro tratamiento teniendo en cuenta una serie de factores, unos centrados en el paciente, tales como factores preoperatorios, dolor preoperatorio, enfermedades sistémicas (p. ej., diabetes mellitus o enfermedades cardiovasculares), tipo de diente (p. ej., incisivo, canino, premolar o molar) y tamaño de la lesión y otros centrados en las técnicas y materiales endodónticos empleados durante el tratamiento y el tipo de reconstrucción posterior²⁻⁴.

Para analizar la imagen de la periodontitis apical utilizamos, tanto en el diagnóstico como en la evaluación del tratamiento, como primera opción, las radiografías periapicales de dos dimensiones (RP2D) cuya interpretación exhibe una gran susceptibilidad y una gran diferencia entre examinadores^{5,6}, aunque se disponga de una cuantificación de los cambios producidos en la mineralización y en la estructura del hueso adyacente al sitio de la inflamación mediante el ÍNDICE PAI siendo un método de registro apical desarrollado por Orstavik en 1986⁷. Actualmente la IA es especialmente adecuada para superar la variabilidad en el examen individual subjetivo de las imágenes radiográficas y aumentar la eficacia de la atención al tiempo que reduce costos al eliminar tareas rutinarias⁸.

La inteligencia artificial (IA) se refiere a la idea de construir máquinas que sean capaces de realizar tareas que normalmente realizan los humanos⁹.

Un subcampo de la IA es el aprendizaje automático, machine learning (ML), en el que se aplican algoritmos para aprender patrones intrínsecos de un conjunto de datos determinado (datos de entrenamiento) con el objetivo de reconocer patrones similares en datos nuevos (datos de prueba). Este objetivo de reconocer patrones puede ser de utilidad en tareas de clasificación, regresión y agrupamiento. Los algoritmos de ML se pueden entrenar de dos formas: supervisada y no supervisada. En el aprendizaje supervisado cada dato del conjunto de entrenamiento tiene una etiqueta con lo cual en este modelo tenemos varias entradas cuyas varias salidas se conocen. El único objetivo con estos datos de entrenamiento es conocer la relación entre los datos de entrada y la salida para posteriormente poder predecir cual será la salida para una entrada de datos de prueba. En cuanto al aprendizaje no supervisado

en el conjunto de entrenamiento los datos no están etiquetados y el objetivo es identificar patrones mediante la extracción de las características más relevantes de este conjunto de datos.

Las redes neuronales artificiales (ANNs) superan a los algoritmos más clásicos de ML, particularmente en estructuras de datos complejos, como son imágenes o lenguaje.

La unidad básica de las ANNs es la neurona artificial, que no es más que un modelo matemático inspirado en la neurona humana. Mediante la concatenación de estas neuronas artificiales y la conexión de estas capas mediante operaciones matemáticas se diseña una red que es capaz de resolver tareas tan específicas como clasificación de imágenes (ejemplo, una radiografía con una imagen de periodontitis apical: si o no)¹⁰.

Las redes neuronales profundas, deep learning (DL), se refieren a ANNs con múltiples capas, de tal manera que los datos de entrenamiento pasan repetidamente por las múltiples capas de las redes neuronales. Este proceso se conoce como entrenamiento de la red, donde en cada iteración o época se ajustan los pesos de la red mediante la retropropagación del error y el uso de optimizadores, como el descenso de gradiente estocástico (SGD). Con esta operación se consigue que las conexiones de las neuronas o pesos de los modelos se optimicen de forma iterativa con respecto a minimizar el error de predicción, es decir, la diferencia entre el resultado verdadero y el predicho. Para determinar la calidad del modelo, se emplean métricas de evaluación tanto en la fase de entrenamiento como en la de validación. Entre las métricas más utilizadas en tareas de clasificación se encuentran la precisión (accuracy), que mide el porcentaje de aciertos del modelo; la sensibilidad (recall), que indica la capacidad del modelo para detectar correctamente los casos positivos; la especificidad, que evalúa la capacidad de identificar correctamente los casos negativos; y la métrica F1-score, que representa un equilibrio entre precisión y sensibilidad. El monitoreo de estas métricas es esencial para evitar problemas como el sobreajuste (overfitting), donde el modelo memoriza los datos de entrenamiento y pierde capacidad de generalización, o el subajuste (underfitting), donde el modelo no logra aprender patrones relevantes. Esta red entrenada puede predecir el resultado de datos ocultos al pasar nuevos datos a través de la red^{10,11}.

El DL tiene la habilidad de aprender complejas representaciones de datos, siendo más robusto contra la variabilidad humana que el ML. En este sentido, el DL sobrepasa al ML. Por otra parte, requiere una gran cantidad de datos y un mayor poder computacional. Ahora bien, en la actualidad, los avances en el poder computacional, la mejora en el almacenaje de datos y los nuevos algoritmos de DL

han permitido a los computadores realizar tareas que antes eran imposibles. Actualmente, hay un aumento en el uso de los instrumentos de la IA en el área de la salud, donde las Redes Neuronales Convolucionales (CNN), una familia de redes neuronales profundas que hacen uso de convoluciones, desempeña un papel muy importante en el procesamiento de imágenes médicas¹⁰.

Estas redes neuronales profundas son particularmente útiles para estructuras de datos complejos, como las imágenes, ya que son capaces de representar una imagen y sus características jerárquicas, como los bordes, las esquinas, las formas y los patrones macroscópicos¹². Sin embargo, su implementación en odontología enfrenta el desafío de la disponibilidad de grandes volúmenes de datos etiquetados. Para abordar esta limitación, se emplean estrategias como el aumento de datos y el aprendizaje por transferencia.

El aumento de datos es una técnica que permite expandir artificialmente el conjunto de datos sin necesidad de recopilar nuevas muestras. En odontología, donde la obtención de imágenes clínicas y radiográficas etiquetadas es un proceso costoso y regulado, este método se vuelve especialmente útil. Se pueden aplicar transformaciones como rotaciones, inversiones, cambios de escala, modificaciones en el contraste, adición de ruido y desenfoque para crear versiones modificadas de las imágenes originales. Estas variaciones ayudan a mejorar la capacidad del modelo para reconocer estructuras dentales bajo diferentes condiciones y perspectivas, reduciendo así el riesgo de sobreajuste y mejorando su generalización a nuevos casos clínicos.

Por otro lado, el aprendizaje por transferencia ofrece una solución eficiente cuando la cantidad de datos disponibles es limitada. En lugar de entrenar un modelo desde cero, se utilizan redes neuronales profundas previamente entrenadas en conjuntos de datos extensos, generalmente de imágenes médicas o incluso de otros dominios visuales, y se ajustan a la tarea específica odontológica. Esto es posible porque las primeras capas de estas redes aprenden características generales, como bordes y texturas, que son útiles para múltiples aplicaciones. Luego, las capas superiores del modelo se refinan mediante reentrenamiento con imágenes odontológicas específicas, permitiendo que la red adquiera conocimientos especializados sin necesidad de un conjunto de datos masivo. Esta técnica no solo reduce el tiempo de entrenamiento y los requerimientos computacionales, sino que también mejora la precisión del modelo al aprovechar conocimientos previos adquiridos en otros dominios, que pueden ser, o no, médicos.

La IA ha comenzado a impactar en la odontología, incluyendo la mejora de las imágenes en radiología, el diagnóstico de quistes y tumores¹³, el diagnóstico de lesiones periapicales¹⁴, la identificación de la anatomía radicular para endodoncia¹⁵, el diagnóstico de periodontitis¹⁶, la localización automatizada de puntos de referencia cefalométricos en ortodoncia¹⁷, la detección del foramen apical¹⁸, la determinación de la longitud de trabajo¹⁹ y la identificación de fracturas verticales²⁰.

Objetivo

Dar a conocer el camino a seguir para que el odontólogo pueda introducir el empleo de la IA, concretamente el DL, en la clínica odontológica y de esta forma favorecer la integración de la IA en el campo odontológico.

Metodología

Esta investigación está aprobada por el Comité de Ética de la Investigación de las Illes Balears (IB4015/19IP).

Para poder realizar nuestro estudio hemos analizado las imágenes radiológicas diagnósticas de pacientes con piezas dentales afectadas de periodontitis apical, en cuyo diagnóstico hemos tenido en cuenta los datos clínicos y pruebas complementarias, a las que se les ha realizado un tratamiento de conductos primarios no quirúrgico y su posterior evolución a partir de los 6 meses hasta los 10 años en algunos casos.

Todas las RX periapicales se realizaron con un X MIMD UNITY ACTEON SATELEC, las imágenes fueron adquiridas con un CARESTREAM 6100 y se utilizó un posicionador Rinn XCD (DENSPLY).

En todos los tratamientos se siguió la misma técnica de instrumentación y de obturación y en la RX final de tratamiento no se visualizaron poros ni sobreobturación.

Para empezar nuestro trabajo exportamos las RP2D de diagnóstico desde la radiovisiografía a una base de datos, asignándole un identificador a cada una de las imágenes e indicando a que tipo de pieza corresponden y estableciendo un valor lógico para determinar su curación (0) o no curación (1) así como la posición que la pieza afectada ocupa en la imagen radiológica otorgando a la pieza de la izquierda el nº1 y a partir de ésta tendremos las siguientes enumeraciones que se precisen dependiendo del número de piezas dentarias que aparecen en la radiografía periapical. Una vez finalizado este proceso, la BBDD (Bases de datos) ya está preparada para importarla al software encargado de hacer el estudio correspondiente.

Tratamiento de endodoncia que presenta curación al año



Base de datos

Id	Tooth	Healed	Position	Id	Tooth	Healed	Position	Id	Tooth	Healed	Position
00001	Molar	1	1	00041	Incisor	0	2	00404	Molar	0	1
00002	Canine	1	1	00042	Incisor	1	2	00406	Canine	0	2
00003	Incisor	1	2	00043	Incisor	1	2	00407	Incisor	0	3
00004	Incisor	1	1	00044	Molar	1	1	00408	Incisor	0	1
00005	Incisor	0	2	00045	Incisor	1	4	00409	Incisor	1	4
00006	Molar	1	2	00046	Premolar	1	1	00410	Premolar	1	1
00007	Molar	1	1	00047	Premolar	1	1	00411	Premolar	0	1
00008	Incisor	1	2	00048	Incisor	0	2	00412	Incisor	1	1
00009	Incisor	0	2	00049	Molar	1	1	00413	Incisor	1	3
00010	Incisor	1	3	00050	Molar	1	1	M1	Incisor	1	2
00011	Incisor	0	2	00051	Incisor	1	1	M3	Premolar	1	2
00012	Molar	1	2	00052	Molar	1	1	M5	Premolar	1	2
00013	Molar	1	1	00053	Molar	1	1	M6	Incisor	0	2
00014	Incisor	1	1	00054	Incisor	1	2	M6	Incisor	0	3
00015	Incisor	1	2	00327	Incisor	0	1	M6	Incisor	0	4
00016	Premolar	1	2	00333	Incisor	0	1	M8	Incisor	0	1
00017	Incisor	1	3	00334	Premolar	0	1	M9	Molar	0	1
00018	Molar	1	1	00335	Premolar	0	1	M11	Molar	1	1
00019	Premolar	1	1	00338	Molar	0	2	M12	Incisor	0	2
00020	Incisor	1	2	00339	Premolar	0	1	M13	Molar	0	1
00021	Molar	1	1	00342	Premolar	0	2	M15	Incisor	0	2
00022	Incisor	1	3	00346	Incisor	1	2	M15	Incisor	0	3
00023	Premolar	1	2	00348	Premolar	0	1	M17	Molar	0	1
00024	Incisor	1	3	00349	Molar	0	1	M18	Bicúspide	0	1
00025	Molar	1	1	00350	Incisor	1	2	M19	Canine	1	2
00026	Premolar	1	2	00351	Premolar	0	1	M20	Premolar	1	2
00027	Molar	1	2	00377	Canine	1	2	M21	Molar	0	1
00028	Canine	1	3	00379	Molar	1	1	M23	Canine	0	2
00029	Molar	1	2	00382	Premolar	0	2	M24	Canine	0	2
00030	Molar	1	1	00387	Molar	0	2	RX1	Molar	1	1
00031	Incisor	1	1	00393	Incisor	0	2	RX2	Molar	1	2
00032	Incisor	1	2	00397	Molar	0	1	RX3	Molar	0	1
00033	Incisor	1	2	00358	Canine	0	2	RX4	Molar	1	2
00034	Premolar	1	1	00363	Molar	1	1	RX5	Premolar	1	4
00035	Incisor	1	2	00370	Incisor	0	1	RX7	Molar	0	1
00036	Premolar	1	1	00373	Molar	0	1	RX8	Molar	0	1
00037	Molar	0	1	00375	Incisor	1	1	RX10	Incisor	1	2
00038	Molar	0	2	00376	Molar	0	1	RX11	Incisor	1	2
00039	Molar	0	1	00402	Incisor	0	1				
00040	Molar	1	1	00403	Incisor	1	2				

En nuestro estudio, para el análisis de las imágenes se ha utilizado el software de AnotIA que permite anotar y segmentar con precisión las radiografías y que ofrece además una serie de herramientas que permiten agregar notas, etiquetas y comentarios detallados (Imagen 1). El proceso se divide en varias fases. En primer lugar, se crea el proyecto (Imagen 2) y a continuación, se procede a cargar las imágenes a analizar y se definen las anotaciones o marcas que se van a realizar asignándoles un identificador y un color a cada una de ellas (Imagen 3).

