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With the collaboration:

G CONSELLERIA
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Fundació Patronat Científic
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CONCESIÓN DE BECAS Y PREMIOS 2022

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

El jurado calificador de los premios y becas convocados por la *Fundació Patronat Científic* del COMIB, reunido el día 6 de octubre del presente, acordó la concesión de las siguientes becas y premios:

BECAS DE INNOVACIÓN

Una beca para una estancia en un centro sanitario extranjero, dotada con 3.000 euros.

· Cristina Pineño Flores, facultativa especialista en Cirugía General y del Aparato Digestivo en la Unidad de Cirugía Oncológica Peritoneal del Hospital Universitario Son Espases, para realizar una estancia formativa de dos meses en la Unidad de Tumores Peritoneales en el *Instituto Nazionale di Tumori* en Milán, Italia.

Queda desierta la adjudicación de la segunda beca para estancias en centros sanitarios extranjeros al no haberse presentado más solicitudes.

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

1. Diego de Sotto Esteban, facultativo especialista en Pediatría y jefe del Servicio de Pediatría de la Clínica Rotger, para una estancia de un mes en el Servicio de Endocrinología Pediátrica del *Hospital Sant Joan de Déu* de Barcelona.

2. Maria Magdalena Rosselló Vadell, FEA en Neurología en el Hospital Universitario Son Espases, para una estancia durante el periodo de junio de 2022 a mayo de 2023 en la Unidad de Epilepsia del Hospital del Mar de Barcelona

BECAS FUNDACIÓ BANC SABADELL DE ROTACIÓN EXTERNA PARA MIR

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

1. Maider Gómez de Segura Solay, residente de la especialidad de Radiodiagnóstico en el Hospital Universitario Son Espases, para una estancia de dos meses en el Servicio de Radiología Abdominal y Genitourinaria del *Centre Hospitalaire Universitaire de Toulousse*, Francia.

2. Adela Álvarez Rio, residente de la especialidad de Cirugía Plástica, Estética y Reparadora en el Hospital Universitario Son Espases, para una estancia de siete semanas en el Servicio de Cirugía Plástica y Reparadora en *The University of Tokyo Hospital*, Japón.

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

1. Carlos García Zanoguera, residente de la especialidad de Oncología Radioterápica en el Hospital Universitario de Son Espases, para una estancia de dos meses en el Servicio de Oncología Radioterápica del Instituto Valenciano de Oncología en Valencia.

2. María Cruz Álvarez-Buylla Puente, residente de la especialidad de Dermatología en el Hospital Universitario Son Llàtzer, para una estancia de un mes en el Servicio de Dermatología del *Hospital Universitari Santa Creu i Sant Pau* de Barcelona, y para una segunda estancia de dos meses en el Servicio de Dermatología Pediátrica del Hospital Sant Joan de Déu de Barcelona.

PREMIOS DE INVESTIGACIÓN

Tres premios de 1.500 euros.

"Premio Mateu Orfila"
Al trabajo científico titulado "Método Matemático de Reconstrucción 3D para la valoración de infiltración tumoral en el cáncer de colon", presentado por Sebastián Jerí Mc Farlane, Álvaro García-Granero García-Fuster y Noemí Torres Marí.

"Premio Damià Carbó"
Al trabajo científico titulado "*A highly effective ultrasonic resective surgery protocol for the Management of MRONJ lesions. An ambispective, unicenter study*", presentado por Juan Martín Zárate González, Marta Monjo Cabrer, Joana Ramis Morey, Andrés García Piñeiro y Víctor Lasa Menéndez.

"Premio Metge Matas"
Al artículo "*Diaphragmatic Peritonectomy and Full-Thickness Resection in CRS/HIPEC May Allow Higher Completeness of Cytoreduction Rates with a Low Rate of Respiratory Complications*", cuyos autores son Andrea Craus Miguel, Juan José Segura Sampedro, Francesc Xavier González Argente y Rafael Morales Soriano.

PREMIO FUNDACIÓ MUTUAL MÈDICA AL MEJOR PROYECTO DE TESIS DOCTORAL

Un premio dotado con 2.000 euros al proyecto titulado "Resultados de la infiltración de toxina botulínica (BTX-A) vs Plasma Rico en Plaquetas (PRP) en el tratamiento de la fascitis plantar", presentado por Isabel María Ruiz Hernández, médica especialista en Traumatología y Cirugía Ortopédica (Área de Pie y Tobillo) en la Clínica Rotger y FEA en Cirugía Ortopédica y Traumatología en el Hospital Universitario Son Llàtzer.

PREMIO CAMILO JOSÉ CELA DE HUMANIDADES MÉDICAS

Un premio dotado con 1.500 euros al trabajo titulado "El lenguaje de la Medicina", cuyo autor es el Dr. Alfonso J. Ballesteros Fernández, médico especialista en Medicina Interna y Aparato Digestivo. Doctor en Medicina *cum laude*.

Un accésit, con la misma dotación económica, al trabajo presentado "Implicaciones legales del diagnóstico serológico del VIH y la comunicación de resultados", cuya firmante es Gemma Jiménez Guerra, médica especialista en Microbiología y Parasitología en el Hospital Can Misses.

CERTAMEN DE CASOS CLÍNICOS PARA MIR

Se otorga un primer premio de 1.000 euros y un segundo premio de 500 euros.

El jurado propuso los cinco mejores casos que se presentarán próximamente en el COMIB y, posteriormente, se notificará el veredicto de los dos premiados.

Los cinco casos finalistas son:

1. "Nódulos subcutáneos como forma de presentación de nocardiosis diseminada en una paciente inmunodeprimida".
Autores: Jorge A. Adsuar Mas, María Cruz Álvarez-Buylla Puente, Verónica Fernández Tapia y Antoni Nadal Nadal.

2. "Despistaje de fístula aortoentérica en paciente con masa pulsátil y hemorragia digestiva".
Autora: Olga Revilla Poza.

3. "Rotura esplénica espontánea con hemorragia masiva durante la Maniobra de *Pringle* en cirugía hepática laparoscópica".
Autora: Patricia Camporro González.

4. "Intoxicación por solución alcalina casera. ¿Conocemos los riesgos de las soluciones de rehidratación oral?".
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Autor: Juan Martínez Andrés.

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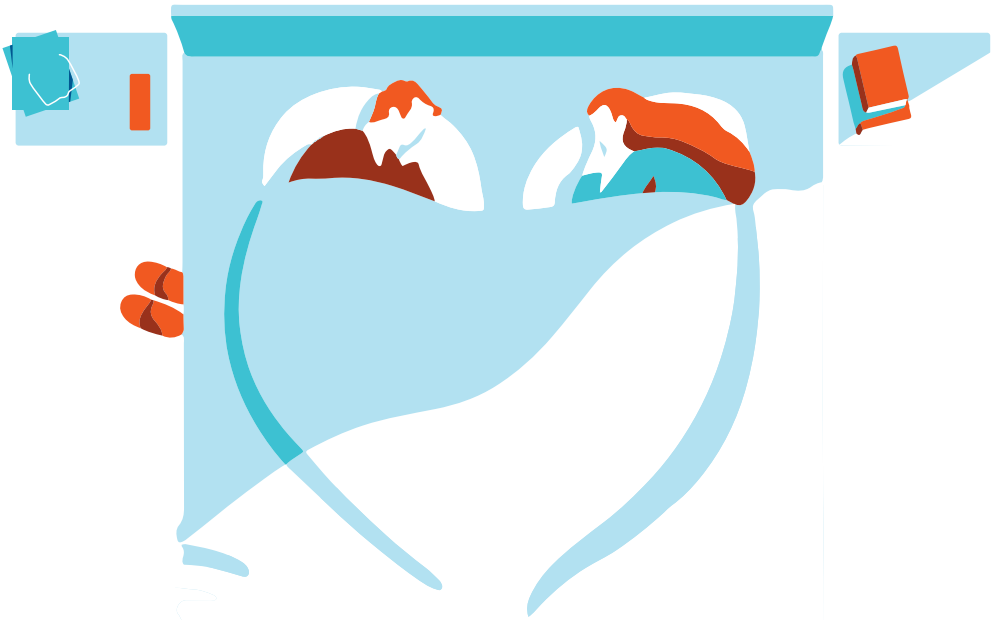

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ORIGINAL

Systematic review evidence on the factors influencing teenage mothers utilization of maternal health services in Sub Saharan Africa

Revisión sistemática de los factores que influyen en la utilización de los servicios de salud materna por parte de las madres adolescentes en el África Subsahariana

David Chinaecherem Innocent[1], Advait Vasavada[2], Stanley Chinedu Eneh[3], Angelica Chinecherem Uwaezuoke[4]

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Abstract

Background: Adolescent pregnancy poses health concerns to both the mother and the fetus. Teenage girls are more likely than older women to experience preterm labor, protracted labor, and cephalic pelvic disproportion according to studies. Understanding the factors that influence adolescent mothers' use of services is essential to ensuring their involvement in maternity health care. The aim of this study was to provide sufficient evidence on the factors influencing the use of maternal health care among teenage women in Sub-Saharan Africa.

Methods: The preferred reporting item for systematic reviews and meta-analysis (PRISMA) was adopted in reporting the findings of this review. Studies reporting post-natal care services, antenatal care services, and skillful birth delivery among teenagers were included, and studies on the socioeconomic determinants, cultural factors, usage level, and social factors associated with teenage women's use of maternal health services in Sub-Saharan Africa published in English from 2000 to June 2022 were considered in the inclusion criteria. Studies focused on HIV-positive teenage mothers were excluded from the review. A literature search was conducted on PubMed, PsycINFO, Web of Science, EMBASE, CINAHL, and African Journal Online which identified 24 eligible studies. The Critical Appraisal Skill Program checklist and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) checklist were used for the quality assessment of the qualitative and quantitative studies included in this review.

Results: An array of factors is seen to influence the utilization and access to maternal health services among teenage mothers in sub-Saharan Africa. These factors range from demographic factors, cultural and economic factors, and inclusively economic-related factors. Interpersonal-level factors which influence young women's use of maternal health care were found to be peer pressure, family traditions and customs, spousal knowledge, opinions, and education, as well as the influence of other family members in this study. In addition, education level, place of residency, economic situation, and knowledge and perception of the need for maternal health care are individual factors that influence how adolescent mothers use of maternity care.

Conclusion: A significant proportion of teenage women do not have reliable access to utilization and access to maternal care throughout pregnancy. Teenage mothers in Sub-Saharan Africa have been shown to utilize and have access to maternal health care in response to a range of socioeconomic and environmental circumstances. Interventions such as educational programs through medical and allied health professionals and teenage female partners are imperative to improve their participation in the use of maternity care.

Keywords: Adolescents, Utilization, Teenage Mothers, Maternal health services, Sub Saharan Africa.

Resumen

Antecedentes: El embarazo en la adolescencia plantea problemas de salud tanto para la madre como para el feto. Según los estudios, las adolescentes tienen más probabilidades que las mujeres mayores de sufrir un parto prematuro, un parto prolongado y una desproporción cefálica-pélvica. Comprender los factores que influyen en el uso de los servicios por parte de las madres adolescentes es esencial para garantizar su participación en la atención sanitaria de la maternidad. El objetivo de este estudio era aportar pruebas suficientes sobre los factores que influyen en el uso de la atención sanitaria materna entre las mujeres adolescentes del África subsahariana.

Métodos: Se adoptó el ítem de reporte preferido para revisiones sistemáticas y meta-análisis (PRISMA) para reportar los hallazgos de esta revisión. Se incluyeron los estudios que informaban sobre los servicios de atención posnatal, los servicios de atención prenatal y el parto con habilidad entre las adolescentes, y se consideraron en los criterios de inclusión los estudios sobre los determinantes socioeconómicos, los factores culturales, el nivel de uso y los factores sociales asociados con el uso de los servicios de salud materna por parte de las mujeres adolescentes en el África subsahariana publicados en inglés desde 2000 hasta junio de 2022. Se excluyeron de la revisión los estudios centrados en madres adolescentes seropositivas. Se realizó una búsqueda bibliográfica en PubMed, PsycINFO, Web of Science, EMBASE, CINAHL y African Journal Online que identificó 24 estudios elegibles. Para la evaluación de la calidad de los estudios cualitativos y cuantitativos incluidos en esta revisión se utilizó la lista de comprobación del Critical Appraisal Skill Program y la lista de comprobación de la International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

Resultados: Se observa una serie de factores que influyen en la utilización y el acceso a los servicios de salud materna entre las madres adolescentes del África subsahariana. Estos factores van desde factores demográficos, culturales y económicos, hasta factores relacionados con la economía. Los factores a nivel interpersonal que influyen en la utilización de los servicios de salud materna por parte de las jóvenes fueron la presión de los compañeros, las tradiciones y costumbres familiares, los conocimientos, las opiniones y la educación del cónyuge, así como la influencia de otros miembros de la familia en este estudio. Además, el nivel educativo, el lugar de residencia, la situación económica y el conocimiento y la percepción de la necesidad de atención sanitaria materna son factores individuales que influyen en el uso que las madres adolescentes hacen de la atención materna.

Conclusiones: Una proporción significativa de mujeres adolescentes no tiene un acceso fiable a la utilización y el acceso a la atención materna a lo largo del embarazo. Se ha demostrado que las madres adolescentes del África subsahariana utilizan y tienen acceso a la atención sanitaria materna en respuesta a una serie de circunstancias socioeconómicas y ambientales. Las intervenciones, como los programas educativos a través de los profesionales médicos y de la salud aliados y las parejas de las adolescentes, son imprescindibles para mejorar su participación en el uso de la atención materna.

Palabras clave: Adolescentes, Utilización, Madres adolescentes, Servicios de salud materna, África subsahariana.

Introduction

Background

One in five adolescent girls gives birth before the age of 18, according to a World Health Organization (WHO) survey, which estimates that 16 million females between the ages of 15 and 19 give birth each year[1]. Adolescents are defined as individuals between the ages of 10 and 19 in a report by the United Nations Population Fund (UNFPA)[2]. In the poorest regions, such as Sub-Saharan Africa and Southeast Asia, this ratio jumps to one in three females[2]. For a variety of causes, from societal to personal ones, adolescent women are at risk for unwanted pregnancies[3,4].