Una vez completado este proceso, se pasa a realizar las anotaciones correspondientes a cada una de las

radiografías. Para ello, utilizando las herramientas de delimitación se marca el área afectada por la lesión (Imagen 4) y se le añade un comentario que hace referencia al tipo de pieza y su numeración y, finalmente, se asigna la etiqueta correspondiente para la realización del análisis estadístico posterior (Imagen 5). En nuestro caso se han utilizado dos etiquetas, una para indicar que la lesión se ha curado (0) y la otra que no ha curado (1).

Dichas etiquetas son las que se utilizan para contrastar la información proporcionada por el especialista con los resultados obtenidos por DL.

Imagen 1

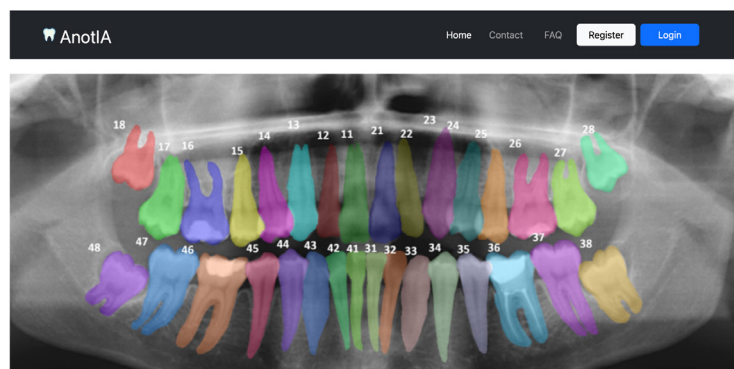


Imagen 2

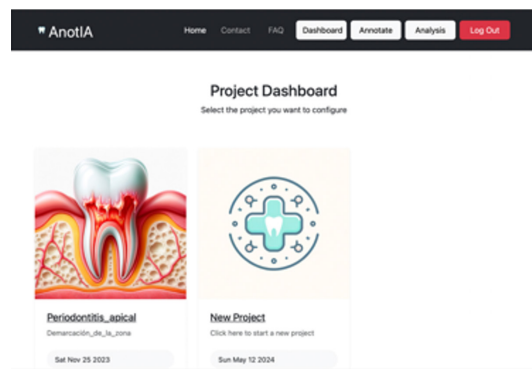


Imagen 3



Imagen 4

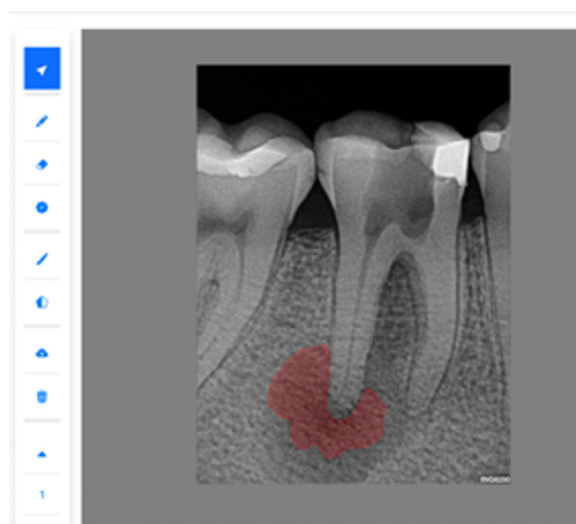
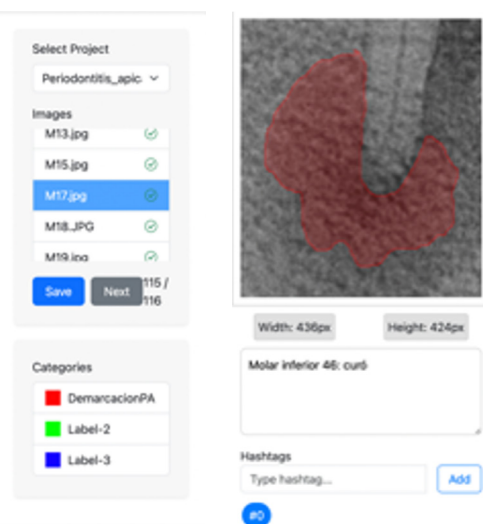


Imagen 5



Discusión

Sólo a partir del año 2015 las ANNs empezaron a utilizarse en investigación, aplicándose a radiografías digitales y estas aplicaciones más recientemente se están incorporando en el territorio clínico¹². Según Schwendicke et al.⁸ este hecho contrasta con tres situaciones que se dan en la odontología haciéndola ideal para que se integre con la IA:

1. En la odontología las imágenes radiológicas son pruebas complementarias muy importantes. Las radiografías periapicales pueden ser usadas para el diagnóstico, planificación, realización y comparación de los resultados de tratamientos de endodoncia al proyectar con más exactitud las estructuras coronales y radiculares de las piezas que nos interesan que las radiografías panorámicas¹³.

2. En odontología empleamos diferentes imágenes de una misma región y estas imágenes las acompañamos de datos clínicos y dentales. Pues bien, la IA puede vincular todos estos datos mejorando el diagnóstico, la predicción y la toma de decisiones.

3. En odontología se dan una serie de alteraciones prevalentes, como son las caries y las alteraciones pulpares. Gracias a ello la creación de un conjunto de datos que presenten estas alteraciones prevalentes no requiere un esfuerzo ilimitado.

Si bien en Odontología se dispone de un material muy apropiado para emplear la IA, en muchas ocasiones los datos son escogidos sin seguir ninguna guía lo cual genera un “sesgo de espionaje de datos”¹⁴. En nuestro caso los datos han sido recogidos siguiendo una plantilla de recopilación de datos que ha sido confeccionada para la estandarización de las investigaciones en endodoncia¹⁵⁻¹⁷.

Cuando utilizamos el PAI para evaluar un tratamiento de endodoncia se nos pueden presentar dudas al tener que diagnosticar si existe éxito o fracaso ya que en caso de duda se asigna al diente el valor más alto⁷. Nosotros para evitar estas dudas, los resultados de nuestros tratamientos los hemos dicotomizado, lo cual también es realizado por otros autores¹⁸⁻²⁰.

Según Schwendicke et al.²¹ la IA esta entrando rápidamente en nuestro campo de la odontología, sin embargo, muchos profesionales presentan unos conocimientos muy limitados para evaluar

las aplicaciones de la IA a la odontología. Estos profesionales de la odontología para conseguir una alta cualidad en la aplicación de la IA necesitan un conocimiento básico y la adquisición de unas habilidades en el terreno de la IA. Para solventar este problema define un currículo tanto para la educación pregrado como en el postgrado con la finalidad de establecer un conjunto mínimo de conocimientos que los estudiantes deben adquirir sobre IA en sus estudios odontológicos. Considera que si este currículum es adoptado por los educadores y los estudiantes en la planificación, desarrollo y evaluación de la educación odontológica de la IA podría aumentar la formación de los profesionales odontológicos en el terreno de la IA.

Conclusión

Si bien hemos empleado una pequeña muestra de imágenes radiográficas, hemos podido exponer como es nuestra sistemática, que a nivel clínico no es difícil teniendo en cuenta que debemos tener conocimiento de la IA (aprendizaje profundo y redes neuronales profundas), para poder hacer posible realizar un estudio de DL y de esta forma poder saber si los resultados conseguidos mediante el estudio de lesiones periapicales mediante redes de aprendizaje profundo coinciden con los de nuestra casuística.

Conflictos de intereses

Las autoras declaran no tener conflictos de intereses.

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ORIGINAL

Management of Cardiopulmonary Bypass Initial Gas Flow Rate: Patient Based Rate and Constant Gas Flow Rate

*Gestión del flujo inicial de gas en la derivación cardiopulmonar:
Velocidad basada en el paciente y velocidad de flujo de gas constante*

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Abstract

Background: Cardiopulmonary bypass (CPB) is an essential component of cardiac surgery and gas flow is recognised as a critical element of the CPB process.

Objectives: In this retrospective study, we aimed to compare these two different initial gas flow methods (fixed initial gas flow rate and personalised gas flow rate) used in the management of the sweep gas flow rate during CPB.

Methods: In this retrospective study, those whose baseline gas flow rate was determined according to patient blood gas values measured after induction of anaesthesia were defined as Group 1 (patient-based personalised gas flow rate) and those whose baseline gas flow rate was calculated by the formula $BSA \times 1.509$ were defined as Group 2 (those with a fixed baseline gas flow rate). After applying the exclusion criteria, adult patients who underwent consecutive CPB-guided cardiac surgery were included in the study. The early clinical outcomes of the groups were then compared.

Results: In this study, demographic and descriptive data of the groups were similar ($p > 0.05$). PCO_2 , PO_2 , pH, glucose intensive care unit stay time and hospital stay time values of the groups were similar and there was no difference between the two groups in terms of these parameters ($p > 0.05$). However, lactate, base deficit and intubation times of the groups were significantly different and were higher in Group 2 ($p = 0.035$; $p = 0.009$; $p = 0.005$, respectively).

Conclusion: The findings that an individualised gas flow rate provides better clinical outcomes than a fixed gas flow rate may lead to the adoption of a new approach to patient management during CPB. Consequently, a patient-based individualised gas flow rate rather than a fixed rate ($BSA \times 1.509$) in gas flow management during CPB may lead to better clinical outcomes.

Key words: Cardiopulmonary Bypass, Sweep Gas Flow, Patient Based Rate, Constant Gas Flow Rate, Perfusion Management.

Resumen

Antecedentes: La derivación cardiopulmonar (DCP) es un componente esencial de la cirugía cardíaca y el flujo de gas se reconoce como un elemento crítico del proceso de DCP.

Objetivos: En este estudio retrospectivo, nos propusimos comparar estos dos métodos diferentes de flujo de gas inicial (flujo de gas inicial fijo y flujo de gas personalizado) utilizados en la gestión del flujo de gas de barrido durante la DCP.

Métodos: En este estudio retrospectivo, aquellos cuya tasa de flujo de gas basal se determinó en función de los valores de gasometría del paciente medidos tras la inducción de la anestesia se definieron como Grupo 1 (tasa de flujo de gas personalizada en función del paciente) y aquellos cuya tasa de flujo de gas basal se calculó mediante la fórmula $BSA \times 1.509$ se definieron como Grupo 2 (aquellos con una tasa de flujo de gas basal fija). Tras aplicar los criterios de exclusión, se incluyeron en el estudio los pacientes adultos que se sometieron consecutivamente a cirugía cardíaca guiada por DCP. A continuación se compararon los resultados clínicos iniciales de los grupos.

Resultados: En este estudio, los datos demográficos y descriptivos de los grupos fueron similares ($p > 0,05$). Los valores de PCO_2 , PO_2 , pH, tiempo de estancia en la unidad de cuidados intensivos de glucosa y tiempo de estancia hospitalaria de los grupos fueron similares y no hubo diferencias entre los dos grupos en cuanto a estos parámetros ($p > 0,05$). Sin embargo, el lactato, el déficit de bases y los tiempos de intubación de los grupos fueron significativamente diferentes y fueron superiores en el Grupo 2 ($p = 0,035$; $p = 0,009$; $p = 0,005$, respectivamente).

Conclusiones: Los hallazgos de que una tasa de flujo de gas individualizada proporciona mejores resultados clínicos que una tasa de flujo de gas fija pueden conducir a la adopción de un nuevo enfoque para el manejo del paciente durante la DCP. En consecuencia, un flujo de gas individualizado en función del paciente en lugar de un flujo fijo ($BSA \times 1.509$) en la gestión del flujo de gas durante la DCP puede dar lugar a mejores resultados clínicos.

Palabras clave: Bypass cardiopulmonar, flujo de gas de barrido, tasa basada en el paciente, tasa de flujo de gas constante, gestión de la perfusión.

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Introduction

Cardiovascular diseases are currently the leading cause of death worldwide, both in developed and less developed countries¹. Heart diseases have become one of the most important socio-health problems of today, with an increasing incidence due to the ageing of the population, inadequate control of risk factors and prolonged survival in individuals with this disease thanks to improved treatment methods. Heart failure is the most common cause of hospitalisation for cardiovascular reasons, especially in individuals over 60 years of age². In addition, congenital heart diseases are one of the leading causes of death in childhood and the primary treatment of these heart diseases is surgery³. Cardiopulmonary bypass (CPB) is generally used in the surgical treatment of these diseases. CPB is one of the basic components of cardiac surgery and gas flow is recognised as a critical element of the CPB process. However, there is no definite scientific consensus on the optimal value of the sweep gas flow rate delivered to the oxygenator during CPB⁴. High sweep gas flow rates may increase the risk of neurological complications by causing respiratory and hypocapnic cerebral alkalosis. One of the basic parameters that should be carefully monitored during CPB is partial carbon dioxide (PCO_2)⁵.

Unless clinical requirements dictate otherwise, maintaining the PCO_2 level in arterial blood within normal physiological limits (35-45 mmHg) is important for maintaining metabolic acid-base balance. Maintaining PCO_2 at physiological levels may help to prevent hypocapnic lactic acidosis, ventricular fibrillation and shifts in the oxyhaemoglobin dissociation curve as well as ensuring the continuity of cerebral perfusion. On the other hand, high PCO_2 levels may lead to hypoxic acidosis-like physiological responses, increasing lactate production and causing depletion of the bicarbonate buffer system⁶.

Complete deactivation of the lungs during CPB may predispose to postoperative pulmonary complications and is frequently associated with lung collapse during CPB. Although maintenance of mechanical ventilation during CPB is recommended to prevent these complications, there is no definite consensus on the clinical efficacy of this practice^{7,8}. However, inadequate oxygenation and hypoperfusion are a serious concern, especially in open heart surgeries performed using CPB⁹.

In adult cardiac surgery patients undergoing CPB, the sweep gas flow rate is usually initially determined according to the formula body surface area (BSA) $\times$ 1.509. However, in some cases, this rate is adjusted based on the patient's blood gas values before CPB and started accordingly. However, the method by which the initial gas flow rate for CPB should be determined and the effects of these two approaches on clinical outcomes have not yet been clarified. Therefore, a comparative

study of different determination methods stands out as an important research topic.

In this retrospective study, we aimed to compare these two different initial gas flow methods (fixed initial gas flow rate and personalised gas flow rate) used in the management of the sweep gas flow rate during CPB.

Methods

This study is a retrospective clinical research.

Ethical Dimension of the Research

In this study, approval was obtained from the relevant institution and local ethics committee (Harran University Clinical Research Ethics Committee) (Date: 10.03.2025 - Approval no: HRÜ/25.05.09). The study was conducted following the principles of the Declaration of Helsinki. Since only anonymized patient data was used and there was no risk or impact on patient care, informed consent was not required. This consent waiver was approved by the Institutional Review Board and Ethics Committee and complies with regulatory and ethical guidelines for retrospective studies.

Research Design and Data Collection

Three months of patient data from the relevant institution were consecutively included in this study after applying the exclusion criteria. Demographic and descriptive data of the patients (age, gender, height, weight, BSA, flow, ejection fraction percentage (EF%), smoking, diabetes, hypertension, hyperlipidemia, aortic cross-clamping time, total perfusion time, type of surgical operation performed), intraoperative; PCO_2 , partial oxygen (PO_2), lactate, power of hydrogen (pH), base excess or base deficit, glucose, and early peroperative variables of intubated stay (duration of mechanical ventilation support), intensive care unit (ICU) stay, and hospital stay.

In the study, those whose initial gas flow rate was determined according to the values in the patient's blood gas measured after induction of anaesthesia were determined as Group 1 (patient-based personalised gas flow rate) and those whose initial gas flow rate was calculated by the formula $\text{BSA} \times 1.509$ were determined as Group 2 (those with a fixed initial gas flow rate).

Exclusion and Inclusion Criteria

Patients who underwent emergency cardiac surgery, patients in whom additional cardiac surgery such as aortic aneurysm or dissection was planned, patients who underwent repeat cardiac surgery, patients with chronic lung diseases, chronic haemodialysis patients, patients with haematological diseases, patients treated with anticoagulant drugs preoperatively, patients with a preoperative haematocrit value lower than 30, patients requiring preoperative blood transfusion were excluded from the study.

After applying the exclusion criteria, 137 patients aged between 20 and 85 years who underwent consecutive CPB-guided cardiac surgery were included in the study. Inclusion criteria also included cases in which PCO_2 values were not less than 30 mmHg and not more than 50 mmHg in the pre-CPB blood gas results. In addition, patients with preoperative PO_2 , lactate, pH, base deficit, glucose values in the normal range were included, and standard coronary and heart valve surgery techniques were performed in all patients included in the study.

Cardiopulmonary Bypass (Perfusion) Technique

Standard coronary and valvular heart surgery techniques were performed in all patients. After midline sternotomy in coronary heart surgery patients, arterial cannulation was performed from the ascending aorta and venous cannulation was performed from the right atrium with a single venous cannula (two-stage venous cannula). Left mammary artery graft was used in all cases. Saphenous vein graft was applied to other coronary grafts. Complete revascularisation was performed in all patients. In valvular heart surgery patients, in addition to standard surgical techniques, in mitral valve replacements after midline sternotomy, arterial cannulation was performed from the ascending aorta and venous cannulation was performed with two venous cannulae from the vena cava superior and vena cava inferior (bicaval cannulation). In aortic valve replacements, arterial cannulation was performed from the ascending aorta and venous cannulation was performed from the right atrium with a single venous cannula (two-stage cannulation). In addition, the same

type of modified del Nido cardioplegia solution and standard extracorporeal circulatory systems (heart-lung machine) were used in all patients.

Statistical Analyses

The patient data collected within the scope of the study were analysed with IBM Statistical Package for the Social Sciences 25 (IBM SPSS Statistics 25®) (IBM Corporation, Armonk, NY, USA). Means and standard deviations were calculated for continuous data. The Kolmogorov Smirnov test was used to assess normality distribution. Student T test and Mann Whitney U tests were used to evaluate normal and non-normally distributed data, respectively. Frequency and percentage analyses were performed for nominal data and Chi-Square test and Chi-Square corrected test were used for comparison. A "p" value less than 0.05 was considered statistically significant.

Results

In this study, the demographic and descriptive data of the groups were similar in terms of age, height, weight, BSA, blood flow, EF%, aortic cross clamp time, total perfusion time, preoperative haemoglobin and haematocrit values, gender distribution, type of surgery (coronary artery bypass graft counts, aortic valve replacement and mitral valve replacement), history of smoking, history of hypertension, history of diabetes and history of hyperlipidaemia ($p > 0.05$) (Table I).

Table I: Demographic and descriptive data of the groups.

Variables		GROUP 1 (N=80)	GROUP 2 (N=57)	P value
		Mean±SD	Mean±SD	
Age (years)		66.10±5.05	65.91±4.20	0.819
Height (cm)		172.30±7.02	170.03±9.00	0.101
Weight (kg)		81.82±11.35	79.61±10.88	0.255
BSA (m ²)		1.94±0.08	1.92±0.05	0.055
Blood Flow (L/min)		4.66±0.17	4.61±0.18	0.091
EF %		49.78±9.19	51.10±7.92	0.383
ACC time (min)		63.63±15.09	63.80±14.81	0.948
Total perfusion time (min)		97.95±21.34	98.77±14.03	0.800
Haemoglobin (g/dL)		13.70±1.78	14.01±1.63	0.721
Haematocrit (%)		41.16±4.05	42.12±5.03	0.965
		N, (%)	N, (%)	
Gender (n, %)	Female	29, (36.3%)	26, (45.6%)	0.298
	Male	49, (61.3%)	31, (54.4%)	
Type of surgical procedure	CABGX1	1, (1.3%)	0, (0.0%)	0.634
	CABGX2	10, (12.5%)	6, (10.5%)	
	CABGX3	26, (32.5%)	19, (33.3%)	
	CABGX4	25, (31.3%)	24, (42.1%)	
	AVR	11, (13.8%)	4, (7.0%)	
	MVR	7, (8.8%)	4, (7.0%)	
Smoking	None	58, (72.5%)	44, (77.2%)	0.535
	Yes	22, (27.5%)	13, (22.8%)	
Hypertension	None	32, (40.0%)	25, (43.9%)	0.651
	Yes	48, (60.0%)	32, (56.1%)	
Diabetes	None	43, (53.8%)	35, (61.4%)	0.373
	Yes	37, (46.3%)	22, (38.6%)	
Hyperlipidaemia	None	48, (60.0%)	39, (68.4%)	0.313
	Yes	32, (40.0%)	18, (31.6%)	

Mean±SD: Mean±Standard Deviation, N: Frequency, %: Percent, BSA: Body surface area, EF: Ejection fraction, ACC: Aortic cross clamp.

As shown in **table II**, PCO_2 , PO_2 , pH, glucose, ICU time and hospitalisation time values of the groups were similar and there was no difference between the two groups in terms of these parameters ($p > 0.05$). However, there was a significant difference between the lactate, base deficit and intubation times of the groups and they were higher in Group 2 ($p = 0.035$; $p = 0.009$; $p = 0.005$, respectively) (**Table II**) (**Figure 1**).

Figure 1: Comparison of lactate, base deficit and intubation times of the groups.

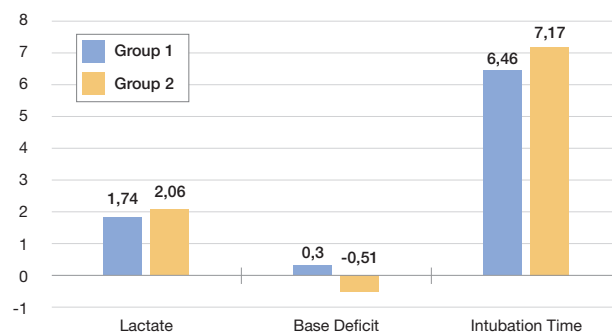


Table II: Early data of the groups that may be related to sweeping gas flow.

Variables	GROUP 1 (N=80)	GROUP 2 (N=57)	P value
	Mean±SD	Mean±SD	
PCO_2 (mmHg)	37.61±4.11	38.35±4.68	0.334
PO_2	296.22±59.57	300.42±71.35	0.709
Lactate (mmol/L)	1.74±0.72	2.06±0.89	0.035
pH	7.41±0.05	7.42±0.05	0.216
Base Deficit (mEq/L)	0.30±2.19	-0.51±2.42	0.009
Glucose (mg/dL)	158.06±43.26	166.82±35.56	0.211
Intubation Time (hours)	6.46±2.03	7.17±1.83	0.004
ICU time (days)	2.98±1.06	2.87±0.70	0.496
Duration of Hospitalisation (days)	11.13±3.03	11.92±2.50	0.108

Mean±SD: Mean±Standard Deviation, PCO_2 : Partial Carbon Dioxide, PO_2 : Partial Oxygen, pH: Power of Hydrogen, ICU: Intensive Care Unit.

Discussion

The rate of CO_2 exchange within an oxygenator used in open heart surgery is primarily based on the sweep gas flow rate. There is no consensus on the ideal sweep gas flow volume to achieve targeted blood partial gas pressures during CPB. In this study, it was aimed to determine the initial gas flow rate during CPB and the results showed that a constant gas flow rate was associated with higher lactate and base deficit and intubation time than an individualised gas flow rate. These findings reveal the superiority of our study. In other words, it can be considered that individualised gas flow rate offers more favourable results. In addition, when the results are evaluated, it is suggested that the patient-based personalised method of gas flow management decreases the base deficit and lactate values, which results in less intubation time, or on the contrary, fixed rate gas flow management increases the base deficit and lactate levels, which results in more intubation time. Therefore, it would be useful to evaluate the results together with different biochemical and clinical variables.

Tissue hypoperfusion during CPB affects the outcome of cardiac surgery. Lactate, the end product of anaerobic glycolysis caused by oxygen deficiency, is a marker of tissue hypoxia. In the literature, it is stated that adequate systemic oxygenation and perfusion are provided during cardiac operation by adjusting blood flow rate, temperature, oxygen concentration and haemoglobin level during CPB. Hyperlactatemia may occur during or immediately after initiation of CPB due to hypoperfusion¹⁰.

It is well known that oxygen delivery in physiological conditions depends on haemoglobin level, arterial oxygen saturation and cardiac output. It has also been reported that oxygen delivery in CPB is associated with early postoperative hyperlactatemia. It has been demonstrated that patients with higher peak lactate values during CPB have an increased risk of postoperative morbidity and mortality¹⁰⁻¹⁴. This reveals the importance of individualised gas flow rate, which was found to be more advantageous in terms of lactate in our study findings.

Zante B, et al.¹⁵ aimed to investigate the relationship between lactate and base deficit levels on intensive care unit mortality in patients hospitalised in the intensive care unit after cardiac surgery performed under CPB guidance. As a result of their study, they found that severely decreased base deficit was superior to hyperlactatemia in terms of predicting intensive care unit mortality in patients after cardiac surgery¹⁵. When the findings of our study are compared with this study in the literature, the fact that the base deficit was positively lower in the personalised gas flow rate group (Group 1) reveals its superiority in terms of possible adverse outcomes. In addition, it has been reported in the literature that acid-base imbalances may be a predictor of major infections (clostridioides difficile infection)¹⁶. This aspect of the literature supports the importance of the results in our study.

Another important finding in our study was the duration of intubation between the groups. Prolonged duration of

mechanical ventilation support in patients after CPB has been associated with oxidative stress in the literature¹⁷. In addition, intubation time has also been reported to be associated with postoperative delirium¹⁸. It has also been emphasised that intraoperative serum lactate levels are important in predicting early extubation after isolated coronary artery bypass graft surgery¹⁹. The importance of intubation time in our study appears to be compatible with this literature.