Numerous studies have found that teen pregnancy is unhealthy for both the teen and the unborn child and these studies also show that preterm delivery, protracted labor, and cephalic pelvic disproportion are more common in adolescent girls than in older women[5,6,7,8]. There is a 50% probability that a baby delivered to an adolescent would die before reaching their first month of life, and teenage women are more likely to have babies with low birth weights and Apgar scores, as well as higher rates of admission to critical care units[3,6,8,9]. In addition to the physical risks to their health outlined previously, adolescent mothers in Sub-Saharan Africa typically endure social deprivation[6]. Due to the fact that many of them are unable to finish their schooling and are thus required to raise their children alone, many of them have inadequate resources to sustain themselves and their children[8,4]. Teenage mothers find it difficult to adjust to their new roles and deal with these concerns while simultaneously managing "adolescence" and all of its challenges[9,13,14,15].

According to a publication, it's important to recognize a variety of factors that can affect and improve access to and utilization of professional maternal health care, but it's also crucial to support young women in having a healthy and safe pregnancy, delivery, and infant. These factors include economic, cultural, and medical factors[10]. In the publication it was posited that teenagers who survive adolescent pregnancies may be more susceptible to pregnancy complications[10,11],

pre-eclampsia, anemia, and postpartum hemorrhage [9] as a result of these circumstances and factors. Additionally, some studies have demonstrated that teenage women are more likely to have complications such as obstetric fistulas and adoption of mainstream maternal health services has significantly impacted the reduction of mortality and morbidity through the early detection of risk indicators and the management of potential issues with the maternal health care package, which includes postoperative care, skilled birth delivery care, and antenatal care[4,7,12,11,13,14].

Despite these benefits, teenage women still underuse maternal health interventions. Young women in Sub-Saharan Africa reportedly encounter issues including unlicensed births and inadequate antenatal care, according to one research[15]. Only 25% of Nigerian teenage women obtain safe birthing procedures, according to a poll[16]. Only one-third of teenage mothers in Sub-Saharan Africa receive postnatal care[18,19]. Given that a number of factors influence how frequently young women in Sub-Saharan Africa use the services for maternal health, the empirical basis is tenuous. When women lack access to maternity care, negative effects on children, mothers, governments, and communities are inevitable, as outlined in the sustainable development goals[20]. The use of maternal health services throughout the continuum of care, including antenatal, intrapartum (by trained birth attendants), and postpartum care, has been shown to depend on lowering maternal mortality and improving survival, as well as the health, quality of life, and outcomes for adolescent mothers[19,20]. This study employed a social model to identify characteristics that influence how Sub-Saharan African teenage women use healthcare and related services, cutting through several elements including demographic, socioeconomic, and culturally connected issues to produce complete recommendations.

There have been several primary studies and systematic reviews looking at teenage use of maternity care in various parts of the world, according to a scoping search of the available data. However, although some of these studies and publications only analyzed data from a select few nations, others considered all women worldwide, in both wealthy and developing nations. The goal of this systematic review is to close this knowledge gap by providing clinicians, program designers, and policymakers with advice on how to improve young women's access to maternal health care in Sub-Saharan Africa. As a result of this review, significant evidence on the factors influencing maternal health service utilization by Sub-Saharan African teenage mothers will be provided to inform decision-making among concerned groups.

Aims and Objectives

This study seeks to offer enough information on the factors influencing the use of maternal health care among teenage women in Sub-Saharan Africa. However, the specific goals given below will be looked at in order to achieve the overall purpose of this evaluation;

1. To analyze the use of maternal health care by teenage women in Sub-Saharan Africa.
2. To offer evidence on the socio-demographic and interpersonal variables that impact teenage women's use of maternal health services in Sub-Saharan Africa.
3. To evaluate the structural and organizational elements that affect teenage women's use of maternal health services in Sub-Saharan Africa.
4. To investigate how cultural and economic variables in Sub-Saharan Africa affect teen mothers' usage of maternal health care.

Methods

This research followed the PRISMA-P guidelines for reporting systematic reviews.

Inclusion Criteria

Inclusion criteria are the features or characteristics of potential participants that are regarded as suitable for inclusion in research. Nonetheless, the following were included in the review's inclusion criteria:

1. Studies published in the English language
2. Studies reporting post-natal care services, antenatal care services, and skillful birth delivery among teenagers
3. Studies on the socioeconomic determinants, cultural factors, usage level, and social factors associated with teenage women's use of maternal health services in Sub-Saharan Africa.
4. Quantitative, mixed methods and qualitative studies.
5. Primary studies addressing the research question of this review

Exclusion Criteria

The exclusion criteria for the review were:

1. Studies not in line with the inclusion criteria of this review
2. Studies addressing factors influencing maternal healthcare service use among HIV-positive adolescent mothers
3. Studies reporting post-natal care services, antenatal care services, and skillful birth delivery among HIV-positive teenagers
4. Studies are not published in English.
5. Studies that posit insufficiency in reporting design and methods utilized.

Database/Search Strategy

The following internet databases were explored to acquire evidence on variables impacting contemporary contraception use in Nigeria and Sub-Saharan Africa:

- MEDLINE
- SCOPUS
- Web of Science
- PUBMED
- EMBASE
- African Online Journal
- CINAHL
- Goggle Scholar

Search Strategy

The right Boolean operators were applied with the right search phrases and word variants. In order to merge similar search synonyms and words, the Boolean operator 'OR' was used inside each domain[21]. The 'AND' Boolean operator was then used to combine the domains. Depending on the database in use, medical subject headings, for example, are used in electronic search standards (MeSH or indexing words). To recover any alternate ends, the asterisk (*) was used for truncation. Wildcards such as the hash (#) and question mark (?) were also used to substitute one or more characters, depending on the database's capabilities.

Search terms utilized for the study

((Factors) OR (Enablers) OR (Barriers) OR (Determinants) OR (Causes) AND (Utiliz*) OR (Uptake) OR (Usage) OR (Use) AND ("Antenatal Care") OR ("Post-natal Care") OR ("Antenatal Servi*") OR ("Post-natal Serv*") OR ("Skill* Birth") OR ("Maternal Care") OR ("Maternal Servi*") OR ("Maternal Health") OR ("Health Care") AND ("Adolescent* Mothers") OR ("Adolescent Women") OR ("Teen* Women") OR ("Teen* Mother") AND ("Sub-Saharan Africa) OR (Africa)).

Study Selection and Extraction

Study Selection

The databases were searched online, and the results were published for each database. The search results were saved in an electronic reference management program (RefWorks). Duplicate articles were found and removed both within and between databases. The titles and abstracts were checked again to ensure that they met the qualifying criteria. It was also used to check the whole texts of articles that were recognized to be potentially important during the abstract screening phase and the title for eligibility. A reference list search of the publications that were included will be conducted in order to find any further relevant data. The screening stage is carried out by independent reviewers to minimize the likelihood of research being overlooked. This is also required to avoid the misapplication or misinterpretation of qualifying criteria, as well as the rejection of relevant research during the screening process due to a single screener's random error and prejudice. The screening technique was carried out by a single reviewer due to the nature of this review being an academic dissertation. This saved time and money by eliminating the need for two reviewers.

Data Extraction

The strategy for gathering data was to read the reviews' linked articles and comb through them for relevant facts and information regarding the area of interest. Research has been provided in a proper and objective manner by data extraction, and this is why data extraction is important: it makes research simpler to synthesize, get information that may be used to assess the risk of bias, and identify numerical data[22]. The standardized data extraction form can be automated in computer format or manual in paper format, and it can be as short or as long as needed with coding, particularly if a quantitative analysis is necessary[22]. The electronic tool (Excel spreadsheet) established for this review will comprise study groups (inclusion and exclusion criteria), causes and impediments relevant to the review issue, author name and publication year, particular aims, and participant characteristics (age, ethnicity, and educational level, as well as socioeconomic status).

Quality Assessment

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Good Research Practices for Retrospective Database Analysis (CHEERs Checklist) were used to assess the quality of the included quantitative studies, while the Critical Appraisal Skills Program (CASP) checklist was used to assess the quality of the included qualitative studies[23]. This approach has been used to assess the quality of previous studies. The research will be graded on a three-level scale based on 17 factors. A total score of 70% or more suggests a high-quality study, a total score of 50-70% indicates a medium-quality study, and a total score of less than 50% indicates a low-quality study.

Synthesis and Analysis

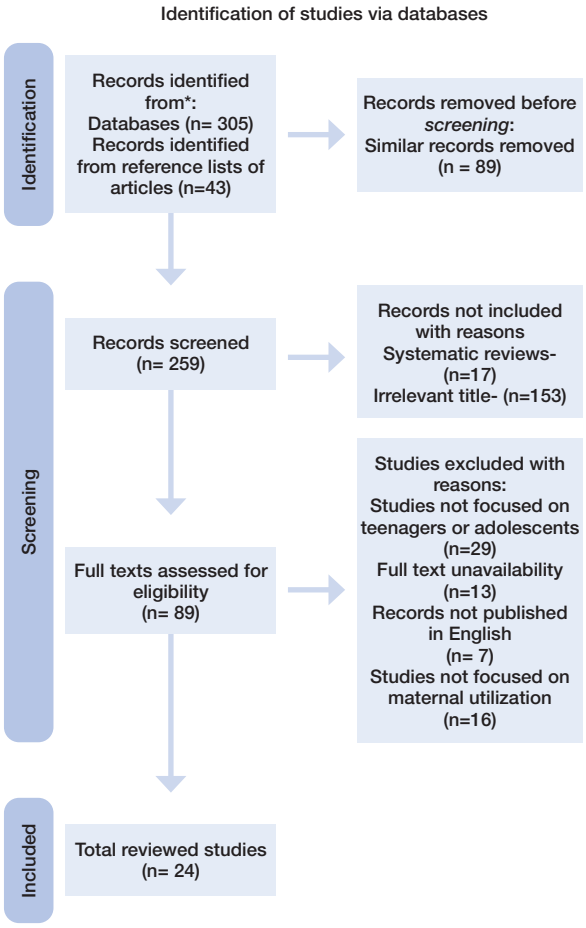
The act of merging data from several studies to develop a conclusion based on a body of evidence and address the research question is known as synthesis[24]. It is critical to look for variability in research findings since there may be methodological discrepancies in the specifics of the included studies[24]. Statistical meta-analysis was not done because the methods used in this review are diverse. In addition, unlike meta-analysis, narrative synthesis is a more subjective process[24], which aids in the integration of research presented in a review. In this strategy, which is akin to storytelling[25], textual and tabular summaries of the findings are used. The technique is rigorous and open to eliminate the chance of prejudice.

Results

A total of three hundred and five (305) studies were identified from the several databases where searches

were conducted. 43 potential studies were identified from the reference list of articles. Following screening of the identified records, a sum of twenty four studies were eligible and added in the review[26-49]. See **figure 1**.

Figure 1: Flow chart for study Identification based on PRISMA.



Characteristics of Studies Included

Considering the features of the studies in **table I** below, it was revealed that of the 24 studies[26-49] included in this review, two studies were conducted in Nigeria[32,46]. Also, it was seen that six studies were conducted in Kenya[29,35,40,42,43,48], three studies were carried out in South Africa[28,31,38], and two studies in Malawi[36,41]. Antenatal care services, postnatal services, and skillful birth delivery were the key focus of 80% of the included studies. Also, it was demonstrated that eighteen studies adopted a quantitative design, whereas four studies adopted a qualitative design, and two studies utilized a mixed method model. Considering the theories adopted in three papers, Donabedian's model, health belief model, and phenomenology were among the theories used in the framework of the primary studies. Three of the four studies that utilized a qualitative technique adopted a thematic model of analysis, whereas in most of the quantitative studies, multivariate logistic regression and binary logistic regression were utilized as data analysis methods. Most qualitative investigations used topic analysis, whereas most quantitative research used bivariate and multivariate logistic regression analysis.

Quality of Included Studies

Considering the assessment of the strength of the qualitative and quantitative studies included in this review based on tables 2 and 3 below, objectives, methods, results, and discussion were major components described in the CASP and CHEERs-ISPOR checklists used for the evaluation of the listed studies' quality For the CASP checklist, (+) shows that the study fulfils the criteria, (-) shows that the study does not fulfil the criteria, while (?) depicts or shows the criterion is unclear. While for the ISPOR checklist, score (2) depicts the criteria as "strong", score (1) illustrates the criteria to be "moderate," while a score of (0) reveals that it is weak. Based on the 19 quantitative studies appraised using the ISPOR checklist, results showed that eight (8) studies were of medium quality, two studies were of poor quality, and nine (9) studies had high quality. A total of four (4) qualitative studies were appraised using the CASP checklist.

Table I: Characteristics of the included studies.

Study	Care type	Measured Outcomes	Theory adopted	Sample Size	Study Design	Analysis of Data Method	Location
Gross *et al.*[26]	Antenatal Care	Factors that affect early and late ANC attendance	Not reported	*N* = 440	Quantitative design	Logistic Regression Model	Tanzania
Rukundo *et al.*[27]	Antenatal Care	Variables Influencing utilization of teenager friendly ANC	Not reported	Key informants	Qualitative design	Thematic Analysis	Uganda
Duggan and Adejumo[28]	Post Natal Care and Antenatal Care	Maternity care perception	Grounded theory	18 adolescent, 15-19 years	Qualitative design	Not reported	South Africa
Mulinge *et al.*[29]	Antenatal Care	Variables and factors affecting teens' use of prenatal care services	Not reported	13-19 years	Quantitative survey design	Logistic regression and chi square	Kenya

Study	Care type	Measured Outcomes	Theory adopted	Sample Size	Study Design	Analysis of Data Method	Location
Singh *et al.*[30]	Antenatal Care Post natal care and Delivery	Variables and factors that influence the use of maternal services	Not reported	1646 adolescent mothers	Quantitative survey design	Multivariate and Bivariate analyses	Mali
Rall *et al.*[31]	Antenatal Care	Communication in ANC	Not reported	12-19 years teenage women (n=20)	Qualitative design	Teach Data analysis method	South Africa
Rai *et al.*[32]	Immunization, safe delivery and ANC	Potential contributing variables to the use of Maternal Health care services	Not reported	934 adolescent mothers aged 15-19	Quantitative survey design	Multivariate logistic regression analyses	Nigeria
Alemayehu *et al.*[33]	Antenatal Care (ANC)	Factors that affect the use of Antenatal Care	Not reported	14-19 years teenage women (n=994)	Quantitative survey design	Multivariate and Bivariate analyses	Ethiopia
Ebeigbe and Gharoro[34]	PNC, safe delivery and Antenatal Care	Pregnancy frequency Interventions and complications	Not reported	*N* = 114	Quantitative design	Fishers exact Test	Nigeria
Banke-Thomas *et al.*[35]	Skilled Birth Attendance, PNC and ANC	Variables that affect the use of maternity care	Not reported	15-19 years married teenage women (n=898)	Quantitative survey design	Multivariate and Bivariate analyses	Kenya
Brabin *et al.*[36]	Antenatal Care	Why adolescent antenatal care (Antenatal Care) programs would need to be improved?	Not reported	10-19 years married teenage women (n=615)	Quantitative design	Binary logistic regression and Chi-square test	Malawi
Adam *et al.*[37]	Safe Delivery and ANC	Risk of prenatal problems, surgical delivery, and anemia	Not reported	459	Quantitative design	Chi-square Test and Fishers test	Sudan
Worku and Wolde-senbet[38]	Antenatal Care	Factors that affect the uptake of Antenatal Care	Not reported	383	Quantitative and Qualitative design	Bivariate and Multivariate Analysis	South Africa
Chaibva *et al.*[39]	Antenatal Care	Factors that prevent teenagers from using Antenatal Care services	Health belief model	19 years of age or less (80 adolescent women)	Quantitative design	Descriptive Analysis of frequency and proportion	Zimbabwe
Ronen et al. [40]	Antenatal Care	Factors influencing the use of Antenatal Care	Not reported	19 years below married teenage women (n=278)	Quantitative survey design	Multivariate and Bivariate analyses	Kenya
Rai *et al.*[41]	Post-natal care and Antenatal Care	Factors influencing Antenatal Care and Post Natal care	Not reported	15-19 years married teenage women (n=2160)	Quantitative survey design	Multivariate and Bivariate analyses	Malawi
Birungi *et al.*[42]	PNC, skilled birth attendance and ANC	Antenatal Care and Post-natal care-influencing factors	Not reported	15-19 years old adolescents	Quantitative design	Multilevel Logistic models	Kenya
Banke-Thomas *et al.*[43]	Safe delivery, Post-natal care and Antenatal Care	Maternity care utilization	Not reported	15-19 years	Quantitative survey design	Multivariate and Bivariate analyses	Kenya
Hokororo *et al.*[44]	RH service and Antenatal Care	Barriers to SRH care	Phenomenology	Adolescents aged 15-20 years	Focus group and Qualitative design	Thematic Analysis	Tanzania
Helle-ringer[45]	Antenatal Care	HIV testing in Antenatal Care	Not reported	10-19 years	Quantitative survey design	Multivariate and Bivariate analyses	Central and West Africa
Reynolds *et al.*[46]	Delivery, Post-natal care and Antenatal Care	Factors associated with maternity services	Not reported	2434 adolescents (married) of 15-24 years	Quantitative survey design	Binary Logistic Regression and Chi-square	Nigeria

Study	Care type	Measured Outcomes	Theory adopted	Sample Size	Study Design	Analysis of Data Method	Location
Musaran-dega *et al*.[47]	PMTCT and Antenatal Care	Gaps in service uptake	Not reported	*N*=40	Retrospective and Quantitative design	Multi variable binomial regression analyses	Zimbabwe
Ochako *et al*.[48]	Antenatal Care	The time of Antenatal Care and the type of delivery aid are related	Not reported	1675 women of 15-24years	Quantitative survey design	Multivariate Logistic regression analyses	Kenya
Mngadi *et al*.[49]	PNC and Safe Delivery	Quality of maternity care	Donabedian Model	*N*=33 pregnant adolescent mothers	Quantitative and qualitative design	Content Analysis	Swaziland

Table II: CASP Findings for Qualitative included Studies.

Criteria	Rukundo *et al*. (2015)	Duggan and Adejumo (2012)	Hokororo (2015)	Rall (2013)
Is the objective of the research clearly stated?	+	+	+	+
Does a qualitative technique make sense?	+	+	+	+
How well did the research plan to take into consideration and account of the researches objective?	?	+	+	?
Was the recruitment strategy suitable for the objective of the research?	?	+	+	+
Did the data collection method address the topic of the study?	+	+	+	+
Has the relationship between the researcher and the participants been properly taken into account?	+	?	+	+
Have ethical considerations been made?	+	+	-	+
Was the data analysis thorough enough?	+	+	+	+
Is the conclusion made in a clear manner?	+	?	+	?
How valuable is the Research	+	+	+	+

Key: Fufill Criteria (+)
Doesn't fufill criteria (-)
Unclear (?)

Table III: ISPOR Checklist for Quality of Quantitative Included Studies.

Section	Item	Quality Criteria Description	Reynolds *et al*.	Brabin *et al*.	Ebeigbe *et al*.	Elhassan *et al*.	Chaibva	Alemayhue *et al*.	Gross *et al*.	Banke-Thomas *et al*.	Birungu *et al*.	Ochako *et al*.
Objectives	1	Specific goals should be stated, along with any established hypotheses	2	2	1	2	2	2	2	1	2	2
Study design	2	Describe the main research design components	2	1	1	1	2	1	2	2	1	2
Setting	3	Describe the environment or setting, the locations, and the pertinent times, such as the recruiting, exposure, follow-up, and data collecting times	1	2	2	1	2	2	2	1	2	2
Participants	4	Provide the qualifying requirements, as well as the sources and procedures used to choose the participants	2	1	1	1	2	2	2	2	2	1
Variables	5	All outcomes, exposures, predictors, possible confounders, and effect modifiers should be precisely defined.	2	2	1	2	1	2	1	2	1	1
Data sources/ measurement	6	Provide sources of information and information on the evaluation techniques for each variable of interest (measurement)	2	1	0		2	2	1	2	1	2
Bias	7	Describe any steps made to address any bias sources	2	1	0	0	1	1	1	2	1	1
Study size	8	Describe how the study size was determined.	2	1	0	2	1	2	2	1	1	2

Section	Item	Quality Criteria Description	Reynolds *et al.*	Brabin *et al.*	Ebeigbe *et al.*	Elhassan *et al.*	Chaibva	Alemayhue *et al.*	Gross *et al.*	Banke-Thomas *et al.*	Birungu *et al.*	Ochako *et al.*
Quantitative variables	9	Describe the methods used to handle quantitative variables in the analysis. Describe the classifications that were chosen, if relevant, and why5	1	2	1	1	2	2	0	2	2	1
Statistical methods	10	List all statistical techniques, including those that are used to account for confounding	2	2	1	1	1	1	1		1	1
	11	Describe how missing data were handled	1	1	1	1	0	0	0	1	1	1
Participants	12	Report on the study's participation and response rates	2	1	1	1	2	1	2	2	1	2
Descriptive data	13	Give details on the research participants' demographic, clinical, and social features, as well as information about their exposure to and potential for confounders.	2	2	2	2	1	2	1	2	2	2
Main results	14	Give unadjusted estimates and, if necessary, estimates that have been confounder-adjusted along with their accuracy (e.g 95 percent confidence interval) Make it clear which confounders were taken into account and how	2	1	1	0	1	1	0	2	1	1
Key Results	15	Summarize the main findings in relation to the study's goals	2	2	2	1	1	2	2	2	1	2
Limitations	16	Address the study's limitations while considering the potential bias or imprecision sources, OR discuss the direction and amount of any potential bias	2	1	1	0	2	1	1	2	2	1
Interpretation	17	Give a careful overall interpretation of the findings while taking into account the goals, restrictions, variety of analyses, outcomes from related research, and other pertinent data	2	1	1	2	1	2	2	2	2	1
Score			24	17	32	17	23	23	24	31	19	25
Quality Score (%)			70	50	94	50	67	67	70	91	55	73

Table III (contd): ISPOR Checklist for Quality of Quantitative Included Studies.

Section	Item	Quality Criteria Description	Singh	Rai 2014	Worku	Rai *et al*. 2012	Rai 2013	Banke-T	Helleringer	Musaranda	Ronen
Objectives	1	Specific goals should be stated, along with any established hypotheses	2	2	2	2	2	2	2	1	1
Study design	2	Describe the main research design components	1	1	1	2	1	1	2	2	2
Setting	3	Describe the environment or setting, the locations, and the pertinent times, such as the recruiting, exposure, follow-up, and data collecting times	1	1	2	2	2	2	2	1	2
Participants	4	Give the qualifying requirements, as well as the sources and procedures used to choose the participants	1	2	1	2	2	2	2	2	2
Variables	5	All outcomes, exposures, predictors, possible confounders, and effect modifiers should be precisely defined.	2	2	1	2	2	2	1	2	2
Data sources/ measurement	6	Provide sources of information and information on the evaluation techniques for each variable of interest (measurement)	2	1	2	1	1	1	2	2	1
Bias	7	Describe any steps made to address any bias sources	1	1	2	1	1	2	1	2	1
Study size	8	Describe how the study size was determined.	1	2	1	2	2	1	2	2	1
Quantitative variables	9	Describe the methods used to handle quantitative variables in the analysis. Describe the classifications that were chosen, if relevant, and why5	2	2	1	2	1	2	1	2	1
Statistical methods	10	Describe all statistical techniques, including confounding correction techniques	1	2	1	1	1	2	1	1	1
	11	Describe how missing data were handled	1	0	0	1	0	0	0	0	0
Participants	12	Report on the study's participation and response rates	2	1	1	1	1	1	1	1	1
Descriptive data	13	Give details on the research participants' demographic, clinical, and social features, as well as information about their exposure to and potential for confounders.	2	2	2	2	2	2	1	2	1
Main results	14	Give unadjusted estimates and, if necessary, estimates that have been confounder-adjusted along with their accuracy (e.g 95 percent confidence interval) Make it clear which confounders were taken into account and how	1	1	1	1 1	1	2	1	1	1
Key Results	15	Summarize the main findings in relation to the study's goals	2	1	2	2	2	2	2	2	1

Section	Item	Quality Criteria Description	Singh	Rai 2014	Worku	Rai *et al*. 2012	Rai 2013	Banke-T	Helleringer	Musaranda	Ronen
Limitations	16	Talk about the study's limitations taking into consideration any sources of potential bias or error, OR talk about the direction and size of any potential bias	1	1	2	0	1	1	1	1	1
Interpretation	17	Give a careful overall interpretation of the findings while taking into account the goals, restrictions, variety of analyses, outcomes from related research, and other pertinent data	1	2	2	2	2	2	1	1	1
Score			24	24	27	29	21	26	24	23	19
Quality Score (%)			70	70	79	85	61	76	70	67	55

Maternal Health Service Utilization

Based on the study, eighteen (18) out of a total of twenty-four (24) studies reported that adolescent mothers engage in antenatal care service utilization. From the studies, a range of women who participated in antenatal care visits showed that 93.7% of women in Malawi had more than three visits; over 90% of women in South Africa, and in Ethiopia, 30% of women had at least one visit and more than four visits respectively.

Maternal Health Service Utilization Influencing Factors

Demographic individual factors, social and family factors, and organizational or institutional factors were explained in the included studies based on the socio-ecological model.

Demographic Individual factors

According to this study, there are a number of individual characteristics that affect how frequently teenage mothers in Sub-Saharan Africa seek maternity care, including age, education level, domicile or place of residency, economic position, awareness of and perception of the need for maternal health care. Women's education is the most important predictor of their use of maternal health services, according to the majority of the research examined in this review, as those who have completed secondary school or higher are more likely to seek maternity care than those who have not[48,41,36,35,32,43]. Women who have access to education are more equipped to make health-related decisions[33]. In addition, four studies found that women who reside in rural locations are less likely to seek maternity care than those who live in urban areas[48,43,32,29]. The disparity between urban and rural locations and the attitudes, cultural expectations, and convictions that prevent women from obtaining maternity care have been the subject of some studies[33,48,30,42]. The reviewed research indicates that rural women are more likely to be underprivileged than urban women, which has an influence on access disparities to maternal health resources[35] and contributes to the explanation of the rural-urban difference in the use of health services. Because they are concerned about declaring their pregnancy and lack the funds for prenatal care registration, young women opt to give birth with the assistance of a skilled practitioner and employ local procedures with long-lasting benefits rather than antenatal care[39]. In comparison to individuals who had fewer children or more than two years between pregnancies, adolescent women who had more than three children and had less than two years between pregnancies were likewise less likely to use postnatal services[32]. A number of factors, including media exposure[35,32,43], poor parity[48,40], work status[40], and others, have been associated to young mothers' use of maternal healthcare.

Social and family factors

In this synthesis, it was discovered that peer pressure, family traditions and customs, spouse knowledge, opinions, and education, as well as the impact of other family members, are additional interpersonal-level variables that affect young women's utilization of maternal health care. According to the viewpoints of health professionals gathered in a specific study, adolescent women usually have unintended pregnancies, which further complicates their maternal health-seeking behaviors and itineraries. In these circumstances, teenage mothers commonly experience social exclusion and romantic rejection[44]. As a result of these rejections, some young women were lucky enough to continue living with their parents, but with little in the way of social, emotional, or financial assistance[26]. Other adolescent women may not be asked to leave, rejected, or sent away from their homes and communities[44]. These issues are caused by negative sociocultural notions about young pregnancies, which are frequently infused into the system by widely held spiritual, religious, or traditional beliefs[44].

Additionally, a research indicated that teenage women were less likely to get maternity care if they said their pregnancy was undesired[32]. Due to these factors,

adolescent women who are pregnant cannot obtain or use reproductive health care services[27]. But being married and having a smart husband[32] were linked to a higher likelihood of young women seeking out maternal health care[48]. Young women's relationships with medical professionals had a positive and negative impact on how they felt about receiving prenatal care. Studies[27,31] claim that when it comes to protecting patient confidentiality, medical practitioners are "cruel," "condemnatory," and "not reliable"[27,31]. Adolescent women were deterred as a result from obtaining maternity care[44].