Limitations

This study has several limitations. Limitations include the single-centre and retrospective nature of the study. Inadequate data are also among the limitations of the study. We think that multicentre and prospective studies with a larger patient population and more data will provide more comprehensive results. With these studies, more detailed morbidity analyses will be possible.

Conclusion

Although this study is an important step in gas flow management during CPB, it shows that further research is needed. In particular, it is of great importance for perfusionists to determine the optimal gas flow rate when managing gas flow and to validate the results in different patient groups. The findings that an individualised gas flow rate provides better clinical outcomes than a fixed gas flow rate may lead to the adoption of a new approach to patient management during CPB. This also points to the need for more advanced perfusion systems and integrated patient safety systems in heart-lung machine management. In conclusion, this study suggests that a patient-based individualised gas flow rate rather than a fixed rate is more effective in gas flow management during CPB.

Descriptions

Ethical Dimension of the Research

In this study, approval was obtained from the relevant institution and local ethics committee (Harran University Clinical Research Ethics Committee) (Date: 10.03.2025 - Approval no: HRÜ/25.05.09). The study was conducted following the principles of the Declaration of Helsinki. Since only anonymized patient data was used and there was no risk or impact on patient care, informed consent was not required. This consent waiver was approved by the Institutional Review Board and Ethics Committee and complies with regulatory and ethical guidelines for retrospective studies.

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Author Contributions

BA was the major contributor to the writing of the manuscript. BA, ME, AH and NK are involved in the design, conception, data collection and analysis of the study. All authors read and approved the final version of the manuscript.

Availability of data and materials

The data supporting this study's findings are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Consent for publication

The original article is not under consideration by another publication, and its substance, tables, or figures have not been published previously and will only be published elsewhere.

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SPECIAL ARTICLE

La investigación clínica en la era de la innovación: fundamentos, desafíos y perspectivas futuras

Clinical research in the age of innovation: rationale, challenges and future prospects

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Resumen

La investigación clínica es un pilar fundamental en la evolución de la medicina moderna, permitiendo la traducción del conocimiento biomédico en avances diagnósticos y terapéuticos. Este artículo analiza los fundamentos de la investigación clínica, sus desafíos metodológicos y éticos, así como su impacto en la práctica asistencial y la sostenibilidad de los sistemas de salud. Se destacan las exigencias normativas internacionales, la necesidad de una metodología rigurosa y la importancia de la multidisciplinariedad y multicentricidad en los estudios clínicos. Además, se abordan las transformaciones tecnológicas y sociosanitarias que han redefinido el paradigma de la investigación clínica, enfatizando el papel de la medicina de precisión y la digitalización del conocimiento médico. Finalmente, se discuten los retos futuros y las mejores prácticas para garantizar una investigación de alta calidad, con impacto real en la salud pública y la formación de profesionales sanitarios.

Palabras clave: Investigación clínica, metodología científica, ética en investigación, innovación médica, medicina traslacional, medicina de precisión, bioética, impacto asistencial, telemedicina, regulación internacional.

Abstract

Clinical research is a cornerstone of modern medicine, enabling the translation of biomedical knowledge into diagnostic and therapeutic advancements. This article examines the foundations of clinical research, its methodological and ethical challenges, and its impact on healthcare practice and the sustainability of health systems. International regulatory requirements, the need for rigorous methodology, and the importance of multidisciplinary and multicenter approaches in clinical studies are highlighted. Furthermore, the article explores technological and socio-health transformations that have redefined the clinical research paradigm, emphasizing the role of precision medicine and the digitization of medical knowledge. Finally, future challenges and best practices are discussed to ensure high-quality research with a real impact on public health and the training of healthcare professionals.

Key words: Clinical research, scientific methodology, research ethics, medical innovation, translational medicine, precision medicine, bioethics, healthcare impact, telemedicine, international regulation.

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Introducción

Antes de abordar el objeto de este estudio, resulta fundamental establecer una diferenciación conceptual sobre el término "investigación" en el ámbito médico. La investigación médica comprende dos vertientes principales: la investigación básica y la investigación clínica. La primera se centra en el estudio de mecanismos biológicos fundamentales, mientras que la segunda aplica dicho conocimiento en seres humanos para mejorar la salud, la calidad de vida, el pronóstico de enfermedades y la prevención de problemas de salud. Ambas disciplinas, aunque distintas en su enfoque, convergen en la denominada investigación trasnacional (*translational research*), que busca trasladar hallazgos de la investigación básica a la práctica clínica con el fin de optimizar diagnósticos y tratamientos.

Históricamente, la investigación clínica ha estado vinculada a la epidemiología, pero su alcance es mucho más amplio, integrando metodologías provenientes de la biología molecular y celular. La combinación de estos enfoques se ha vuelto cada vez más relevante, impulsando un modelo de investigación interdisciplinario y altamente especializado.

La principal diferencia entre la investigación clínica y la investigación básica radica en la participación de seres humanos en alguna fase del proceso investigativo. Esta característica impone exigencias metodológicas y éticas estrictas, reguladas por normativas internacionales como la *Declaración de Helsinki* y el *Informe Belmont*. La inclusión de pacientes en estudios clínicos exige una atención rigurosa a aspectos de bioseguridad, consentimiento informado y equidad en el acceso a tratamientos experimentales.

El presente trabajo analiza los requisitos fundamentales que debe cumplir la investigación clínica para ser considerada válida desde un punto de vista científico. Asimismo, se examinarán los criterios metodológicos que los investigadores deben seguir para obtener resultados robustos y alineados con los estándares científicos contemporáneos. A lo largo de este estudio, se enfatizará la necesidad de un enfoque ético, riguroso y basado en evidencia para garantizar que la investigación clínica contribuya de manera efectiva al avance del conocimiento médico y a la mejora de la práctica asistencial.

Relevancia de la investigación clínica

Como se ha mencionado en la introducción, la investigación clínica constituye el eslabón final e imprescindible en la cadena de la investigación biomédica¹. Todo conocimiento generado en la experimentación básica (molecular, celular o animal)

debe ser eventualmente trasladado y evaluado en el contexto de la investigación clínica, si se pretende lograr un impacto real en la práctica médica.

Debido a ello, la investigación clínica reviste una importancia extraordinaria, y su exigencia de calidad y rigor metodológico debe ser, cuanto menos, equivalente a la exigida y utilizada en la investigación experimental. No deben establecerse excesivas distinciones entre investigación clínica e investigación básica; más bien, la diferencia sustancial radica en la dicotomía entre buena investigación y la mala, pues la segunda no es, en esencia, investigación.

Además de su relevancia intrínseca de la investigación clínica discutida en el apartado anterior, ésta tiene una serie de implicaciones "ocultas" (tanto asistenciales como institucionales) que, en nuestra opinión, se revelan de gran importancia. Entre las implicaciones asistenciales, nos parece acertado con el objeto de este trabajo resaltar dos:

1. Mejora de la práctica asistencial. El investigador clínico desarrolla un marcado espíritu crítico, lo que le lleva a basar sus decisiones (también las derivadas de su práctica clínica) en la mejor evidencia disponible. Contribuyendo a una mejora de la calidad asistencial prestada;
2. Estímulo profesional. La masificación y burocratización de los actuales sistemas públicos de salud, unidos a la falta de carrera profesional y bajos salarios, facilitan el desarrollo del síndrome de "burn-out" entre sus profesionales. La participación en proyectos de investigación clínica, la presentación y publicación de sus resultados en foros y revistas nacionales e internacionales tiene un plus de reconocimiento personal que contribuye en gran medida a combatir este síndrome. Como consecuencia, de nuevo, se produce un "efecto rebote" positivo y una mejora de la práctica asistencial del profesional².

En este contexto, es esencial garantizar que los estudios clínicos sean metodológicamente sólidos y éticamente responsables. Como ya hemos referido en las notas introductorias, normativas internacionales como la *Declaración de Helsinki* y el *Informe Belmont* establecen principios fundamentales para la protección de los participantes en investigación, asegurando que los beneficios potenciales superen los riesgos inherentes a los estudios clínicos.

Implicaciones institucionales y económicas

Desde una perspectiva institucional, la investigación clínica no solo representa un mecanismo de mejora en la atención sanitaria, sino que también, tiene un impacto significativo en la gestión de recursos y en la sostenibilidad financiera de los centros hospitalarios. Sus principales implicaciones incluyen:

1. Fuente adicional de financiación. En efecto, si la investigación clínica se gestiona adecuadamente, es fuente de recursos económicos adicionales que, en parte (generalmente en forma de adquisición de nueva tecnología), pueden revertir de nuevo en la mejora de la asistencia prestada a los pacientes del centro al que pertenece el investigador;

2. Imagen institucional. La mayoría (por no decir la totalidad) de centros sanitarios de referencia en el mundo son conocidos por la cantidad y calidad de investigación biomédica que desarrollan (muchas de tipo clínico). Dado que existe una relación evidente entre la imagen institucional de un centro y su capacidad de generar recursos económicos, la importancia estratégica (en este caso institucional) de la investigación clínica adquiere una nueva dimensión.

En la actualidad, la producción científica ha alcanzado niveles sin precedentes, lo que ha generado el desafío de discriminar entre estudios de alto impacto y publicaciones de calidad cuestionable. La creciente necesidad de establecer criterios rigurosos de selección y validación de investigaciones refuerza la importancia de contar con profesionales capacitados en el análisis crítico de la literatura científica.

En conclusión, la investigación clínica es un pilar fundamental en la evolución de la medicina moderna. Su integración en la práctica asistencial, su impacto en la formación de profesionales y su papel en el desarrollo institucional y económico hacen de ella una actividad esencial para la mejora continua de los sistemas de salud. Para que su potencial se traduzca en beneficios tangibles, es imprescindible garantizar su calidad metodológica, su ética irreprochable y su alineación con las necesidades reales de la sociedad.

Requisitos de la investigación clínica

Habiendo destacado la importancia de la investigación clínica, resulta necesario realizar un examen de las fases por las cuales la investigación clínica debe pasar para ser considerada esta del tipo científica. Para poder desarrollar investigación clínica de calidad (la que no es de calidad no es investigación de ningún tipo) se precisan tres requisitos fundamentales: (a) saber clínica; (b) conocer metodología de investigación; y, sobre todo, (c) vocación y disfrute del proceso investigativo.

El conocimiento de los aspectos clínicos de la enfermedad objeto de investigación es imprescindible para plantear una pregunta de investigación relevante y colocar el análisis de los resultados obtenidos en el contexto de un hipotético beneficio del paciente o, cuanto menos, una mejor comprensión de la enfermedad en cuestión. El tema de "la pregunta" no es baladí. Al contrario, formular una "buena" pregunta es el inicio imprescindible de un proyecto de investigación clínica de calidad y, posiblemente, su parte más difícil. En efecto, una buena pregunta debe ser: (1) relevante (en el contexto clínico de

la enfermedad objeto de estudio); (2) novedosa (no tiene sentido investigar lo ya conocido); y, (3) factible (tanto desde un punto de vista ético como metodológico).

Con el fin de formular una pregunta que cumpla estas tres características es imprescindible un conocimiento amplio de la literatura sobre el tema y un sentido clínico muy desarrollado. Tras la formulación de una pregunta adecuada, debe seguir una reflexión sobre el método o métodos más adecuados para constarla.

La cuestión que revelamos en este estudio, que en la práctica científica-clínica con frecuencia se altera el orden de esta ecuación y se plantean "preguntas" sobre la base de los métodos o técnicas disponibles en un laboratorio u hospital determinado y no sobre la necesidad de generar conocimiento nuevo y relevante sobre algún tipo de enfermedad en concreto. En este particular caso, el orden de los factores sí altera el resultado.

Este tipo de investigación suele aportar información poco relevante y, en la mayoría de los casos, repetitiva, por lo que es muy importante no invertir la ecuación: el proceso de investigación clínica siempre debe iniciarse por la formulación de la pregunta objeto de estudio (que en la investigación clínica nace con frecuencia de la observación del paciente) y, sólo a continuación, debatir sobre la mejor forma de contestarla. En otras palabras, el "método o técnica debe ser la consecuencia de la pregunta, ¡no su origen!"

En este sentido, presuponemos que el investigador clínico debe conocer diversos aspectos de "metodología de la investigación"³. Estos conocimientos "metodológicos" deben ser más "diversos", que "profundos" e incluyen, entre otros, aspectos relacionados con:

- Diseño experimental. Entre ellos cabe señalar la necesidad de establecer: (a) una hipótesis de trabajo clara (¡de nuevo "la pregunta"!); y unos objetivos congruentes con la hipótesis establecida; (b) *outcomes* definidos y con relevancia clínica; (c) un tamaño muestral adecuado (lo que, como se discute más adelante, obliga con frecuencia a plantear estudios multicéntricos); y, (d) un grupo control real, no simplemente "cosmético" (en palabras del Dr. JM Antó, Barcelona).
- Metodología experimental (fisiológica, celular o molecular). Considero que, un investigador clínico no necesita saber "cómo" se hace, sino "cuando" debe hacerse y "qué tipo de información" proporciona una metodología o técnica concreta para, con ello, poder valorar la utilidad potencial de una técnica determinada para generar más y mejor conocimiento sobre una patología determinada. En este sentido, es clara la necesidad de establecer alianzas con investigadores básicos, capaces de aportar este tipo de conocimiento, pero incapaces, salvo excepciones, de aportar la visión clínica necesaria en la investigación con pacientes.