Factors from Institutional and Organizational level

We outline a number of organizational or institutional characteristics that either favorably or unfavorably affects how frequently young women in Sub-Saharan Africa seek maternity care. Despite the fact that healthcare professionals are aware that teenage mothers are a special population that needs particular care, young mothers still choose to go to adult-oriented prenatal care services that do not provide enough training, privacy, time, or knowledge on adolescent pregnancy. As a result, fewer women are using prenatal care services[44,27]. Due to their lack of faith in medical experts, young pregnant women have also had trouble connecting with them when they require prenatal care[31]. Other mothers said that there was a major scarcity of healthcare providers, which extended waiting periods for the pregnant adolescents seeking antenatal care services and dissatisfaction with the programs[38,27,28]. The ability of adolescent mothers to make use of maternity care was also reported to be restricted by the distance from their home to the health institution[38]. Although many of the young women who participated in the research thought that they needed information to better get them ready for pregnancy and parenthood responsibilities, many of them did not get it because there were not enough resources and services accessible[28]. The teenage women's claims that there were insufficient laws and tools to educate young mothers about maternal health[49] were also supported by medical professionals. A minimum of four prenatal visits (antenatal care)[42] substantially affected the use of postnatal care services and promoted the use of safe or skilled birth delivery care[32]. These findings highlight the need for integrated maternal health care services to promote young women's usage of maternity care[41]. This was essential for improving newborn health as well since infants whose mothers received prenatal care were more likely to receive the full course of recommended vaccines[41]. Four further investigations further uncovered any connections between skilled labor, delivery services, and prenatal care. Other studies[29,41,32 and 42] found that frequent antenatal care visits, with at least four visits, increased the use of skilled birth delivery, contrary to the findings of Ochako and colleagues[48], who found that frequent antenatal care visits, with at least four visits, had a significant impact on young women's use of skilled birth delivery care. However, a research showed that adolescent Malawian women in rural areas who received prenatal care throughout the first and early second trimester were less likely to deliver their babies safely[36].

Cultural and Economic Factors

According to the papers included in this review, several cultural and economic variables were shown to have an impact on adolescent mothers' usage of maternal health care. According to several studies, use of all three maternal healthcare services rises as income quintiles rise[33,48,35,43], with middle- and upper-income adolescent women far more likely to do so[48,41,35,43]. Teenagers who were alone and pregnant were afraid to visit medical facilities because of shame and embarrassment from acquaintances, neighbors, and even family members[44]. Based on their faith, it was discovered that Islamic teens were more receptive to getting maternity care than other teenagers[32]. The accessibility of prenatal care services, such as antenatal care with traditional birth attendants, has proven difficult for young adolescents as a whole, which lessens the perceived necessity for teenage women to get professional maternity care[39]. Thus, a variety of factors and interventions aimed at adolescent women in an effort to protect their safety and well-being have an influence on the utilization of maternal health care by adolescent women.

Discussion

The objective of the review was to provide enough proof of the factors influencing young mothers' use of maternity care in Sub-Saharan Africa. Low rates of maternal health use are found in much of Sub-Saharan Africa[2,5,10]. The study found that young women use maternity care facilities quite differently depending on whatever Sub-Saharan African country they are in. The data in this paper have been analyzed, and the results highlight the need for a variety of multi-layer interventions aimed at this group. These components include demographic features, culturally linked factors, economic considerations, and social aspects. This is crucial since pregnancies, deliveries, and postpartum complications among young women are more likely to result in long-term health problems or even the death of the mother or the child. The majority of research found that young girls began their prenatal care visits later than the advised minimum of four visits during pregnancy[31,42,28], often in the second or third trimester. This is true even though the global health organization categorizes adolescent pregnancy as high risk and advises careful monitoring by experienced professionals from the beginning[3].

Despite the recommendations[1,4], the findings revealed that many teenage women delayed their attendance at prenatal care appointments until the second or third trimester[26,29-37,48]. In two studies conducted in Kenya, it was shown that young mothers benefited by being aware

of the common pregnancy warning symptoms[35,45]. This shows that women who have reported at least one prenatal care visit now have a greater level of understanding. The majority of the study also found, according to the analysis, that women's and their partners' educational backgrounds had a significant impact on their usage of prenatal care, professional delivery, and postpartum care. This agrees with past studies[12]. Men and women with higher levels of education are more likely to be aware of the advantages of professional maternity care and to be empowered enough to seek it[12,13,51,52]. Expanding the non-formal educational choices accessible to adolescent ladies and encouraging them to return to school after having children are two strategies for increasing school attendance. This is significant since, in Sub-Saharan Africa, cultural and institutional attitudes make it difficult for adolescent mothers to return to school[53]. Without a doubt, governments and non-governmental organizations (NGOs) must work to remove these barriers because they prevent young women from accessing education, potential employment, financial stability, and empowerment all necessary components for boosting maternal health care utilization and access and so continue cycles of disadvantage[54]. Another strategy utilized to improve young women's attendance at school was paying for direct unneeded expenditures such books, uniforms, and transportation as well as indirect (opportunity) costs of education[53]. The socioeconomic position of young mothers and their use of maternity care were connected, with teens in the richer group reporting higher levels of engagement in maternity care than those in the poorer group. Low-income teenagers may not be able to afford medical treatment. Activities intended to increase teenage women' utilization of maternal health care are also less likely to reach them because poor adolescents are more likely to be socially isolated[54]. Therefore, poverty-reduction initiatives targeted directly at adolescent girls may have a greater impact and improve the consequences of their future sexual and reproductive health. Socio-cultural beliefs about conception, pregnancy, and delivery have a big impact on maternal health[55]. For instance, in South Asia and Sub-Saharan Africa, the use of effective maternal health treatments is commonly influenced by religious beliefs, practices, and values[56]. For instance, some communities and women could believe that giving birth is a test of one's courage that asking for aid is a sign of weakness, or that hospital births should only be performed in very difficult or protracted labors[56,57]. However, prior research indicates that many Nigerian women, particularly those who reside in rural areas, believe that traditional birth attendants (TBAs) provide superior care to modern medical experts, particularly when it comes to interpersonal connections and communication[58]. When teens attend prenatal care, promoting the advantages of maternal healthcare must be given high emphasis. A staffing shortfall is a major obstacle to provide high-quality services, hence improving the workforce is a priority in order to achieve this[41]. Adolescent females require more access to family planning services if they are to avoid early births and poor maternal health outcomes[14]. It is essential that family planning education and services are offered as part of an integrated system involving schools, communities, health organizations, and governments to ensure that young women are empowered to make decisions about their sexual and reproductive health as soon as possible rather than after birth, when such counselling is typically provided. Additionally, appropriate actions must be taken to persuade local authorities and other significant players to participate as change agents[54]. Rural areas[56,57] require such organizational restructuring because of the numerous barriers that these women must surmount in order to access and subsequently use maternal health care.

The study's findings imply that the traits of health professionals such as unfavorable views, a lack of knowledge, and insensitivity to the requirements of teenage women have an impact on how frequently adolescent mothers in Sub-Saharan Africa seek out maternal health care. These findings are consistent with past research that showed adolescent mothers are perceptive to healthcare experts' judgments and soon lose interest in obtaining care[59,60,61,62,63]. According to this study, adolescent mothers have trouble communicating with medical professionals since they don't feel confident in or trustworthy with them. Because they are more likely than older parents to have extra diseases like STIs and HIV and because they need more knowledge on maternity care and parenthood, adolescent mothers need greater attention from medical experts[41]. Healthcare providers will also need additional training to deliver care that is sensitive to and responsive to the requirements of teenage women[33]. The majority of research on young women's use of maternal health care in Sub-Saharan Africa focuses on prenatal care, whereas just a small number of studies have looked at skilled delivery of babies and postnatal care. This suggests that further research is required to understand how young women obtain skilled delivery and postnatal care. Despite the relatively modest number of teenage females, the great majority of the studies also used quantitative techniques. The representativeness of this research is thus questioned given the high prevalence of adolescent fertility in Sub-Saharan Africa. The major window of opportunity for avoiding unplanned births among this vulnerable population is the provision of contraceptive services through maternity care, therefore it is essential. More research is needed to better understand how medical personnel see and cope with care for young women during their pregnancies.

The Limitations and Strengths of the Findings

It is essential to stress a few limitations in light of this review. Since French is the official language of some Sub-Saharan African nations, it may be challenging to generalize from research that have not been published

in English for this region. Additionally, results could only have been based on research that was published, leaving out unpublished studies that would have been relevant to this analysis. Additionally, it is probable that the involvement of just few reviewers throughout the screening process and the small sample sizes from some of the included studies would make it hard to have a completely representative sample. The distinctiveness of the enhanced search approach used to find the primary papers is this systematic review's strength. It is also the first to specifically model a few sub-Saharan African nations.

Conclusion

Based on this review, in sub-Saharan Africa, it could be said that a significant proportion of teenage women do not have reliable access to utilization and access to maternal care throughout pregnancy. A wide array of factors is seen to influence the utilization and access to maternal health services among teenage mothers in sub-Saharan Africa. These factors span from demographic variables to cultural, economic, and even economic-related variables. To enhance their involvement in using maternal health care, it appears that interventions like training programmed offered by medical and allied health professionals to teenage female partners are essential. Additionally, this would enhance their prenatal appointments and offer them more choice in choosing treatments that would result in better outcomes for mother health. Adolescent mothers in rural regions and the vast majority of communities should be made aware of the importance of these treatments using community mobilization strategies.

Ethics Approval and consent to Participate
Not Applicable.

Consent to Publish
Not applicable.

Availability of Data and Materials
The Data set from the study are available to the corresponding author upon request.

Competing Interests
Authors have declared that they have no competing interests.

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Authors Contribution
All Authors contributed in the drafting and execution of this systematic review

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ORIGINAL

Estimation of heart age in 139.634 spanish workers: influence of sociodemographic variables and healthy habits and determination of cut-off points.

Estimación de la edad cardiaca en 139.634 trabajadores españoles: influencia de variables sociodemográficas y hábitos saludables y determinación de puntos de corte

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Abstract

Aim: To assess the relationship of sociodemographic variables and healthy habits with heart age values. To establish cut-off points for moderate and high cardiac age.
Methods: Heart age was determined in 139.634 workers and its relationship with sociodemographic variables (age, sex, social class and educational level) and healthy habits (tobacco and alcohol consumption, physical activity and adherence to the Mediterranean diet) was assessed. The cut-off points for moderate and high cardiac age were determined by applying ROC curves.
Results: The mean values and prevalence of high heart age values are influenced by all the sociodemographic variables and healthy habits analyzed, especially by age and tobacco consumption. The cut-off points established for moderate and high heart age are set at +11 and +17 years respectively.
Conclusions: All sociodemographic variables, especially age, and healthy habits, mainly smoking, influence heart age values. Heart age values 11 and 17 years higher than chronological age are considered moderate and high respectively.

Key words: Heart age, cardiovascular risk, smoking, adherence to Mediterranean diet, physical activity, social class.

Resumen

Objetivo: Valorar la relación de variables sociodemográficas y hábitos saludables con los valores de edad del corazón. Establecer puntos de corte para edad cardiaca moderada y alta.
Metodología: Se determina la edad del corazón en 139.634 trabajadores y se valora su relación con variables sociodemográficas (edad, sexo, clase social y nivel de estudios) y hábitos saludables (consumo de tabaco y alcohol, actividad física y adherencia a la dieta mediterránea). Se determinan los puntos de corte de la edad cardiaca moderada y alta aplicando curvas ROC.
Resultados: Los valores medios y la prevalencia de valores elevados de edad del corazón se ven influidos por todas las variables sociodemográficas y hábitos saludables analizados, especialmente por la edad y el consumo de tabaco. Los puntos de corte establecidos para edad cardiaca moderada y alta se establecen en +11 y +17 años respectivamente.
Conclusiones: Todas las variables sociodemográficas, especialmente la edad, y los hábitos saludables, principalmente el tabaco, influyen en los valores de edad del corazón. Valores de edad cardiaca superiores en 11 y 17 años a la edad cronológica se consideran moderados y alto respectivamente.

Palabras clave: Edad del corazón, riesgo cardiovascular, tabaco, adherencia a la dieta mediterránea, actividad física, clase social.

Introduction

Cardiovascular diseases continue to be the leading cause of morbidity and mortality in all countries of the world, although their prevalence is particularly high in the most developed countries, and is continuously increasing[1]. Many scales have been developed to determine the level of risk of presenting a cardiovascular event, generally over a given period of time, which has mostly been estimated to be 10 years. The oldest scale is the Framingham scale developed on the basis of a cohort of people from this North American population[3]. Subsequently, this scale was adapted to the characteristics of different countries[4]. Years later, country-specific scales that were not based on Framingham began to be developed[5,6]. However, despite their undoubted usefulness, all these scales suffer from a common defect, which is the relativization of risk, for example, if we apply the REGICOR scale[7] (adaptation of the Framingham scale to the Spanish population) to a 60-year-old male smoker, with a systolic blood pressure of 145 mmHg and diastolic of 95 mmHg, total cholesterol of 250 mg/dL and HDL of 38 mg/dL, the probability of suffering a cardiovascular event in the next 10 years is 16%, or in other words, he has an 84% probability of not suffering it.

For this reason, in recent years tools have been developed to assess cardiovascular risk not as a percentage but as an absolute number. Based on this, the heart age tool was created[8] which, if applied to the same individual as above, will give us a value of 77 years, that is, 17 years older than his biological age. This value has been, according to a study by our group, more useful for modifying healthy habits and thereby reducing cardiovascular risk than the use of traditional risk scales.

The aim of this study is to determine, on the one hand, the cut-off points for heart age that are considered moderate and high and, on the other, to assess the influence of sociodemographic variables (age, sex, social class and level of education) and healthy habits (physical exercise, Mediterranean diet, tobacco and alcohol consumption) on heart age values.

Methods

A descriptive, cross-sectional study was carried out using data from occupational medical examinations performed between January 2019 and June 2020 on 139,634 Spanish workers (83,282 men and 56,352 women) in the primary, secondary and tertiary sectors.

Inclusion criteria were:
- Age between 18 and 69 years.
- Working in one of the companies included in the study.
- Agreeing to participate in the study.

The flow chart is presented in **figure 1**.

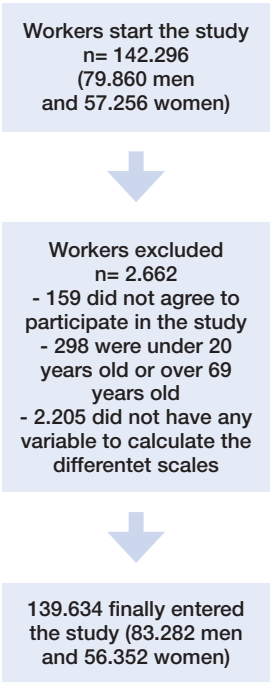
Determination of variables
The health professionals of the different companies were responsible for obtaining all the clinical, analytical and anthropometric variables necessary for the calculation of heart age. Interobserver bias was minimized by standardizing the measurements.

Waist circumference was measured with a tape measure placed at the level of the last rib, with the person in bipedestation and the abdomen relaxed.

Blood pressure was obtained with an OMRON M3 sphygmomanometer, while the patient was seated and after a 10-minute rest. Three measurements were taken and the mean was obtained.

The analysis was performed after a 12-hour fasting period using enzymatic techniques for glucose and using enzymatic techniques for blood glucose, triglycerides and cholesterol and precipitation techniques for HDL-cholesterol. LDL-cholesterol was obtained indirectly using the Friedewald formula (valid only for triglyceride values below 400). All analytical parameters were expressed in mg/dL.

Figure 1: Flow chart.



It is a tool based on the classic Framingham cardiovascular risk scale that allows calculation of a patient's probability of developing cardiovascular disease in the next ten years[9].To calculate the age of the heart, the following are required: age, sex, height (in centimeters), weight (in kilograms), waist circumference

(in centimeters), family history (parents) of cardiovascular disease and age when they first suffered it, presence or absence of diabetes, tobacco use (if not currently smoking, we ask whether smoking has been stopped in the last year), total cholesterol and HDL cholesterol values, systolic blood pressure values, and whether the patient is currently under antihypertensive treatment.

For the calculation, the "Heart age calculator" tool is used, which, in its Spanish version, is available on the web page: http://www.heartage.me. The scale is applicable between the ages of 18 and 80 years. The range of years gained or lost is 20, with a minimum age of 18 years and a maximum of 80 years.

An interesting concept is avoidable lost life years ALLY[10] which we can define as the difference between chronological age and heart age.

The baseline blood glucose results were classified based on the recommendations of the American Diabetes Association[11], whereby the individual was considered to have diabetes if the values were >125 mg/dl in two different determinations, if he/she also had HbA1c ≥ 6.5% or if the individual was receiving hypoglycemic treatment.

Any person who had consumed one or more cigarettes per day, or the equivalent in other consumption modalities, during the last 30 days or who had quit smoking less than one year before was considered a smoker. The heart-healthy diet was assessed with the "Mediterranean diet adherence questionnaire" of the PREDIMED study[12]. It consists of 14 questions that are scored with 0 and 1 point. Values of 9 or more indicate good adherence and that the diet is heart-healthy. Physical activity is assessed using the International Physical Activity Questionnaire IPAQ (International Physical Activity Questionnaire)[13], which assesses physical activity in the last week. Alcohol consumption is assessed using the units of alcohol (UA). In Spain, one UA is equal to 10 grams of pure ethanol. High consumption was considered as from 14 UA in women and 21 in men per week[14].

Based on the 2011 National Classification of Occupations (CNO-11) and applying the criteria of the Spanish Society of Epidemiology[15], the workers were classified into three social classes: I. Managers, university professionals. II. Intermediate occupations and skilled self-employed workers. III. Unskilled workers.

Ethical considerations and aspects

The ethical standards of the institutional research committee and the 2013 Declaration of Helsinki were respected in the study. Anonymity and confidentiality of the data collected could be guaranteed at all times. The study had the approval of the Research Ethics Committee of the Balearic Islands (CEI-IB): IB 4383/20. The data of each of the workers included in the study were coded and only the person responsible for the study was able to know the identity of each person. The research team undertook to strictly comply with the Organic Law 3/2018, of December 5, on the protection of personal data and guarantee of digital rights, guaranteeing the participant in this study the exercise of the rights of access, rectification, cancellation and opposition of the data collected.

Statistical analysis

For quantitative variables, the Student's t-test was used to determine the mean and standard deviation. For qualitative variables, the chi-square test was applied and prevalences were determined. The cut-off points to determine the cardiac age considered moderate and high were obtained using ROC curves. The area under the curve (AUC), the cut-off points with their sensitivity, specificity and Youden index were calculated. Multivariate analysis was performed by multinomial logistic regression. SPSS 28.0 was used for the statistical analysis. The accepted level of statistical significance was $p<0.05$.

Results

Table I shows the anthropometric and clinical characteristics of the individuals included in the study. A total of 139.634 (83.282 men 59.6% and 56.352 women 40.4%) were included in the analyses. The mean age of the sample was slightly over 40 years, the majority group being between 30 and 49 years of age. Anthropometric, clinical and analytical values were more unfavorable in men. Most of the workers were of social class III and with primary education. In men, most of them did not perform regular physical activity and did not have a healthy diet (in women the situation was better). Almost one in three workers were smokers.

Table II shows the mean values of ALLY heart age according to different sociodemographic variables and healthy habits in men and women. The mean values of ALLY heart age are higher in men, increase with age and as one descends in social class or level of education. The values are also higher in smokers, sedentary people, people with low adherence to the Mediterranean diet or those who consume a lot of alcohol. In all cases these increases in mean ALLY values are greater in men.

Table III, which shows the prevalence of ALLY vascular age values according to different sociodemographic variables and healthy habits in men and women, shows a trend similar to that observed with the mean values, ie, higher prevalence of high ALLY vascular age values as age increases, social class or level of education decreases, and the person has unhealthy habits

(smoking or alcohol consumption, little or no physical activity, and low adherence to the Mediterranean diet).

Table IV shows the results of the multivariate analysis using multinomial logistic regression. The risk with this analysis of presenting moderate-high or high values of ALLY vascular age is also affected by sex, age, social class, level of education, adherence to the Mediterranean diet, physical activity, tobacco and alcohol consumption. Of these, those with the highest ORs were age and tobacco consumption.

Table I: Characteristics of the population.

	Men n=83,282	Women n=56,352	
	Mean (SD)	Mean (SD)	p-value
Age (years)	41.4 (10.7)	40.1 (10.4)	<0.0001
Height (cm)	173.8 (7.1)	161.2 (6.5)	<0.0001
Weight (kg)	83.2 (14.6)	66.3 (13.9)	<0.0001
Body mass index (kg/m²)	27.5 (4.5)	25.5 (5.3)	<0.0001
Waist circumference (cm)	90.2 (10.3)	76.3 (10.5)	<0.0001
Waist to height ratio	0.52 (0.06)	0.47 (0.07)	<0.0001
Systolic blood pressure (mmHg)	126.2 (15.9)	115.6 (15.7)	<0.0001
Diastolic blood pressure (mmHg)	76.6 (10.9)	71.1 (10.7)	<0.0001
Total cholesterol (mg/dl)	199.6 (38.6)	194.6 (36.9)	<0.0001
HDL-cholesterol (mg/dl)	50.0 (7.7)	54.7 (9.2)	<0.0001
LDL-cholesterol (mg/dl)	122.6 (37.4)	121.5 (37.1)	<0.0001
Triglycerides (mg/dl)	133.8 (95.6)	90.8 (49.7)	<0.0001
Glycaemia (mg/dl)	93.0 (25.4)	86.8 (18.1)	<0.0001
	n (%)	n (%)	p-value
18-29 years	12558 (15.1)	10110 (18.0)	<0.0001
30-39 years	24648 (29.6)	17460 (31.0)	
40-49 years	25178 (30.2)	17094 (30.3)	
50-59 years	17370 (20.9)	9984 (17.7)	
60-70 years	3528 (4.2)	1704 (3.0)	
Social class I	6234 (7.5)	7632 (13.6)	<0.0001
Social class II	19856 (23.8)	18112 (32.1)	
Social class III	57192 (68.7)	30608 (54.3)	
Primary school	55306 (66.4)	27086 (48.1)	
Secondary school	22408 (26.9)	22574 (40.0)	
University	5568 (6.7)	6692 (11.9)	
Non-smokers	55618 (66.8)	38252 (67.9)	<0.0001
Smokers	27664 (33.2)	18100 (32.1)	
Non physical activity	51984 (62.4)	28962 (51.4)	<0.0001
Yes physical activity	31298 (37.6)	27390 (48.6)	
Non healthy food	54792 (65.8)	29764 (52.8)	<0.0001
Yes healthy food	28490 (34.2)	26588 (47.2)	
Non alcohol consumption	56022 (67.3)	47536 (84.4)	<0.0001
Yes alcohol consumption	27260 (32.7)	8816 (15.6)	

HDL -cholesterolHigh density lipoprotein cholesterol. LDL -cholesterol Low density lipoprotein cholesterol.

Table II: Mean values of ALLY heart age according sociodemographic variables and healthy habits by sex.

	Men			Women		
ALLY heart age	n	Mean (SD)	p-value	n	Mean (SD)	p-value
18-29 years	12558	1.3 (4.9)	<0.0001	10110	-2.0 (5.0)	<0.0001
30-39 years	24648	4.2 (6.7)		17460	-1.8 (7.7)	
40-49 years	25178	7.9 (8.1)		17094	2.8 (10.2)	
50-59 years	17370	11.7 (7.9)		9984	8.4 (10.6)	
60-70 years	3528	11.8 (7.4)		1704	8.6 (9.9)	
Social class I	6234	4.9 (7.5)	<0.0001	7632	-2.0 (7.7)	<0.0001
Social class II	19856	6.3 (8.1)		18112	0.5 (9.3)	
Social class III	57192	7.1 (8.1)		30608	3.3 (9.9)	
Primary school	55306	6.7 (7.9)	<0.0001	27086	3.4 (10.0)	<0.0001
Secondary school	22408	7.3 (8.5)		22574	0.7 (9.4)	
University	5568	5.2 (7.6)		6692	-2.1 (7.7)	
Non-smokers	55618	4.2 (7.3)	<0.0001	38252	-0.6 (9.2)	<0.0001
Smokers	27664	11.8 (7.2)		18100	6.5 (8.9)	
Non physical activity	51984	8.9 (7.9)	<0.0001	28962	5.5 (9.8)	<0.0001
Yes physical activity	31298	3.2 (7.0)		27390	-2.3 (7.7)	
Non healthy food	54792	8.7 (8.0)	<0.0001	29764	5.1 (9.9)	<0.0001
Yes healthy food	28490	3.0 (7.0)		26588	-2.2 (7.8)	
Non alcohol consumption	56022	5.8 (7.8)	<0.0001	47536	0.1 (8.9)	<0.0001
Yes alcohol consumption	27260	(8.8 (8.2)		8816	10.0 (9.5)	

ALLY Avoidable lost life years

Table III: Prevalence of values of ALLY heart age according sociodemographic variables and healthy habits by sex.

ALLY heart age		Normal	Moderate	High			Normal	Moderate	High	
	n	%	%	%	p-value	n	%	%	%	p-value
18-29 years	12558	96.8	2.5	0.7	<0.0001	10110	98.1	1.6	0.3	<0.0001
30-39 years	24648	85.2	9.2	5.6		17460	93.8	3.3	2.9	
40-49 years	25178	66.0	12.9	21.1		17094	77.2	8.5	14.3	
50-59 years	17370	45.2	15.8	39.0		9984	54.5	11.8	33.7	
60-70 years	3528	41.6	21.9	36.5		1704	49.3	20.4	30.3	
Social class I	6234	80.4	8.3	11.4	<0.0001	7632	92.8	3.4	3.7	<0.0001
Social class II	19856	73.0	10.7	16.3		18112	85.1	6.0	8.9	
Social class III	57192	69.2	11.7	19.1		30608	76.0	7.7	16.2	
Primary school	55306	71.6	11.6	16.8	<0.0001	27086	75.6	8.0	16.4	<0.0001
Secondary school	22408	67.5	10.9	21.6		22574	84.6	5.9	9.6	
University	5568	79.2	8.5	12.2		6692	92.9	3.3	3.7	
Non-smokers	55618	83.0	8.1	8.9	<0.0001	38252	87.1	4.8	8.1	<0.0001
Smokers	27664	46.7	17.5	35.8		18100	68.8	10.4	20.8	
Non physical activity	51984	61.6	13.5	24.8	<0.0001	28962	69.4	10.0	20.7	<0.0001
Yes physical activity	31298	86.5	7.4	6.2		27390	93.8	3.0	3.2	
Non healthy food	54792	62.7	13.3	24.1	<0.0001	29764	70.3	9.6	20.0	<0.0001
Yes healthy food	28490	87.0	7.2	5.8		26588	93.4	3.2	3.4	
Non alcohol consumption	56022	75.4	11.0	13.6	<0.0001	47536	87.1	5.3	7.5	<0.0001
Yes alcohol consumption	27260	61.9	11.7	26.4		8816	49.5	13.3	37.2	

ALLY Avoidable lost life years

Table IV: Multinomial logistic regression.

	ALLY moderate		ALLY high	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Female	1		1	
Male	1.61 (1.56-1.67)	<0.0001	1.24 (1.19-1.29)	<0.0001
20-29 years	1		1	
30-39 years	1.41 (1.31-1.50)	<0.0001	1.98 (1.91-2.05)	0.528
40-49 years	4.41 (4.12-4.72)	<0.0001	3.06 (2.84-3.30)	<0.0001
50-59 years	17.32 (16.07-18.67)	<0.0001	15.05 (13.81-16.40)	<0.0001
60-70 years	88.19 (79.11-98.30)	<0.0001	121.27 (99.96-147.11)	<0.0001
Social class I	1		1	
Social class II	1.69 (1.61-1.77)	<0.0001	1.93 (1.82-2.03)	<0.0001
Social class III	2.38 (1.98-2.85)	<0.0001	3.02 (2.39-3.82)	<0.0001
Primary school	1		1	
Secondary school	1.15 (1.05-1.24)	0.08	1.18 (1.13-1.24)	0.03
University	1.49 (1.23-1.80)	<0.0001	1.91 (1.50-2.44)	<0.0001
Non-smokers	1		1	
Smokers	15.89 (15.26-16.53)	<0.0001	14.66 (14.02-15.33)	<0.0001
Yes physical activity	1		1	
Non physical activity	2.51 (2.34-2.69)	<0.0001	2.55 (2.34-2.78)	<0.0001
Yes healthy food	1		1	
Non healthy food	1.82 (1.70-1.96)	<0.0001	1.94 (1.78-2.12)	<0.0001
Non alcohol consumption	1		1	
Yes alcohol consumption	1.85 (1.78-1.92)	<0.0001	2.37 (2.27-2.48)	<0.0001

Figure 2: ROC curve ALLY heart age moderate-high.