- Análisis de los resultados, tanto estadístico, como gráfico. El análisis de los resultados de un proyecto de investigación debe iniciarse siempre por su análisis gráfico. Si se me permite, creo que la estadística sirve "para poner asteriscos a las gráficas". Además, es importante aprender a diferenciar significación estadística ($p < 0.05$) de significación clínica o biológica. En efecto, un resultado experimental determinado puede ser muy consistente y reproducible (lo que le conferirá un valor estadístico muy elevado) pero de escasa magnitud (por tanto, relevancia) clínica. En otras ocasiones, no obstante, un pequeño efecto biológico puede tener gran relevancia clínica. Desarrollar metodología capaz de valorar de forma objetiva la relevancia clínica de una observación, a semejanza de los test estadísticos ya conocidos desde hace tiempo, es uno de los grandes retos de la investigación clínica futura.

El futuro de la investigación clínica

En virtud de lo expuesto, y considerando el avance continuo de la ciencia, la aplicación de nuevas tecnologías en los procesos metodológicos y el desarrollo de innovadoras técnicas de investigación han llevado a una transformación profunda del paradigma tradicional de la investigación clínica⁴.

Dentro de los principales factores que impulsan este cambio destacan:

1. Transformaciones sociosanitarias. El envejecimiento de la población y el aumento del costo de los tratamientos innovadores han generado una reconfiguración de las prioridades sanitarias, exigiendo un enfoque más eficiente en la distribución de los recursos y en la planificación de la atención médica⁵.
2. Avances en el conocimiento biológico. El progreso en la genética y la biología molecular ha permitido una mayor comprensión de las bases patológicas de numerosas enfermedades. Además, el desarrollo y la aplicación de terapias basadas en células madre han dado lugar a la consolidación de la denominada "medicina regenerativa"⁶.
3. Innovaciones metodológicas. El perfeccionamiento de técnicas diagnósticas como la tomografía axial computarizada (TAC), la tomografía por emisión de positrones (PET) y la resonancia magnética nuclear (RMN), junto con el desarrollo de herramientas avanzadas como los *microarrays* de ADN, han revolucionado la capacidad de detección y análisis clínico.
4. La revolución de las tecnologías de la información. La digitalización del conocimiento médico ha permitido:
 - El acceso inmediato a información sobre diagnóstico y tratamiento por parte de los pacientes.
 - La proliferación de una cantidad masiva de datos científicos, lo que ha convertido la selección de información en un proceso cada vez más complejo y exigente.

- El avance en la telemedicina, que facilita el seguimiento clínico a distancia y abre nuevas posibilidades en la investigación clínica.

Todos estos vectores están contribuyendo a mutar un nuevo paradigma de la investigación clínica, caracterizada por una doble necesidad: la multidisciplinariedad y la multicentricidad. La primera es una necesidad imperiosa para sumar conocimiento proveniente de muy diversas áreas (clínica, básica, epidemiológica, económica, ética, informática, social, etc). La segunda es imprescindible para sumar casuística y garantizar la aplicabilidad clínica de los resultados.

Fruto de este nuevo paradigma es la proliferación de "redes" de investigación a la que asistimos, tanto en la comunidad europea (VI Programa Marco⁷, con sus "Networks of excellence" y "Research training networks"), como en los EEUU (*National Institutes of Health*, "Roadmap to accelerate medical research")⁸.

Consideraciones finales

La investigación clínica se ha consolidado como un elemento esencial en el desarrollo del conocimiento biomédico. Su importancia no solo radica en la generación de nuevas evidencias científicas, sino también en su impacto directo en la práctica médica y en la mejora de la calidad asistencial.

Si bien este trabajo ha abordado diversos aspectos metodológicos y conceptuales, también es importante reconocer el componente subjetivo que influye en la percepción de la investigación. Como ejemplo de ello, los Dres. Paydarfar y Schwartz⁹, en un influyente artículo publicado en *Science*, propusieron un "algoritmo para el descubrimiento", que resume los principios fundamentales que todo investigador debería seguir para lograr avances significativos:

1. *Slow down to explore*. Tomarse el tiempo necesario para explorar nuevas hipótesis y reflexionar sobre ellas es crucial para generar hallazgos significativos.
2. *Read, but not too much*. Si bien la lectura es fundamental, la sobrecarga de información puede ser contraproducente. La clave está en desarrollar la capacidad de seleccionar y filtrar la literatura relevante.
3. *Pursue quality for its own sake*. La búsqueda de la excelencia debe primar sobre la urgencia de publicar. La producción científica sin calidad compromete el avance real del conocimiento.
4. *Look at the raw data*. Analizar detenidamente los datos originales, incluyendo los valores individuales, permite obtener interpretaciones más precisas y evitar conclusiones erróneas basadas en promedios engañosos.
5. *Cultivate smart friends*. Rodearse de colegas inteligentes y comprometidos enriquece el proceso de investigación y potencia la calidad del trabajo realizado.

Estos principios representan una guía fundamental para orientar la investigación clínica hacia un futuro más sólido, riguroso y con un impacto tangible en la medicina y en la salud pública global.

Conflicto de intereses

Los autores declaran no tener ningún conflicto de intereses.

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CASE REPORT

Los ojos no ven lo que el cerebro no conoce: en razón a un caso clínico

The eyes do not see what the brain does not know: a clinical case report

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Resumen

El dolor abdominal es uno de los motivos más frecuentes de consulta médica y afecta a entre el 22% y el 25% de la población. Su amplio diagnóstico diferencial puede suponer un reto para el clínico. De hecho, entre el 24% y el 35% de los casos permanecen sin diagnosticar incluso tras años de seguimiento, como en el caso de nuestra paciente. Presentamos a una mujer de 33 años, con una larga historia de consultas por dolor abdominal, que acude de nuevo al servicio de urgencias por este motivo. Una investigación exhaustiva revela un diagnóstico sindrómico poco frecuente, cuyo tratamiento etiológico y específico mejorará significativamente su calidad de vida.

Palabras clave: Dolor abdominal, displasia septo-óptica, síndrome de Morsier.

Abstract

Abdominal pain is one of the most common reasons for seeking medical attention, affecting 22% to 25% of the population. Its broad differential diagnosis can be challenging for the clinician. In fact, between 24% and 35% of cases remain undiagnosed even after years of follow-up, as in the case of our patient. We present a 33-year-old woman with a long history of consultations for abdominal pain, who once again presents to the emergency department for this reason. A thorough investigation reveals a rare syndromic diagnosis, for which etiological and specific treatment will significantly improve her quality of life.

Key words: Abdominal pain, septo-optic dysplasia, Morsier syndrome.

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Descripción del caso clínico

Mujer de 33 años sin hábitos tóxicos, ni alergias medicamentosas, ni factores de riesgo cardiovascular. Como antecedentes pediátricos cabe destacar retraso en la adquisición de las habilidades motoras con retraso psicomotor residual moderado (desarrollo del lenguaje y actitud infantil) y ceguera congénita. Respecto a los antecedentes obstétricos, su gestación fue a término de madre de 17 años con parto eutócico, Apgar 8/9; antropométricamente, presentaba un peso de 3400gramos (P50-75), talla de 50 centímetros (P50-75) y perímetro cefálico 34cms (P50-75). A las 15 horas del nacimiento presentó cianosis, hipotonía, apatía generalizada e hipoglucemia e ingresó en UCI infantil con mejoría progresiva tras tratamiento de sostén y rehabilitador, siendo dada de alta posteriormente si tratamiento específico.

Respecto a los antecedentes digestivos, había presentado dolor abdominal asociado a náuseas y vómitos de 4 años de evolución (desde los 27 años). Durante este periodo, la paciente realizó repetidas visitas a urgencias hospitalarias y al centro de salud por dicho motivo. Se realizó estudio gastroscópico en 2020 (1 año antes del ingreso) con hallazgo de una pequeña hernia de hiato y esofagitis por reflujo grado B. En cuanto a los antecedentes endocrinológicos, consta una determinación analítica ambulatoria de TSH que se catalogó como hipotiroidismo subclínico que no precisó tratamiento (TSH 5 µUI/mL, T4L no determinada). Entre los antecedentes familiares, hay que destacar problemas cognitivos no especificados en la rama paterna. Previamente al ingreso la paciente seguía tratamiento únicamente con Omeprazol 20mg/díarios y, si precisaba, paracetamol y metoclopramida.

En el momento del ingreso, la paciente acude a urgencias por dolor abdominal, náuseas y vómitos crónicos que han empeorado y que se acompañan de intolerancia oral en las últimas 24 horas. Se revisan analíticas previas solicitadas para control del hipotiroidismo subclínico y se objetiva un cortisol plasmático de primera hora de 3µg/dL (Normal > 5 µg/dL). No polidipsia ni poliuria.

En la exploración física realizada presentaba una tensión arterial de 105/65 milímetros de mercurio, frecuencia cardíaca de 56 latidos por minuto y saturación de oxígeno del 97%. Su estado general estaba muy afectado, con gran postración. A nivel respiratorio y abdominal no existían signos de alarma. A nivel neurológico cabe destacar la presencia de retraso psicomotor, ceguera

bilateral y disminución moderada del nivel de consciencia, con ausencia de focalidad neurológica aguda.

En urgencias, se realiza analítica general donde no existe leucocitosis ni neutrofilia, o anemia; perfil digestivo compatible con la normalidad y único hallazgo de proteína C reactiva de 44 (rango de normalidad de 0-5 mg/L). Sedimento de orina compatible con la normalidad. Se realiza desde urgencias, consulta al servicio de endocrinología dado antecedente de cortisol de 3 µg/dL, por lo que se procede a ingreso en endocrinología y se administra cobertura esteroidea endovenosa a dosis de estrés.

Durante el ingreso en endocrinología, procedemos a completar el estudio.

Se realizó una amplia analítica general con banda hormonal completa entre cuyos datos cabe destacar: Glucosa 86 (70-110 mg/dL), Filtrado glomerular 104 mL/min, Sodio 139.5 (135-145mmol/L), Potasio 3.99 (3.5-4.5mmol/L), **TSH 1.5** (0.35-4.95 µUI/mL), **ftT3 1.37** (1.59-3.91pg/mL), **ftT4 0.59** (0.7-1.48 pg/mL), **ACTH 15.8** (<46.0 pg/mL), **Cortisol 5.20 pg/mL**, **FSH 2.59** (Folicular: 3,0 - 8,1 mUI/mL Ovulatorio: 2,5 - 16,7 mUI/mL Lútea: 1,4 - 5,5 mUI/mL), **LH 0.99** (Folicular: 1.8 - 11.8 mU/mL Ovulatorio: 7.6 - 89 mU/mL Lútea: 0.6 - 14 mU/mL), **Beta- Estradiol <24 pg/mL** (20-649 pg/mL), Prolactina 14.45 (1.2-29 ng/mL), **Testosterona 0.03** (0.17-0.33 ng/mL), **Dehidroepiandrosterona sulfato <0.15** (0.35-4.30mcg/mL), GHG 0.06 (0.05-7.4 ng/mL), Somatomedina C (IGF-1) **<15.00** (41-260 ng/mL).

Los resultados fueron compatibles con panhipopituitarismo con déficit de ejes corticotropo, tirotrópico, gonadotropo y somatotropo sin déficit neurohipofisario.

Se completó la valoración del eje corticotropo mediante el test de ACTH clásico (250 µg ACTH1-24) (ver **tabla I**). La respuesta normal al test de ACTH consiste en un aumento del cortisol plasmático de al menos 7 µg/dL por encima del valor basal (a menos que el valor basal exceda ya los límites normales), con un nivel máximo a los 60 minutos excediendo 18 µg/dL. Por tanto, observamos una respuesta claramente patológica al estímulo.

Se realizó estudio morfológico mediante resonancia magnética craneal e hipofisiaria con los siguientes hallazgos:

Tabla I: Respuesta alterada al test de ACTH clásico (250 µg ACTH1-24).

ACTH BASAL	< 5,00 pg/mL
CORTISOL SANGRE BASAL	5,10 µg/dL
CORTISOL SANGRE 30 MINUTOS	8,00 µg/dL
CORTISOL SANGRE 60 MINUTOS	8,70 µg/dL

Silla turca de tamaño normal. Adenohipófisis de tamaño y morfología normales, sin alteraciones claras en su intensidad de señal. Neurohipófisis visible en situación ectópica (adyacente al suelo del III ventrículo). Tallo hipofisario de grosor escaso, en situación normal. Nervios ópticos, quiasma y cintillas visibles, pero de escaso grosor. Ausencia de septum pellucidum, con fusión de los ventrículos laterales; las astas frontales presentan un margen inferior con morfología en punta. El III y IV ventrículo, así como el acueducto mesencefálico son de morfología normal.

Ausencia de septum pellucidum, con fusión de los ventrículos laterales; las astas frontales presentan un margen inferior con morfología en punta. El III y IV ventrículo, así como el acueducto mesencefálico son de morfología normal. Cuerpo calloso presente, arqueado, con rodilla y rodete de escaso grosor e istmo poco formado. Cisura silviana derecha anormalmente oblicua. En relación con ambas cisuras se observan surcos con orientación anómala; la operculización es escasa, especialmente los opérculos temporales. En la profundidad de ambas cisuras de Silvio la corteza es aparentemente más gruesa de lo normal y de aspecto polimicrogírico. Profundas a la corteza insular se identifican sendas imágenes de morfología más o menos lineal isointensas con la corteza cerebral, sugerentes de heterotopias subcorticales. Por tanto, la conclusión diagnóstica fue:

- Ausencia de septum pellucidum.
- Neurohipófisis ectópica.
- Hipoplasia de nervios ópticos y quiasma.
- Anomalías del desarrollo cortical (escasa operculización temporal principalmente izquierda, cisura silviana derecha oblicua, corteza de aspecto polimicrogírico en ambas cisuras silvianas, heterotopias subcorticales subinsulares).

Es relevante comentar que en el momento del ingreso hospitalario la familia no había aportado ningún informe clínico de la paciente, que había residido en otra zona del país desde su nacimiento hasta 8 años antes. Solamente en el séptimo día de hospitalización fue cuando la familia pudo aportar la siguiente información:

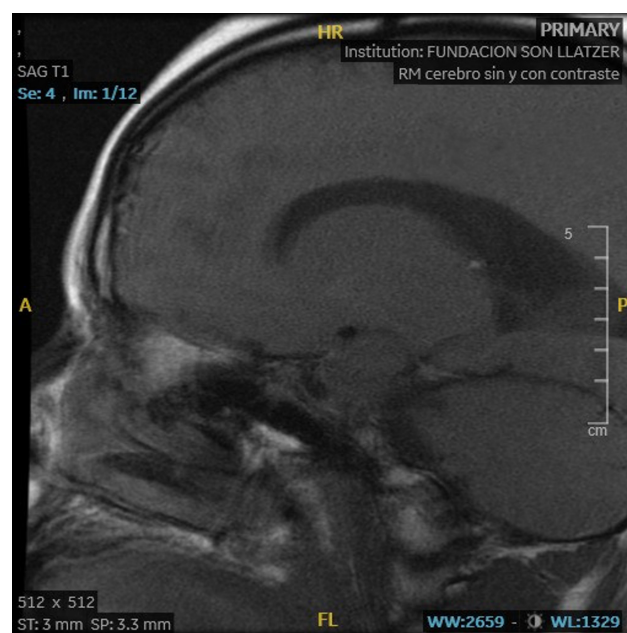
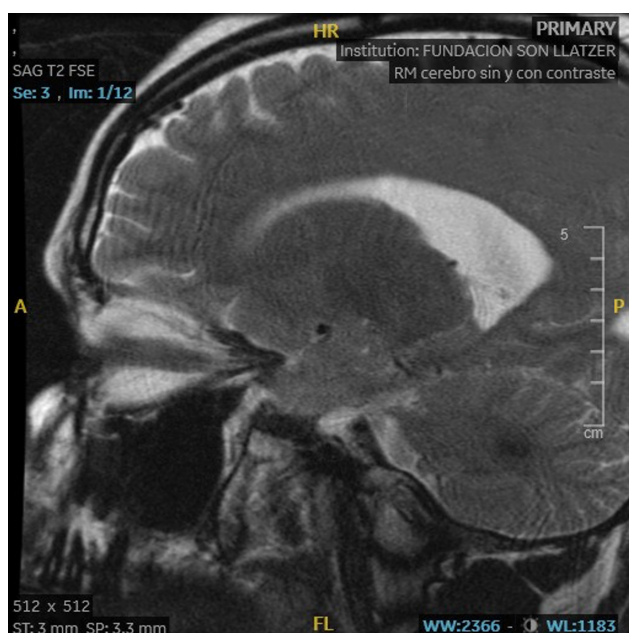
- Ecografía cerebral (realizada en la 1º semana de vida): dilatación de ventrículos cerebrales y presencia de cavum pellicedum y cavum vergae.
- TAC cerebral (a los 6 a de edad): se constata ausencia de septum pellucidum y se recomienda RM cerebral y seguimiento por su pediatra y medico habituales.
- No consta descripción de alteración, tratamiento ni seguimiento hormonal con posterioridad.

Ampliamos el estudio durante el ingreso con las siguientes pruebas complementarias:

- Ecografía abdominal: Estudio sin alteraciones ecográficas.
- Resonancia magnética pélvica: Útero y ovarios de morfología normales, pero de pequeño tamaño para la edad de la paciente.
- Densitometría ósea: Osteoporosis en fémur y columna lumbar.

Se completó un abordaje multidisciplinar con interconsultas a varios servicios del hospital. A destacar, la interconsulta a oftalmología dónde se objetiva: Estrabismo convergente con nistagmo; movimientos extraoculares incompletos por defecto visual sin limitación muscular; pupilas muy levemente reactivas; y en el fondo de ojo se aprecia atrofia nervio óptico bilateral.

Imagen 1 y 2: Corte transversal de resonancia magnética nuclear.



Durante su estancia en hospitalización, y coincidiendo con el inicio de la corticoterapia endovenosa, la paciente mejoró espectacularmente tanto de la sintomatología por la que ingresó (con desaparición del dolor abdominal) como su estado general a nivel neurológico y cognitivo. Paulatinamente, se ajustó la dosis de corticoides al estrés de la paciente y a las 48 horas, se inició levotiroxina oral. Posteriormente, se inició tratamiento con anticonceptivos orales para prevención de riesgo cardiovascular, mejora de la calidad de vida y prevención de fracturas...

Discusión y juicio clínico final

Con los resultados obtenidos, llaman la atención tres cosas: ausencia de septum pellucidum y anomalías del desarrollo cortical, hipoplasia de nervios ópticos y quiasma y panhipopituitarismo. Esta tríada de hallazgos nos permite realizar el juicio clínico final de **Displasia Septo-Óptica (DSO)** o síndrome de Morsier.

La DSO fue descrita por primera vez por Reeves en 1941^{1,2}. El diagnóstico de DSO puede realizarse cuando existe dos o más características de la tríada clásica: hipoplasia del nervio óptico, alteraciones hipofisarias y/o defectos anatómicos/funcionales en la línea media cerebral³. La incidencia de DSO es de 1 por 10.000 habitantes.

Su presentación clínica es heterogénea lo que ha hecho a muchos autores hablar del espectro o complejo del DSO y no definirlo como una entidad única⁴. Inicialmente, algunos autores afirmaban que el 30% de los casos de DSO expresaban las manifestaciones completas de la tríada, el 62% de los casos sufrían hipopituitarismo y el 60% tenían ausencia del septo pálido, siendo las alteraciones endocrinológicas la características más frecuente⁵.

Una sospecha clínica precoz con la solicitud de una prueba de imagen de sistema nervioso central y una analítica con banda hormonal hipofisaria, confirmarían

el diagnóstico permitiendo un tratamiento precoz hecho que demuestra mejorar el pronóstico de nuestros pacientes⁶.

Evolución

Tras la instauración del tratamiento, con excelente tolerancia y respuesta, se decide alta hospitalaria y seguimiento en consultas de forma periódica.

Durante el seguimiento en nuestra consulta externa, y tras constatar la correcta sustitución del resto de ejes hipofisarios anteriores, se confirmó el déficit de HGH (que era muy severo, con IGF-1 < 7 ng/mL) y se procedió a su tratamiento.

En el momento actual, a ya tras 2 años de seguimiento, la paciente cumple y tolera adecuadamente el tratamiento y, aunque presenta un importante déficit cognitivo, mantiene un buen estado general y anímico, con normalización de los hallazgos en la gastroscopia y con gran mejoría de su calidad de vida respecto a su situación previa.

Conclusión

Finalmente, es interesante señalar que nuestro caso, "redescubierto" a una edad tardía, se presentó con una sintomatología atípica, con síntomas abdominales de larga evolución en relación con déficit glucocorticoideo crónico. Por ello es importante recordar la necesidad de investigar (tanto inicialmente como de manera periódica) la presencia de patología hormonal hipofisaria en recién nacidos y niños con antecedentes de alteraciones de la línea media cerebral y/o del nervio óptico, así como la necesidad de un abordaje y seguimiento multidisciplinar.

Conflicto de intereses

La autora declara no tener ningún conflicto de intereses.

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CASE REPORT

Influence of nutritional composition on the circadian rhythms of patterns of urinary pH and its role in kidney stone prevention

Influencia de la composición nutricional en los ritmos circadianos de los patrones del pH urinario y su papel en la prevención de cálculos renales

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Abstract

This study assessed the impact of nutritional composition on circadian rhythms of urinary pH to analyze dietary influence on urine acidity, which could support the medical management of urolithiasis. A healthy 21-year-old male followed four different diets (usual, acidic, alkaline, and DASH) over four weeks, recording micturition, nutritional, and anthropometric data. Urinary pH was measured multiple times daily, yielding average values of 6.02, 5.66, 6.06, and 5.93 per week, respectively, while Net Acid Excretion (mEq/day) presented values of 65.54, 134.93, 29.60, and 16.27 in the same order. A significant correlation ($r = 0.49$, $P < 0.01$) was found between water intake and urinary pH. The findings confirm that diet influences urinary pH and highlight the value of circadian analysis, which provides more detailed information on daily variability compared to a single 24-hour measurement.

Key words: Urinary pH, nutritional composition, kidney stones, dietary habits, circadian rhythm.

Resumen

Este estudio evaluó el impacto de la composición nutricional en los ritmos circadianos del pH urinario para analizar la influencia de la dieta en la acidez urinaria, lo que podría apoyar el manejo médico de la urolitiasis. Un hombre sano de 21 años siguió cuatro dietas diferentes (habitual, ácida, alcalina y DASH) durante cuatro semanas, registrando datos de micción, nutrición y antropometría. El pH urinario se midió varias veces al día, obteniendo valores promedio semanales de 6.02, 5.66, 6.06 y 5.93 respectivamente, mientras que la Excreción Neta de Ácido (mEq/día) presentó valores de 65.54, 134.93, 29.60 y 16.27. Se encontró una correlación significativa ($r = 0.49$, $P < 0.01$) entre la ingesta de agua y el pH urinario. Los hallazgos confirman que la dieta influye en el pH urinario y destacan el valor del análisis circadiano, que proporciona información más detallada sobre la variabilidad diaria en comparación con una única medición en 24 horas.

Palabras clave: pH urinario, composición nutricional, cálculos renales, hábitos dietéticos, ritmo circadiano.

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Introduction

The nutritional composition of a nephrolithiasis patient's diet has a significant correlation with the likelihood of kidney stone formation and recurrence. As a result, most patients receive dietetic and lifestyle recommendations to decrease the probability of kidney stone formation. The most relevant factor is daily water intake, as it may significantly reduce the risk of kidney stone development. The general recommendation is to increase the daily fluid intake to 2.5 – 3 L, resulting in less concentrated urine and a minimum daily diuresis of 2.5 L of urine¹. On the other hand, it has been proved that an effective diet against urolithiasis is based on a high content of fruits (high in citrate) and vegetables (low in oxalate), reduction of animal protein, and a normal calcium intake¹⁻⁴. Additionally, the lithiasis formation process is strictly related to urinary pH. In fact, acidic pH values ($\text{pH} < 5.5$) induce the precipitation of uric acid crystals, whereas alkaline pH values ($\text{pH} > 6.2$) induce the precipitation of phosphate crystals⁵.

It is also important to highlight the relevance of measuring the urinary pH at different times of the day. This approach allows to examine the impact of diet and postprandial peaks, which cannot be assessed with a 24-hour urine test since it only represents the overall result of the day. On the other hand, the formation process of kidney stones depends on urine composition, urinary pH, and the stagnation duration of urine⁴⁻⁵. Therefore, circadian rhythm enables a more detailed and specific analysis of urinary pH and time between micturition, whereas a 24-hour urine test only provides a single urinary pH value instead of the overall daily variability.

Thus, diet and urinary pH are factors that are directly related to urolithiasis. For this reason, a detailed monitoring and evaluation is key for the medical management of this pathology.

Case Report

This study included a single volunteer, a healthy 21-year-old male without prior history of kidney stone disease. After providing signed informed consent, the subject was provided with instructions and the following products to carry out the procedures of the study: a mobile application (myLit-Control® App)⁶ linked to a portable pH meter (Lit-Control® pH Meter), and a smart bottle (Lit-Control® Smart Bottle) to track the water intake, a food scale (Soehnle Page Compact 300) to weigh the food, a validated nutrient database (USDA National Nutrient Database for Standard Reference), and a template for data collection.

The participant was asked to register micturition data (urinary pH value and timestamp), nutritional composition data (quantity in grams of ingredients consumed), and

anthropometrical data for a total duration of 4 weeks. The dietary regimen changed each week, with the following sequence: usual diet on week 1 (typical participant's diet used as control diet), acidic diet on week 2 (increased intake of animal protein and restriction of fruits and vegetables), alkaline diet on week 3 (increased intake of fruits and vegetables and restriction of animal protein), and Dietary Approaches to Stop Hypertension (DASH) diet on week 4. No specific recommendations were given for fluid intake. No alcohol intake was reported.