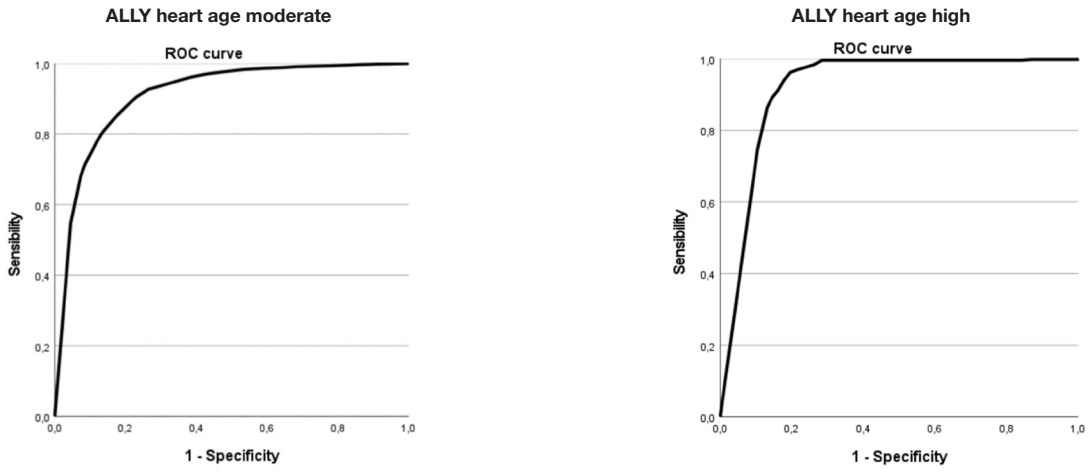


Figure 2 shows the ROC curves for predicting moderate ALLY and high ALLY. The areas under the curve are very high, namely 0.911 (95% CI 0.908-0.913) for moderate ALLY and 0.919 (95% CI 0.915-0.923) for high ALLY. The established cut-off points are 11 (sensitivity 0.844 specificity 0.832 and Youden index 0.676) for moderate ALLY and 17 (sensitivity 0.878 specificity 0.862 and Youden index 0.740) for high ALLY.

Discussion

In our study, the cut-off points for assessing heart-age ALLY were set as moderate if they exceeded the biological age by 11 years and as high if they exceeded it by 17 years.

The mean value and prevalence of high heart age ALLY values increase with increasing age, decreasing social class and educational level. Worse values are also observed in people with unhealthy habits (smokers, high alcohol consumption, low adherence to the Mediterranean diet and low physical activity). The most influential variables are age and tobacco use.

Unfortunately, we have not found any article that assesses the influence of sociodemographic variables and healthy habits on heart age values. Nor have we found any article that establishes cut-off points for cardiac age. Due to this situation, we cannot compare our results with those obtained by other authors. To resolve this situation, we will assess the effect of sociodemographic variables and healthy habits on other cardiovascular risk scales.

Many studies have related age to an increase in cardiovascular risk and in the prevalence of cardiovascular disease[16-17]. There is unanimous agreement that cardiovascular risk is higher in women than in men[18-19], although this gap decreases as the menopause approaches[20-21].

Data from a study by Psaltopoulou et al[22] show the existence of a gradient in the incidence, morbidity and mortality of cardiovascular disease across the spectrum of socioeconomic status, defined by educational level, occupation or income. A study by Panagiotakos et al[23] in a Greek population showed that educational level appears to be an important determinant of disease incidence, concluding that low educational level was associated with an increased risk of CVD. This was mainly explained by the association of low educational level with unhealthy choices.

Tobacco consumption is an important cardiovascular risk factor that has been known for decades, with many mechanisms being involved[24-25]. A negative effect of alcohol consumption and cardiovascular risk has also been found26 as we have found.

A systematic review by Ciumărnean et al[27] showed the positive effect of physical activity on cardiovascular risk. A study by Lavie et al[28] assessing the effect of physical activity of different intensities also found a beneficial effect on cardiovascular risk levels. Members of the EXPERT (EXercise Prescription in Everyday practice & Rehabilitative Training)[29] working group systematically reviewed the literature for meta-analyses, systematic reviews and/or clinical studies addressing exercise prescription in cardiovascular disease risk factors and concluded that physical activity had a significant beneficial effect on cardiovascular risk.

Strengths and limitations

As strong points we can highlight the large sample size (almost 140,000 people) and the large number of sociodemographic variables and healthy habits used. A second strong point is that it is the first study to establish cut-off points for classifying heart age values.

The main limitation is that diet and physical activity were determined by questionnaire and survey, respectively, and not by objective methods.

Conclusions

Although all the variables, both sociodemographic and healthy habits, influence the ALLY heart age values, we should emphasize that those that show the greatest influence are age and tobacco consumption.

The cut-off points for ALLY moderate heart age are set at 11 and for ALLY high heart age at[17].

Conflict of interest

None

Financing

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ORIGINAL

Assessment of the burden placed on caregivers of patients with dementia using the ZARIT-MOR scale in Morocco

Evaluación de la carga de los cuidadores de pacientes con demencia mediante la escala ZARIT-MOR en Marruecos

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Abstract

Introduction: Family carers play an essential role in dementia care. This noble role is a significant burden that requires special support from family members and society in general.
Objective: Describe and analyse the characteristics of the dementia patients and the experiences of their primary caregivers according to the ZARIT-MOR scale (Moroccan dialect version) in the prefecture of Marrakech.
Methods and materials: An analytical and quantitative study of 110 care-givers in the district of Marrakech contacted through pharmacists, the private neurologists' offices, and the diagnostic centers of the Mohamed VI University Hospital, and also through the contact of care-givers directly via family and friends.
Results: The mean age of the patients was 77.3 ± 6.58 years, while the mean age of the caregivers was 44.7 ± 8.9 years. The gender of the patients is 69% female, whereas 83% of the caregivers are also female. In the relationship between the caregiver and the patient, 48% are the child and fraternity with 20%. The Zarit score shows a moderate to severe burden (56.8 ± 14.3). This study also found that the burden on the male caregivers (63.1 ±10.5) is high as compared with the female ones (55.4 ±14.6) (p= 0.013). Altogether, the study population presented a positive correlation between total Zarit score and the hours that the caregiver had spent caring for the patient per day (Spearman's correlation = 0.29, p<0.01).
Conclusion: The findings showed a high caregiver burden in dementia patients, requiring focused intervention to reduce primary caregivers' burdens and to improve their quality of care and their quality of life.

Key words: Dementia, family caregivers, burdens, Zarit-MOR.

Resumen

Introducción: Los cuidadores familiares desempeñan un papel esencial en el cuidado de la demencia. Este noble papel es una carga importante que requiere un apoyo especial de los familiares y de la sociedad en general.
Objetivo: Describir y analizar las características de los pacientes con demencia y las experiencias de sus cuidadores principales según la escala ZARIT-MOR (versión dialectal marroquí) en la prefectura de Marrakech.
Materiales y métodos: Estudio analítico y cuantitativo de 110 cuidadores del distrito de Marrakech contactados a través de farmacéuticos, las consultas de neurólogos privados y los centros de diagnóstico del Hospital Universitario Mohamed VI, y también a través del contacto de los cuidadores directamente o mediante familiares y amigos.
Resultados: La edad media de los pacientes fue de 77,3 ± 6,58 años, mientras que la edad media de los cuidadores fue de 44,7 ± 8,9 años. El género de los pacientes es 69% femenino, mientras que el 83% de los cuidadores son también mujeres. En la relación entre el cuidador y el paciente, el 48% son hijos y hermanos el 20%. La puntuación Zarit muestra una carga de moderada a severa (56,8 ± 14,3). Este estudio también encontró que la carga de los cuidadores masculinos (63,1 ± 10,5) es alta en comparación con los femeninos (55,4 ± 14,6) (p= 0,013). En conjunto, la población de estudio presentó una correlación positiva entre la puntuación total de Zarit y las horas que el cuidador había dedicado a atender al paciente por día (correlación de Spearman = 0,29, p<0,01).
Conclusiones: Los hallazgos mostraron una elevada carga de los cuidadores en los pacientes con demencia, que requiere una intervención focalizada para reducir la carga de los cuidadores primarios y mejorar su calidad de atención y su calidad de vida.

Palabras clave: Demencia, cuidadores familiares, cargas, Zarit-MOR.

Introduction

Over the past decade, a great deal of research has been conducted on the phenomenon of caregiver's burden. Although the concept is relatively new in the literature, the responsibility and potential consequences of caring for a loved one have existed for centuries. An experience that has many benefits, including personal fulfilment; however, it is also associated with physical, psychological and financial burdens[1].

This term came to the fore in Canada in 1980[2] is legally recognized for the first time in the French law n 2005-102 of 11 February for the equality of rights the rights of caregivers. In the literature and in the collective imagination, there are several terminologies referring to the same general idea (caregiver, natural caregiver, main caregiver, informal caregiver, accompanying caregiver, family caregiver[3].

While the exact definition is elaborated by the Confederation of Family Organizations in the European Union (CFOFEU) and the Collective departmental Inter Associative for help caregiver's Family in France which defined "The family caregiver or de facto carer is the person who provides non-professional assistance, in part or in full, to a dependent person in his or her family circle, for the activities of daily life[2]. A definition that reflects the range of activities of family caregiver's and its complexity[2].

The notion of burden began in 1960 with Grad and Sainsbury[4] who measured burden as a significant family cost. Furthermore, family giver's often accept the multiple and complex tasks involved in caring for another family member[5]. In relation to dementia, studies by Irvin and Acton[6] concluded that caregiving for Alzheimer's patients was more stressful because of the many behavioural problems that this population presents. According to these burdens, nearly 40% of caregivers[7] feel depressed and almost nine out of 10 caregivers feel a high burden and moral fatigue. And to assess this burden, several studies have tried to make it objective through scales that are essentially based on active listening and participant observation[8].

Finally, Steven H. Zarit conducted pioneering research on caregiver burden and stress. This led to the development of the Zarit scale, which provides an objective measure of burden based on several factors (emotional, physical and financial). With its 22 items, this scale has been translated into several languages, making it possible to assess the difficulties felt by caregivers. This test can be carried out with a social worker, the attending physician or the geriatrician in consultation[9]. On the other hand, in Morocco, despite the absence of a statute for natural caregivers, a Moroccan dialect version was created in 2022, which will make it possible to reveal the experiences of caregivers in a more objective way[10].

Materials and methods

Data collection: realised in the city of Marrakech, which is the third most populous city in Morocco with 45,205,569 inhabitants[11], of which the population aged over 65 years constitutes 9%. Contact with caregivers was made through several sites, pharmacies, private neurology practices, the diagnostic centre affiliated with the University Hospital Centre, health centres and also through direct contact with caregivers through friends and family.

Population and sample size: The sample is calculated on the basis of patients living in the city with an age above 65 years, as well as the target population was represented by the primary caregivers of demented patients living in the Marrakech and its regions (n=110).

Tool for data collection: Data collection was conducted by using the adapted and the translated version of the Zarit score. This was the Zarit Moroccan version (Zarit-MOR)[10]. Each item is scored from 0 to 4 according to its importance; 0=never, 1=rarely, 2=sometimes, 3=fairly often and 4=almost always. The sum of the scores obtained for each of the 22 items will vary from 0 to 88. Interpretation is done according to the number of points: Score lower than 20 (slight), score between 20 and 40 (mild to moderate), score between 40 and 60 (moderate to severe), score between 61 and 88 (severe).

Data analysis methods: performed by Microsoft Office Excel, SPSS21, Pvalue.io. The comparisons between groups were made on percentage numbers, using Student (T) and Chi-square tests. The Spearman correlation coefficient was used to quantify the strength of the linear association between two continuous variables. Due to the unequal sample size, the premise of equality of variances was checked systematically. If the test is significant (unequal variances), the Welch test was used.

Ethical considerations: this study took place after the authorisation of those in charge of the health care institutions following the agreement of the Bioethics Advisory Commission of the Faculty of Sciences of Agadir (N°: FCR-CS-09/2021-0001). Also, the investigators explained the purpose of the study with respect to the anonymity and confidentiality of the persons.

Results

The present study revealed that the mean Zarit score is 56.8 ± 14.3. Concerning the patients' characteristics, table 1 illustrates the predominance of the female gender (69%) and the urban origin is also dominant with 67%. for the level of education, it is observed that the illiterate present 51% against only 31% for the secondary level and 13% for the primary. In relation to marital status, 54% of the patients were married, 28% were divorced

and 12% were single. The statistical analysis of these variables did not show any significant relationship with the Zarit score (see **table I**).

Table II reveals that the mean age of the patients is 77.3 ± 6.58 years with no significant relationship with the Zarit score (p=0.39). The mean duration of the disease is 6.05 ±2.14 years which significantly increases the burden on caregivers (p<0.001).

For the characteristics of the principal caregivers, table 3 shows that the female gender represents 83% with a significant relationship with the Zarit score (p=0.011). The data from this study also shows that the mean age of the caregivers is 44.7 ± 8. 90 years but this time with no significant relationship with Zarit burden (p=0.51) (see **Table II**). Looking at the marital status of the caregivers we find that married caregivers constitute 65% followed by single caregivers with 21% but with no significant statistical relationship with the Zarit score (p=0.88) (**Table III**).