Nutritional data was converted from weight of the ingredients to nutritional values in terms of Water, Protein, Calcium, Magnesium, Potassium, and Phosphate content due to their influence on the urine's acid-base equilibrium⁷. These nutritional values enabled the estimation of the Potential Renal Acid Load (PRAL), Organic Acids (OA), and Net Acid Excretion (NAE), as described by T. Remer et al⁷.

Urinary pH data was analyzed using descriptive statistics, as well as the daily average number of micturition readings. The relationship between the nutritional variables and urinary pH was analyzed with the Pearson correlation coefficient and mean value of each nutritional variable. The circadian rhythm of urinary pH was examined according to the averaged pH values of the urines collected during the 4 time-regions of the day (Midnight to 6 am, 6 am to noon, noon to 6 pm, and 6 pm to midnight), which was the approach used by Murayama et al⁸.

Urinary pH and the associations with dietary components

The readings from the pH meter yielded average values of 6.02 (SD = 0.35), 5.66 (SD = 0.23), 6.06 (SD = 0.48), and 5.93 (SD = 0.41) for the first, second, third, and fourth week, respectively. The mean urinary pH of all readings was 5.92 (SD = 0.41). The daily average number of micturition readings was 7.71 (SD = 1.38), 5.86 (SD = 1.07), 5.86 (SD = 0.90), and 6.28 (SD = 0.76) during the first, second, third, and fourth week, respectively.

Water and potassium intake were the only two nutritional variables that had a significant linear dependency with urinary pH. The results of the Pearson correlation coefficients for water intake were 0.49 ($P < 0.01$) and 0.27 ($P < 0.16$) for potassium intake (not relevant for the study).

The average protein intake (expressed in grams) was 123.19 (SD = 13.02), 167.01 (SD = 34.19), 74.36 (SD = 24.79), and 107.07 (SD = 18.51) for the first, second, third, and fourth week, respectively; whereas the average calculated Net Acid Excretion (expressed in mEq/day) was 65.54 (SD = 19.22), 134.93 (SD = 24.95), 29.60 (SD = 16.63), and 16.27 (SD = 9.02) for the first, second, third, and fourth week, respectively.

Circadian rhythm

The circadian variability of urinary pH is shown in **table I** and **figure 1**. The readings in the morning (6 am to noon) yielded averages of 5.85 (SD = 0.31) for week 1, 5.57 (SD = 0.28) for week 2, 5.83 (SD = 0.42) for week 3, and 5.79

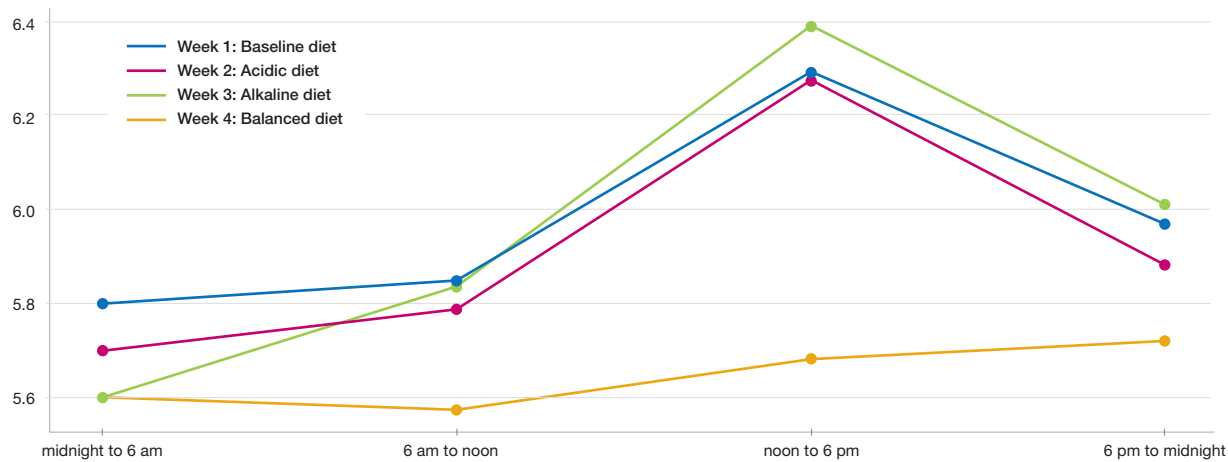
(SD = 0.29) for week 4. On the contrary, readings in the afternoon (noon to 6 pm) yielded averages of 6.29 (SD = 0.32) for week 1, 5.68 (SD = 0.23) for week 2, 6.39 (SD = 0.38) for week 3, and 6.28 (SD = 0.22) for week 4.

Table I: Urinary pH circadian rhythm evaluation for each week.

	Week 1	Week 2	Week 3	Week 4
00:00 - 06:00	5.80 (SD = 0.00)	5.60 (SD = 0.12)	5.60 (SD = 0.30)	5.70 (SD = 0.00)
06:00 - 12:00	5.85 (SD = 0.31)	5.57 (SD = 0.28)	5.83 (SD = 0.42)	5.79 (SD = 0.29)
12:00 - 18:00	6.29 (SD = 0.32)	5.68 (SD = 0.23)	6.39 (SD = 0.38)	6.28 (SD = 0.22)
18:00 - 00:00	5.97 (SD = 0.31)	5.72 (SD = 0.20)	6.01 (SD = 0.42)	5.88 (SD = 0.37)

SD, standard deviation.

Figure 1: Diurnal variability of urinary pH.



Discussion

This study examined the relationship between the nutritional composition of the diet and the impact on the diurnal variability of urinary pH (circadian rhythm) in a healthy, male subject. The measurement of urinary pH was performed using a portable pH meter instead of 24-hour urine test since it has been proved that the latter does not provide a valid representation of the diurnal variation of urinary pH⁹. Moreover, reactive strips were not employed since several studies support that they have not enough accuracy and precision⁹⁻¹³. On the other hand, portable electronic pH meter has been shown to be more accurate compared to reagent strips readings¹⁰.

During the whole study period, the subject had an average urinary pH value of 5.92 (SD = 0.41), with a minimum value of 5.0 and maximum value of 7.4. These results verified his healthy urological conditions, since the European Association of Urology states that a healthy adult is expected to produce urine with a urinary pH in the range of 4.8 and 7.4, with an average value around 6.03^{4,9,14}. As presented in **figure 1**, the circadian variation of the volunteer showed the diurnal pattern of

non-lithogenic individuals. This pattern had three peaks that correspond to the postprandial alkaline tide (noon to 6 pm) in contrast to the acidic urinary pH early in the morning (6 am to noon) and late at night (6 pm to midnight). It is important to clarify that the postprandial alkaline tide showcases the influence of the diet intake on the acid-base equilibrium of urine, whereas the acidic pH values may also represent the acidification of urine after long periods of stagnation (e.g., sleep).

During the second week, the subject consumed an acidic diet based on a limitation of fruits and vegetables, and an increased intake of animal protein. This week was characterized by the highest protein intake and Net Acid Excretion values, which confirm the acidifying effect of this dietary regimen. Additionally, the circadian pattern showed values below 6.0, characteristic of healthy individuals (6 am to noon was 5.57 [SD = 0.28] and noon to 6 pm was 5.68 [SD = 0.23]). In fact, the readings from the pH meter yielded an average value of 5.66 (SD = 0.23), which was significantly more acidic than other weeks.

The diet of the third week was based on alkaline foods, with limited intake of animal protein, and increased intake of fruits and vegetables. Accordingly, the value of Net Acid Excretion was 29.60 mEq/day (SD = 16.63), which clearly demonstrates the alkalinization effect of this dietary regime on urinary pH. Furthermore, the diurnal variation clearly presented postprandial alkaline tides between noon and 6 pm, 6.39 (SD = 0.38), and between 6 pm and midnight, 6.01 (SD = 0.42). In fact, the readings from the pH meter yielded an average value of 6.06 (SD = 0.48) which, unlike to the acidic diet, it is around the expected value of 6.03.

It is interesting to highlight that weeks 1 and 4 (usual and DASH diets) had a higher daily average amount of micturition: week 1 had 7.71 (SD = 1.38) compared to 5.86 (SD = 1.07), 5.86 (SD = 0.90), and 6.28 (SD = 0.76) for week 2, week 3, and week 4, respectively. A limitation of this study is that there was no washout period between diets, so it cannot be ruled out that the pH results may be contaminated in the first days after the change.

Conclusion

This case study supports the hypothesis that nutritional composition of the diet has a significant impact on the diurnal variation of urinary pH and in the daily urine volume excreted, which play a key role in kidney stone formation. Therefore, nutritional recommendations and habits should be strongly considered in the medical management of kidney stone patients, focusing on

water intake and dietary supplementation. These measures can effectively modulate the urinary pH during the day, increase the diuresis, and reduce the risk of crystallization of the main stone components, such as uric acid, calcium oxalate, calcium phosphate, ammonium magnesium phosphate and/or cystine. For example, high urine pH favors formation of phosphate-containing stones, whereas low pH is associated with uric acid and cystine stones^{5,15}. Thus, depending on the stone composition, the recommendations should include an acidic or alkalinizing diet.

Additionally, this case report describes a new approach to analyze urinary pH, recording the circadian rhythm of urinary pH using a portable pH meter. This approach enables a detailed analysis of the variability of urinary pH throughout the day. This is significant to study postprandial peaks, stagnation time, and other parameters that must be considered to prevent the formation of kidney stones.

Further studies will be performed to continue evaluating the impact of dietary habits and composition on the circadian rhythms of urinary pH on a larger population, which may include healthy participants and patients from multiple urological pathologies.

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Conflict of interests

The author(s) declared no potential conflicts of interest.

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CASE REPORT

Malignant phyllodes tumor management - a case report

Manejo del tumor filoides maligno: un reporte de caso

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Abstract

Phyllodes tumor is a rare fibroepithelial neoplasm of the mammary gland, accounting for 0.3 to 1% of all primary breast neoplasms. The name "phyllodes" comes from the ancient Greek terms "phylon" and "eidos", meaning "leaf-like". The clinical picture is characterized by the appearance of a painless mass in the mammary gland, which progressively grows and can reach giant sizes. In this case report we present management of a giant phyllodes tumor of the left mammary gland measuring 25 cm with regional lymphadenopathy in a 73-year-old woman. Surgical excision with a free margin of 1 cm is advisable and, while lymph node metastases are present in approximately 1% of cases, sentinel lymph node assessment can be performed in suspicious cases to decide the necessity of lymph node dissection.

Key words: Phyllodes tumor, sentinel lymph node biopsy, malignancy, sarcoma.

Resumen

El tumor filoide es una neoplasia fibroepitelial rara de la glándula mamaria, que representa entre el 0.3 y el 1% de todos los tumores primarios de mama. El término "filoides" proviene del griego antiguo phylon y eidos, que significan "en forma de hoja". El cuadro clínico se caracteriza por la aparición de una masa indolora en la glándula mamaria, que crece de forma progresiva y puede alcanzar tamaños gigantes. En este reporte de caso, presentamos el manejo de un tumor filoides gigante en la glándula mamaria izquierda, de 25 cm, con linfadenopatía regional, en una mujer de 73 años. Se recomienda la escisión quirúrgica con un margen libre de 1 cm y, aunque las metástasis ganglionares se presentan en aproximadamente el 1% de los casos, en casos sospechosos puede realizarse la evaluación del ganglio centinela para determinar la necesidad de una disección ganglionar.

Palabras clave: Tumor filoide, biopsia del ganglio centinela, malignidad, sarcoma.

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Introduction

Phyllodes tumor is a rare fibroepithelial neoplasm of the mammary gland, accounting for 0.3 to 1% of all primary breast neoplasms¹. It can develop at any age, but is predominantly found in women aged 30 to 50 years. Phyllodes tumor was first described by Johannes Müller in 1838 and called it "leaf-shaped cystosarcoma"². The name "phyllodes" comes from the ancient Greek terms "phyllon" and "eidos", meaning "leaf-like". In 1943, Cooper y Ackermann reported a case of phyllodes tumor with metastases³.

Histologically, phyllodes tumor consists of two components: epithelial and stromal. The epithelial component consists of a single-layer epithelium that lines the ducts of the mammary gland. The stromal component surrounds the ducts and consists of connective tissue and fibroblasts. Phyllodes tumor is characterized by hyperplasia of connective tissue and proliferation of fibroblasts⁴. The clinical picture is characterized by the appearance of a painless mass in the mammary gland, which progressively increases and can reach giant sizes.

In this case report we present management of a giant phyllodes tumor of the left mammary gland with regional lymphadenopathy in a 73-year-old woman.

Case description

A 73-year-old female patient was admitted to the oncological surgery department with complaints of her left breast increase in size. It is known from the patient's medical history that the mass was discovered by chance on a chest CT scan in 2021, when the patient was undergoing treatment for COVID-19 pneumonia. Apart from that the patient also had concomitant diseases that included hypertension, type 2 diabetes, cerebrovascular disease with chronic cerebral ischemia, and osteoporosis. According to the CT scan results, a soft mass measuring 52 x 73 mm with clear and uneven contours was found in the left breast. However, the patient was lost to follow up and did not consult an oncologist. In 2024, the patient came to the clinic with signs of her left breast enlargement (**Figure 1**).

Ultrasound of the mammary glands showed a mass of the left breast with axillary lymphadenopathy on the left. A core-needle biopsy (CNB) of the mass was performed under ultrasonography (USG) guidance. According to the histological examination, the morphological picture corresponded to sclerosing adenosis of the left breast. Mammography revealed that the entire volume of the left mammary gland was represented by a heterogeneous multinodular mass with the size of 18 x 13 cm and macroscopic calcification up to 13 x 8 mm visualized at the border of the posterior third quadrants of the mammary gland (**Figure 2**).

Figure 1: Patient with breast enlargement (A, B, C – different positions).

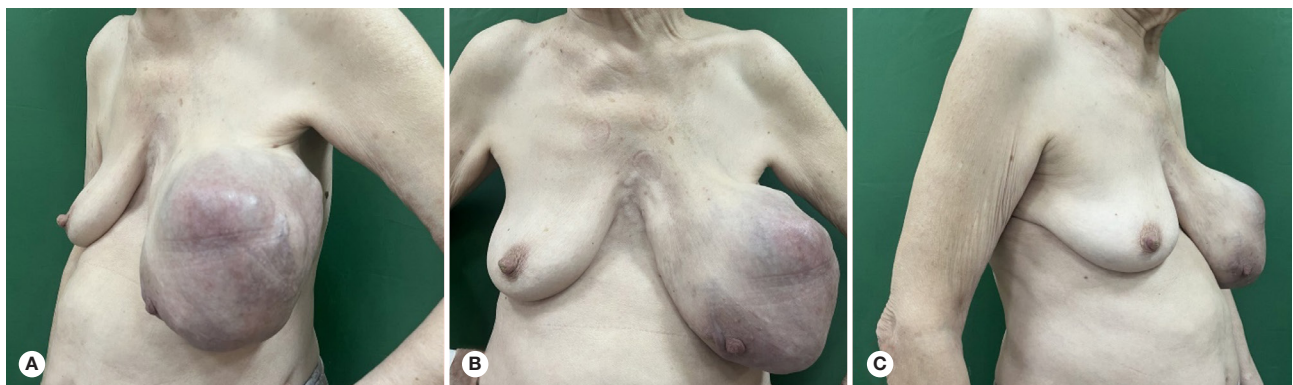
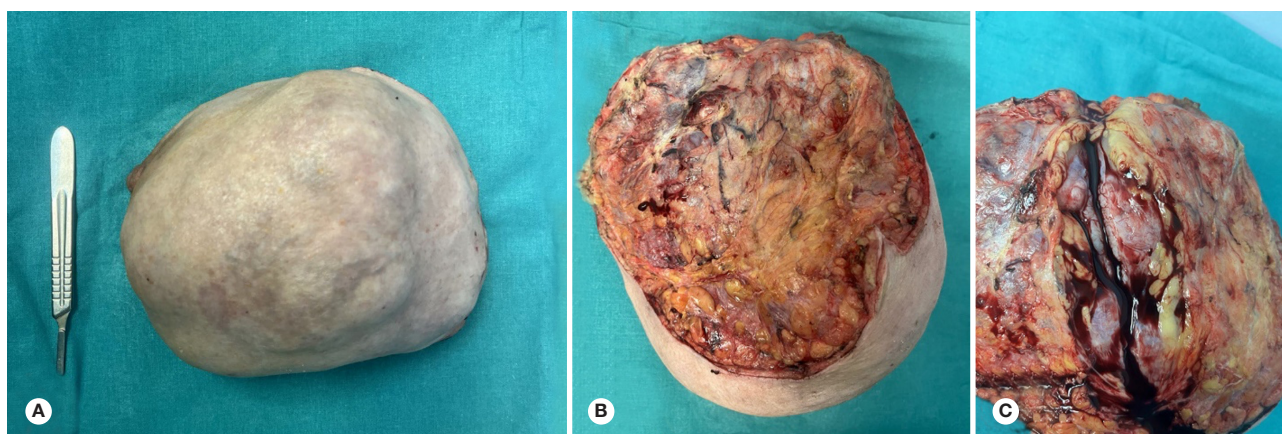


Figure 2: Imaging of the breast. A – mammography; B – Chest CT (frontal view); C – Chest CT (axial view).



Figure 3: Breast mass. **A** – Macroscopic specimen (anterior view); **B** – Macroscopic specimen at the level of the surgical margin; **C** – Macroscopic specimen (dissected, indicating areas of tumour degeneration and bleeding).



Loci of diffuse fibrocystic adenosis were noted in the right mammary gland. A repeated CNB was performed under USG guidance. Histological examination revealed the morphological picture most consistent with a benign phyllodes tumor of the left mammary gland. The cytogram of the left axillary lymph node contained a small number of lymphoid elements with signs of degeneration. According to CT of the chest, the patient had a giant mass of the left mammary gland and ipsilateral axillary lymphadenopathy. The patient was referred to surgical department for operative treatment with the diagnosis: "Benign phyllodes tumor of the left mammary gland". Clinical examination revealed asymmetry of the mammary glands. The left mammary gland was enlarged and deformed, the nipple-areolar complex was displaced relative to the breast meridian, the skin was pale-blue and on its surface dilated collateral veins were visible. On palpation, the left mammary gland was completely replaced by a dense neoplasm measuring up to 20 x 25 cm. The left axillary lymph nodes were not palpable. An independent expert USG scan of the mammary gland and axillary region on the left was performed. The left mammary gland was replaced by a volumetric formation measuring 30 x 20 cm, with wavy contours, heterogeneous structure, with zones of reduced and lower echogenicity, with non-echogenic zones, areas of calcification and intranodular vascularization. Axillary lymphadenopathy on the left was identified. The lymph nodes had no cortico-medullary differentiation and central echogenicity, with increased vascularization. Taking into account the gigantic size of the mass, the impossibility of performing an organ-preserving surgery and lymphadenopathy, a multidisciplinary team meeting decided to perform mastectomy of the left mammary gland with sentinel lymph node biopsy (**Figure 3**). Preoperatively, an intravenous injection of ceftriaxone in a volume of 1 g was performed and 1 mg of indocyanine green (ICG) was injected subcutaneously in sterile conditions. The patient underwent mastectomy on the left, with excision of a "sentinel" lymph node under ICG guidance. Intraoperatively, there were 3 lymph nodes

identified, all without tumor growth. The postoperative period was uneventful. The patient received intravenous injections of non-steroidal anti-inflammatory drugs (NSAIDs) (Ketorolac in a volume of 30 mg/ml), oral gastroprotection (Omeprazole 20 mg x 2 times a day), subcutaneous anticoagulant therapy (Enoxaparin 0.4 mg in the evening), daily dressing changes with an antiseptic solution of chlorhexidine. The drain was removed on the 3rd day after surgery. The patient was discharged on the 5th day after the operation.

A routine histological examination showed total replacement of breast tissue with a large-tuberos lobular tumor. Malignant phyllodes tumor of the left mammary gland on the left was investigated. Microscopic picture of breast tissue was characterized by pronounced proliferation of the stromal component and increased stroma cellularity, presented with proliferating ductal epithelium. The lymph nodes were 1.5 x 1 x 1 cm in size, without tumor growth. There was no evidence of recurrence 6 months after surgical treatment.

Discussion

The phyllodes tumor is a rare disease of the mammary gland and there is no unified management protocol¹. Phyllodes tumor mainly develops in women of reproductive age, however, in our clinical case, the patient was 73 years old. The World Health Organization classifies this type of tumor into histologically benign, borderline and malignant. Benign tumor is the most common type among all forms. It is characterized by a pronounced growth of the stromal component, increased stroma cellularity. Such features are commonly seen, as atypical stromal cells having nuclear polymorphism and more than 10 mitoses in 10 fields of view⁵.

Our patient undergone several diagnostic procedures, after which a diagnosis of "benign phyllodes tumor" was established. The benign form of the phyllodes tumor

is similar to fibroadenoma, which can lead to a false negative result and influence treatment tactics.

To establish tumor histology, it is necessary to perform histological examination using a CNB or vacuum aspiration biopsy. Given the fact, that a benign phyllodes tumor has the potential for malignancy, the most optimal diagnostic method is surgical excision⁶. To date, the surgical treatment is the main management approach. It is possible to perform an organ-preserving operation, however, in case of large tumours patients usually undergo mastectomy⁷.

Data analysis of Zhang et al. demonstrated that patients with malignant phyllodes tumor who had undergone mastectomy had better disease-specific and overall survival⁸. Nevertheless, in the study group 44.3% of tumours were more than 5 cm limiting the possibility to perform resections⁹. According to the National Comprehensive Cancer Network guidelines for the treatment of phyllodes tumors, when performing an organ-sparing surgery, it is necessary to excise a tumor with a thickness of the surgical edge of at least 1 cm, regardless of its type⁹. In the current case report, according to histological study, the mass was considered benign, but the presence of lymphadenopathy could indicate a malignancy and metastasis. Moreover, given the total mammary gland replacement by the tumor, the patient undergone a mastectomy with excision of the sentinel lymph node. Since benign forms of phyllodes tumors are more frequent, regional and distant metastases are uncommon. In our clinical case, regional lymphadenopathy was revealed. The decision to perform excision of sentinel lymph node was taken. Nonetheless, histological examination showed no metastases. Therefore, axillary lymph nodes changes on the side of the lesion were most likely reactive.

Yu and et al. conducted systematic review and meta-analysis of real data on the treatment of a phyllodes tumor. They found that among 1686 patients with malignant phyllodes tumor 406 patients had recurrence, which comprise 25.1%⁷. They did not find association between the size of the mass and recurrence⁷. Although, the meta-analysis revealed no significant difference in the recurrence rate between the >5-mm and <5-mm margin groups, a significantly higher recurrence rate was in the <1-mm margin group compared with the ≥1-mm margin group. The risk of recurrence was also associated with tumor histopathology features, such as stromal overgrowth, a mitotic count of >5, tumor necrosis, an infiltrative tumor border, and positive resection margin⁷. However, it should be noted that there is clear paucity of data related to borderline and malignant phylloid tumors. In this individual case, given the pronounced stromal growth, presented by ductal epithelium proliferation, we assumed that the patient had a high risk of recurrence.

Histological examination of the sentinel lymph node revealed no metastases. It should be noted that nodal metastases are rare and metastases are seen approximately in 1% of cases¹⁰. Discussion about the further tactics of treating patients with malignant phyllodes tumors remains open. Our patient had a mastectomy with excision of a “sentinel” lymph node. The need for the use of post-operative chemotherapy and radiation therapy requires research. Zhang and et al. conducted a study that showed that adjuvant radiation therapy and chemotherapy does not affect the long-term survival of patients with a malignant phyllodes tumor⁸.

The management of this group of patients depends on the size of the tumor and lymph node involvement. Assessment and management of large breast tumors may be complicated and require reconstructive surgery^{11,12}.

There are several important points for discussion related to the case report. As it is demonstrated in our case the CNB did not indicate malignant type of tumor. The sensitivity of CNB for diagnosing benign, borderline, and malignant phyllodes tumors is 4.9%, 4.2%, and 25.0%, respectively¹³. The corresponding specificity is 92.0%, 98.2%, and 100%, respectively¹³. Therefore, the results of CNB should interpreted in lights of the clinical picture and imaging.

Axillary nodal metastasis is rare for malignant phyllodes tumor but distant metastasis can occur in up to 22% of cases^{4,14}. Axillary lymph node biopsy can be performed in cases of lymphadenopathy for differential diagnosis, however there are no large scale studies. Alternatively, FDG PET/CT imaging may be beneficial in high risk group of patients to diagnose metastatic lesions, however there is no consensus of its application in the case of phylloides tumor^{4,14}. A whole body scan may be beneficial in the detection of unexpected distant metastasis but his data is mostly limited to selective case studies¹⁴. Our patient did not undergo PET/CT imaging as it is not indicated in the local guidelines.

The National Comprehensive Cancer Network and MD Anderson guidelines recommend wide local excision of phyllodes tumors, aiming for margins 1 cm or greater^{15,16}. It seems that surgery is the main approach for phylloides tumors since adjuvant radio- and chemotherapy is controversial¹⁷. Chemotherapy does not improve survival in patients without distant metastasis^{8,18,19}. Although radiotherapy may be effective for disease control without prolonging survival¹⁹. As our patient was 73 years old with a negative surgical margin more than 1 cm the patient did not undergo chemotherapy and radiotherapy. Local guidelines recommend abstaining from chemotherapy and radiotherapy after surgical treatment with a negative surgical margin.

Conclusion

Giant phyllodes tumors are quite uncommon but potentially malignant. Surgical excision with a free surgical margin of 1 cm is advisable. If lymph node metastases are present, which is seen in approximately 1% of cases, sentinel lymph node assessment can be performed in suspicious cases to decide the necessity of lymph node dissection.

Conflict of interests

The author(s) declared no potential conflicts of interest.

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