Daughters and sons predominate in the caregiver-patient relationship with 48%, followed by spouses with 20%, but no relationship with burden was found (p=0.24). In relation to education level, the results show that secondary and primary education are in first place with 36% and 33% respectively (**Table III**).

In relation to socio-economic level, caregivers working in the private sector represent 52% followed by 40% who do not have a fixed profession; this component is statistically related to the Zarit score (p=0.045). as for the data relating to caregivers' salaries, 55% have a monthly salary of less than 1,000 Moroccan dirhams and only 8.1% have a salary of between 4,000 and 10,000 dirhams. despite this, the relationship is not significant with the burden (see **table III**). Caregivers often need other people for assistance, this study shows that 25% take care of patients alone and 61% are replaced from time to time by one person and only 15% declare to be assisted by two other people. but without any significant relationship with the Zarit score (p=0.12).

In terms of chronic diseases, this study found that 25% of the caregivers had high blood pressure and 25% had diabetes. In terms of relationship with Zarit score, statistical analysis shows that diabetes is significantly related to Zarit score (p<0.01) but not for hypertension (p=0.63) (see **table III**).

In relation to the help needs expressed by the caregivers, the need for financial help was expressed by 72% of the caregivers, followed by the need for psychosocial help with 63% and the need for information on the disease expressed by 37% of the caregivers. Statistical analysis found a significant relationship with the Zarit score for the psychosocial need (p<0.01), however, no relationship was demonstrated with the other help needs (see in **table III**).

The same table also shows that the mean duration of illness (6.05± 2.14) and duration of assistance (5.80 ±2.01) are close, which can be explained by the care of the patients by the same caregivers from the beginning of the disease. We also note that a significant relationship between the Zarit score and the duration of the disease is shown by the Pearson test (p<0.001), as well as for the duration of assistance (p=<0.001) (see **table II**).

The present study found that the mean number of hours required by the patient for his or her caregiver was 16.2 ± 5.15. Bivariate analysis of this variable with the overall burden shows a significant relationship According to Spearman's test (P=<0.01) (see **table II**).

Table I: General characteristics of patients.

Patient's characteristics		n (%)	Zarit scale: Mean (SD)	p
Patient gender	Female Male	76 (69%) 34 (31%)	57.0 (13.7) 56.1 (15.7)	0.89¥
Educational level	None Secondary Primary University	56 (51%) 34 (31%) 18 (16%) 2 (1.8%)	53.8 (11.4) 58.0 (11.4) 51.7 (10.3) 54.5 (4.95)	0.28†
Marital status	Married Widowed Single Divorced	59 (54%) 31 (28%) 13 (12%) 7 (6.4%)	56.6 (14.4) 52.5 (15.2) 62.5 (10.6) 65.7 (7.74)	0.051†

Table II: Patient and caregiver factors that influence caregiver burden (ZBI score).

		Mean ± SD	Correlation coefficient (95% CI)	p
Patient	Patient's age (years ± SD) Duration of the disease (years ± SD)	77.3 ± 6.58 6.05 ±2.14	0.0834 0.609 (0.476; 0.715)	0.39† <0.001†
Caregiver	Caregiver's age (years ± SD) Duration of assistance (years ± SD) Number of hours per day (hours ± SD)	44.7 ± 8.90 5.80 ± 2.01 16.2 ± 5.15	0.0632 (-0.126; 0.247) 0.583 (0.444; 0.694) 0.290	0.51¥ <0.001* <0.01¥

† : Pearson. ¥ : Spearman. * Welch

Table III: General characteristics of caregivers.

		n (%)	Zarit scale: Mean (SD)	p
Caregiver's gender	Female Male	91 (83%) 19 (17%)	55.4 (14.6) 63.1 (10.5)	0.011*
Relationship with the patients	Child Spouse Fraternity Other	53 (48%) 22 (20%) 18 (16%) 17 (15%)	55.6 ± 14.6 62.5 (9.66) 55.1 (13.6) 54.6 (17.6)	0.24 †
Educational level	Secondary Primary None University	40 (36%) 36 (33%) 23 (21%) 11 (10%)	48.8 (11.1) 65.5 (7.63) 67.3 (6.75) 35.2 (11.4)	<0.001†
Marital status	Married Single Widowed Divorced	72 (65%) 23 (21%) 11 (10%) 4 (3.6%)	57.0 (14.6) 55.5 (14.0) 57.1 (14.5) 58.2 (12.9)	0.88†
Employment status	Private None Public Retired	57 (52%) 44 (40%) 5 (4.5%) 4 (3.6%)	60.7 (11.3) 51.7 (16.4) 55.2 (18.0) 57.8 (7.80)	0.045 †
Caregiver's salary (dirhams)	<1000 [1000-4000[[4000-10000[	61 (55%) 41 (37%) 9 (8.1%)	55.5 (15.3) 58.5 (12.6) 57.7 (14.4)	0.64†
Co-helpers	None One Two	27 (25%) 67 (61%) 16 (15%)	61.5 (11.3) 55.4 (15.0) 54.6 (14.5)	0.12†
Diabetes	Yes No	27 (25%) 83 (75%)	63.1 (11.9) 54.7 (14.4)	<0.01*
High Blood Pressure	Yes No	27 (25%) 83 (75%)	55.9 (13.8) 57.0 (14.5)	0.63¥
Psycho-social help	Yes No	69 (63%) 41 (37%)	60.0 (12.0) 51.2 (16.1)	<0.01*
Information help	Yes No	41 (37%) 69 (63%)	59.5 (10.8) 55.1 (15.8)	0.09*
Financial help	Yes No	79 (72%) 31 (28%)	57.7 (14.2) 54.4 (14.3)	0.27*

* Welch. ¥ Mann-Whitney. † Kruskal-Wallis.

Discussion of results

The Zarit score is a scale that objectively evaluates the burden of caregivers of dementia patients. In our study, the mean Zarit score was 56.8 ± 14.3, which indicates that the natural caregivers participating in this study suffer from a moderate to high caregiving burden. This is consistent with the finding reported by Tawfik & al., of a moderate to high caregiving burden with an average Zarit score of 61±13.7 from 60 family caregiver[12]. Compared to developed countries, the Zarit score of the population studied in this study is relatively high[13-14]. This may be related to caregiver support as well as their motivation in developing countries[15].

The mean age of the patients was 77.3 ± 6.58 years. This study showed a non-significant increase in the Zarit score in caregivers of elderly patients. This is different from the results of 458 caregivers studied by Win & al[16]. The difference can be related to the sample size in each study. Also the burden of caregivers was not dependent on the patients' level of education or their marital status. This confirms Dauphintot & al result[17].

The caregiver demographic profile shows a gender ratio of 0,34 this same result is also found by Liu & al[18] and Mourgues & al[19]. The reason for this may be that women are comparatively more caring than men, and are more likely to be completely available[20]. In contrast, the present study reported a significant increased burden for male caregivers. Other studies[18-19] noted that the burden in both sexes was similar. The caregivers in this study are younger than in both studies of Dias & al (57.9 ±13.75 years)[21] and Win & al (53.1 ± 11.8 years)[22]. This discrepancy may be explained by the size of the population and the increased age expectancy in Europe in comparison to Morocco. Regarding its relationship with caregiver burden, the present research showed that the burden was not related to the caregivers' age (p=0.39). While the Win Study showed that burden was high in elderly caregivers (p<0.01), this may be due to alteration in their health state with age[16].

About the caregiver' s relationship with their patients, for James & al23, only 15% of the caregivers were

spouses and 48% were descendants of the patients. In the current study, forty-eight percent are progeny while fifteen percent are partners. As per Lucijanić & al (14) reported that the spouses were 38.9% and descendants were 51%, however there was no association with Zarit score from any of these studies.

In another aspect, according with James & al (23) showed that the exercise of a profession significantly increased the level of Zarit (p=0.01). This is supported by present research (p=0.045), possibly explained by additional burdens of occupational activities. Concerning the caregivers' salaries, Thompson & al[24] reported only 4.9% of the caregivers with low salaries (0-15,000 USD), however 37% from this study with no fixed salaries. The Zarit score, on the other hand, had no significant association with salary in this study (P=0.64). The Tunisian study conducted by Thabet & al., confirms the increased burden for caregivers with lower economic status (p=0.034)[25]. This divergence may be caused by the high level of solidarity that exists amongst the Moroccan families.

In the present study, the burden was also significantly elevated for caregivers who had assisted their patient for a longer duration (p<0.001). This is in contrast to the result from the Chinese Study conducted by Liu & al[18] (p=0.34). This could be attributed to the sufficient existence of care institutions as compared to Morocco and also that most of the caregivers in Morocco have additional professional occupations. Regarding the average number of hours per day the caregiver spends with the patient. There was also a significant increase in the Zarit score for caregivers who exceeded a significant number of hours. While, Liu & al., found a daily average of 15 hours per day, but with no significant relationship with the load (p=0.65)[18].

In the analysis of the caregivers' comorbidities and their related to the burden, this research indicated that caregivers suffering of diabetes showed a significantly increase in their burden (p=0.01). Compared to the other caregivers, those with high blood pressure had a similar level of burden to healthy caregivers. This finding is consistent with that of king; study who reported that 18.4% of diabetic caregivers experienced an increased burden (p=0,04)[26]. However, the study of Zubaidi & al[22] revealed that 53 % of the caregivers had various chronic diseases with absolutely no influence on burden (p=0.21). This difference was probably related to caregivers' staging of their chronic diseases and the co-existence of several comorbidities.

The analysis of education level of the caregivers revealed a significant increase of the Zarit score according to the level of education (p<0.001). This is similar to the results reported by Chang & al (27) (p=0.02). We can conclude that a higher level of education gives caregivers more knowledge about the disease and abilities in managing their patients' disease. his is confirmed by the need for information, which was expressed by 37% of the caregivers.

Conclusion

The caregivers of dementia patients constitute the essential component in the care of people with dementia. Quality in care requires supporting and training actions to facilitate the work performed by caregivers. Additionally, the legislation will be important in ensuring that caregivers are not exposed to any risks associated with their complex work.

Declaration of interests

The authors declare that they have no conflicts of interest in relation to this article.

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ORIGINAL

Comparing the efficacy in the intravenous and sublingual administration of midazolam for the sedation of patients during upper gastrointestinal endoscopy

Comparación de la eficacia en la administración intravenosa y sublingual de midazolam para la sedación de pacientes durante la endoscopia digestiva alta

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Abstract

Background: Upper gastrointestinal (GI) endoscopy is a common procedure for the diagnosis and treatment of upper digestive tract diseases. Relief of pain and discomfort during endoscopy is necessary. In our study, the sublingual administration and the injection of midazolam were compared in terms of their efficacy in the sedation of patients undergoing upper gastrointestinal endoscopy.
Methods: In this double-blind clinical trial, 80 patients were divided into two groups. The first and the second groups received 2.5 mg intravenous and 5 mg sublingual midazolam respectively. The patients were evaluated and compared using standard questionnaires in terms of sedation, pain/discomfort, and satisfaction. They were also monitored for blood pressure, heart rate and SPO2. The data were analyzed by the SPSS 16 software using Tukey's test and Spearman's correlation coefficient. The significance level was considered to be $P<0.05$.
Results: According to the results, there was a statistically significant difference between the two groups in terms of the mean Ramsay score after sublingual administration or injection. For the double dose in the sublingual group, this score was higher than that in the intravenous group. There was no statistically significant difference between the two groups in terms of pain and satisfaction. In both methods, the difference between the mean sedation scores was statistically significant before and after the treatment. The effect of each method was also significant on the improvement of the sedation score. There was no significant difference between the two groups in terms of systolic and diastolic blood pressures, heart rate and SPO2.
Conclusion: As it was concluded, double dose of sublingual midazolam has a statistically greater effect on sedation than intravenous administration. The effects of the two methods on oxygen saturation, heart rate and blood pressure are statistically similar.

Key words: Upper endoscopy, Midazolam, Sublingual, intravenous, Sedation, Pain.

Resumen

Antecedentes: La endoscopia del tracto gastrointestinal superior (GI) es un procedimiento común para el diagnóstico y tratamiento de las enfermedades del tracto digestivo superior. Es necesario aliviar el dolor y las molestias durante la endoscopia. En nuestro estudio, se comparó la administración sublingual y la inyección de midazolam en cuanto a su eficacia en la sedación de pacientes sometidos a endoscopia gastrointestinal superior.
Métodos: En este ensayo clínico doble ciego, 80 pacientes fueron divididos en dos grupos. El primer y el segundo grupo recibieron 2,5 mg de midazolam intravenoso y 5 mg de midazolam sublingual, respectivamente. Los pacientes fueron evaluados y comparados mediante cuestionarios estándar en términos de sedación, dolor/malestar y satisfacción. También se controlaron la presión arterial, la frecuencia cardíaca y la SPO2. Los datos se analizaron con el programa informático SPSS 16 utilizando la prueba de Tukey y el coeficiente de correlación de Spearman. El nivel de significación se consideró $P<0,05$.
Resultados: Según los resultados, hubo una diferencia estadísticamente significativa entre los dos grupos en cuanto a la puntuación media de Ramsay tras la administración sublingual o la inyección. En el caso de la dosis doble en el grupo sublingual, esta puntuación fue superior a la del grupo intravenoso. No hubo diferencias estadísticamente significativas entre los dos grupos en términos de dolor y satisfacción. En ambos métodos, la diferencia entre las puntuaciones medias de sedación fue estadísticamente significativa antes y después del tratamiento. El efecto de cada método también fue significativo en la mejora de la puntuación de sedación. No hubo diferencias significativas entre los dos grupos en cuanto a la presión arterial sistólica y diastólica, la frecuencia cardíaca y la SPO2.
Conclusiones: Como se concluyó, la doble dosis de midazolam sublingual tiene un efecto estadísticamente mayor sobre la sedación que la administración intravenosa. Los efectos de los dos métodos sobre la saturación de oxígeno, la frecuencia cardíaca y la presión arterial son estadísticamente similares.

Palabras clave: Endoscopia superior, Midazolam, Sublingual, Intravenoso, Sedación, Dolor.

Introduction

Upper gastrointestinal endoscopy is a commonly used diagnostic and therapeutic procedure whose application requires sedative drugs to reduce patients' anxiety, pain and discomfort. Findings have shown that the use of sedatives increases patients' satisfaction and decreases their discomfort during the GI endoscopy procedure[1]. The intravenous administration of benzodiazepines, with midazolam included, is a common sedation method for upper GI endoscopy candidates[2]. Since the intravenous administration of sedatives requires accurate monitoring and trained personnel and has serious complications such as respiratory depression and apnea (10), oral, sublingual or intranasal administration can be an alternative with fewer side effects[2]. Research has shown that the sublingual administration of midazolam is effective for the sedation of children and adults[3,4]. So far, little research has been conducted on the sublingual administration of midazolam. The present study, therefore, seeks to compare intravenous and sublingual administrations of midazolam for the sedation of adult candidates during upper GI endoscopy.

Patients and methods

The present study is a double-blind RCT (randomized clinical trial) conducted on 80 adult candidates for the diagnostic endoscopy of the GI tract. Once it was approved by the university ethics committee, the research population was selected among the patients of ASA (American Social Anesthesiology), classes I and II, who were in the range of 15-55 years of age. They served as the first-time candidates for the diagnostic endoscopy of the upper GI tract.

The main inclusion criteria were shortlisted as the age range of 15-55 years, ASA classes I and II, and first-time candidacy for upper GI endoscopy. The exclusion criteria were defined as follows:

- Addiction to drugs, alcohol, sedatives and psychotropic drugs
- Psychotics undergoing medical treatment
- Severe systematic diseases (e.g. cardiac, pulmonary, hepatic and renal diseases)
- History of sedatives use within at least the past month
- Pregnancy and breastfeeding

Once the study was approved by the medical ethics committee, 80 patients (40 per group) were selected to participate in the study conducted in the endoscopy ward of Shahid Sadouqhi Hospital of Yazd. Also, informed consent was taken from them individually. All the patients underwent hemodynamic monitoring (for average systolic and diastolic blood pressure and HR) and SPO2, and an IV access was prescribed for them. They were randomly assigned to two groups of 40. The grouping was based on a random number table in the Random Allocation Software. The first group received 2.5 mg of midazolam (from Exir Co.) as an IV bolus injection, and the second group had the sublingual administration of 5 mg of midazolam (from the same company). Both received a placebo as well. There was a sublingual placebo for the first group and IV normal saline for the second one. It was a double-blind study during which neither the researcher nor the patients were informed of the administration of drugs. This was based on the standards of the consort statement. Intermittent doses of intravenous midazolam 1 mg were administered if the sedation was insufficient and the endoscopy was intolerable for the patients. This continued until an optimal sedative score was reached. The results were then recorded in a questionnaire.

The patients' sedation level was assessed based on the Ramsay Score. The pain/discomfort score (0-10) and the satisfaction score (0-10) were both recorded for each candidate. Such therapeutic measures as the administration of intravenous fluids and injection of IV ephedrine 5 mg were performed as the systolic blood pressure dropped by 20% to 90% and more. In the case of SPO2 decrease by 90%, the patients received pure oxygen through a nasal mask and were brought back to consciousness. All the reports on these procedures were recorded in the questionnaire.

Data analysis

Numerical indices (mean ± SD) and frequency tables (percentages) were used for the data illustration in SPSS 16.0, the former for quantitative variables and the latter for qualitative variables. The data were analyzed using ANOVA, Tukey's multiple comparison and T-Test. Probability values less than 0.05 were considered significant.

Results

A total number of 80 patients participated in the study. They were assigned to two groups of 40, and their demographic data, including age and gender, were recorded. As presented in **table I**, the results of the chi-square test refer to no significant difference between the two groups in terms of demography, namely age and gender.

Table I: Comparison of the demographic data of the tested groups.

Variable		IV	SL	P-value
Gender	*Male*	18	17	0.822
	Female	22	23	
Age		41.6	39.3	0.534

Table II and **figure 1** summarize the comparative results of the Ramsay Score evaluation for the sedation monitoring, mean pain score and satisfaction level of the patients. As it can be seen, the two groups had a statistically significant difference in the mean value of

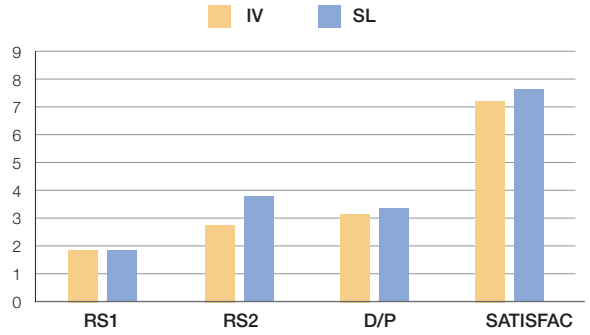
their Ramsay scores after injection; the sublingual group scored a higher value than the intravenous group. This finding along with the t-test results and the p-values indicated that the major difference only belonged to the RS2 mean scores of the methods of administration. In other words, the two groups were not significantly different in terms of pain and satisfaction levels.

Table II: Comparison of the mean values of the intended variables (i.e, sedation, pain and satisfaction scores) in each group.

		Mean	P-value
RS1	IV SL	1.88 1.88	1
RS2	IV SL	2.78 3.88	0.001
D/P	IV SL	3.15 3.40	0.573
SATISFAC	IV SL	7.3 7.7	0.304

RS1 = Ramsay Score before midazolam, RS2 = Ramsay Score after midazolam, D/P=Discomfort/Pain, Satisfac = Satisfaction

Figure 1: Comparison of the mean values of the intended variables (i.e. sedation, pain and satisfaction scores) in each group.



The variation of the mean sedation scores of each group was measured and compared before and after intervention, as presented in **table III**. Based on the results, there was a statistically significant difference between the mean scores of sedation before and after injection in each administration group, implying that both administration methods had a significant impact on the improvement of the sedation scores.

Table III: Comparison of the mean scores of sedation before and after intervention in each group.

Variable		Mean	Mean difference (before and after)	P-value
IV	Before After	1.88 2.78	0.9	0.001
SL	Before After	1.88 3.88	2	0.001

The groups were also compared in terms of the frequency distribution of the administration side effects, such as respiratory depression, hypotension and bradycardia. The results are summarized in **tables IV**, **V, VI** and **VII**. As suggested comparatively, the SBP, DBP, PR, and SPO2 trends brought about no significant change in those groups over time.

Table IV: Determining the mean value of the systolic blood pressure in each group.

Systolic blood pressure (SBP)		Mean ± SD
SBP1	IV SL	117.5 117.37
SBP2	IV SL	117.5 117.37
SBP3	IV SL	117.5 117.37
SBP4	IV SL	117.5 117.37
SBP5	IV SL	117.5 117.37

SBP1= before drug prescription, SBP2= 10 min after drug prescription, SBP3= 20 min after drug prescription, SBP4= during endoscopy (30 min after drug prescription), SBP5= during discharge (one hour after drug prescription)

Table V: Determining the mean value of the diastolic blood pressure in each group.

Diastolic Blood Pressure (DBP)		Mean ± SD
DBP1	IV SL	78.25 79.38
DBP2	IV SL	78.38 79.38
DBP3	IV SL	78.38 79.38
DBP4	IV SL	78.38 79.38
DBP5	IV SL	78.48 79.38

DBP1= before drug prescription, DBP2= 10 min after drug prescription, DBP3= 20 min after drug prescription, DBP4= during endoscopy (30 min after drug prescription), DBP5= during discharge (one hour after drug prescription)

Table VI: Determining the mean value of the heart rate in each group.

Heart rate (PR)		Mean ± SD
PR1	IV SL	78.83 80.40
PR2	IV SL	76.93 79.45
PR3	IV SL	78.98 79.50
PR4	IV SL	48.88 82.87
PR5	IV SL	79.95 80.93

PR1= before drug prescription, PR2= 10 min after drug prescription, PR3= 20 min after drug prescription, PR4= during endoscopy (30 min after drug prescription), PR5= during discharge (one hour after drug prescription)

Table VII: Determining the mean value of the peripheral oxygen saturation in each group.

Peripheral oxygen saturation		Mean ± SD
SPO1	IV SL	96.23 96.00
SPO2	IV SL	96.18 95.98
SPO3	IV SL	96.15 96.00
SPO4	IV SL	96.05 95.95
SPO5	IV SL	96.13 95.98

SPO1= before drug prescription, SPO2= 10 min after drug prescription, SPO3= 20 min after drug prescription, SPO4= during endoscopy (30 min after drug prescription), SPO5= during discharge (one hour after drug prescription)

Discussion

This study was conducted to comparatively investigate the effects of intravenous injection and sublingual administration of midazolam on the sedation of first-time upper-GI endoscopic patients. In this regard, the sublingual administration of midazolam had no complications during the diagnostic endoscopy of the upper GI tract.

Having better anti-anxiety and hypnotic effects, intravenous midazolam is more commonly administered for sedation during upper GI endoscopy[5,6].

Rafiei et al. compared the impacts of IV (.05-.1 mg/kg) and oral (.5 ml/kg) administrations of midazolam on 61 patients who underwent upper GI endoscopy. They found no statistically significant difference between the two administration methods in terms of sedation scores and satisfaction. As for SPO2, the oral method had a lower mean score than the intravenous one[7]. In our study, there was also no significant evidence of difference in satisfaction with intravenous and sublingual methods. The sedation mean score, nevertheless, was higher in the sublingual group. Moreover, no group showed significant superiority in its SPO2 mean values; the decrease in the mean score of SPO2 was considerable in neither group.

Shafa et al. compared the effects of the intravenous administration of dexmedetomidine and midazolam on the quality of sedation during the diagnostic endoscopy of the upper GI tract in 72 children. Based on the results, the recipients of midazolam experienced a higher level of sedation than those that took dexmedetomidine during endoscopy, accentuating the better impact of IV midazolam than dexmedetomidine[8]. In our study, unlike the intravenous drug reception, the sublingual method had a statistically better impact on the patients' sedation level (sublingual 5 mg versus intravenous 2.5 mg).

Khodadad et al. studied the effect of oral (.25-.5 mg/kg) versus IV (.1-.3 mg/kg) midazolam on the sedation of 199 children during upper GI endoscopy. They found that the average duration of sedation was significantly higher in the oral group than in the intravenous recipients. Thus, those in the oral group were significantly more satisfied than the IV group patients. Neither of the oral and IV methods, however, resulted in deep sedation in any of the patients[9]. Consistent with the findings of Khodadad et al., our study reached a statistically significant difference between the sedation levels of the sublingual and intravenous groups; the sublingual recipients had better sedation than the IV patients. These two studies, thus, both confirmed the priority of oral and sublingual methods over intravenous administration.

Gupta et al. compared the sedating impacts of oral and sublingual midazolam. Their findings were suggestive of higher sedation in sublingual administration, but the difference was not statistically significant. Of course, Gupta's study was not performed on patients under endoscopic diagnosis[10]. In line with that investigation, our study showed that sublingual administration could more effectively sedate patients than the intravenous method. It was, however, different from Gupta's study in two ways, namely the type of disease and the type of drug administration; we had a sublingual/intravenous dichotomy, while Gupta et al. focused on the sublingual/oral differentiation.

Roseman et al. conducted another comparative study on the sedation effects of sublingual and intravenous midazolam. Their participants were candidates for elective surgery. A majority of the intravenously-treated patients scored RS2 (Ramsay Score) after 10 minutes of sedation, while the sublingual patients reached RS1-2 after 10 to 20 minutes and RS2-3 after 30 minutes of administration[11]. The sublingual sedation in our study was consistent with that in the research by Roseman et al. This is to say that, in both studies, the Ramsay scores (i.e. sedation levels) before and after the drug administration were significantly different. According to the initial experiments in our study, the sublingual effect constitutes over 50% of intravenous methods. That is, a double dose of sublingual midazolam would result in higher sedation than that created by the intravenous method. This may contribute to the absorption of more than 50% of the drug in the sublingual method. This finding may open a new horizon to researchers for the further investigation of sublingual absorption. In this regard, it is recommended to use a lower dose of sublingual midazolam.

As numerous studies have reported, sublingual administration is not commonly practiced probably due to the bitter taste of the drug. In this respect, the pharmaceutical industry is expected to find a way to improve the taste of midazolam in the future.

Several pieces of research have compared the effects of different midazolam administration methods[12-14]. The results of comparing the sublingual and orogastric routes of midazolam administration have indicated that the plasma level increases after sublingual administration, as compared to the orogastric route[10].

Comparing sublingual and oral methods, Fuji et al. found that the sublingual method had higher bioavailability than the oral one, which was due to the elimination of the hepatic first pass effect in the oral method[15].

According to Odu et al., there was no significant difference between sublingual and intravenous administrations in terms of pharmacokinetic parameters[16]. In general, sublingual administration is apparently preferred to other methods for its kinetic parameters. Similarly, the present

study has provided evidence for the supremacy of a double dose in the sublingual method over intravenous administration; the former has proved to have a better impact on the sedation scores of endoscopic patients.

As Odu et al. confirmed, the sublingual intake of midazolam is highly preferred to other ways of taking the drug due its lower stress, painlessness and higher bioavailability. Besides, sublingual administration involves considerable absorption. Odu et al. did not observe any statistically significant difference between the kinetic parameters of the two groups of recipients[16].

Based on the results of the present research, neither of the methods of drug administration has a significant impact on the SPO2 level, which means they cannot significantly affect the respiratory status of patients. This finding is confirmed by numerous similar studies.

Nejati at al. investigated the effect of midazolam on SPO2 in upper GI endoscopy. They found that midazolam administration would not change SPO2 levels. It is worth noting that they only injected midazolam intravenously[17]. Likewise, in our study, neither the sublingual method nor the intravenous one could significantly change the SPO2 levels.

In their pre-endoscopic intravenous injection of midazolam, Dhariwal et al. found the patients' SPO2 levels to be 94.9%, 92.8% and 91.2% before endoscopy, after sedation and during endoscopy respectively[18]. These three levels had no significant difference, which is in line with the results of our study.

According to the findings of our study, neither way of administrating midazolam had a significant effect on blood pressure and heart rate. Liacouras et al. evaluated 123 upper GI endoscopic patients after a midazolam injection (0.5 mg/kg, maximum 20 mg). They found that the heart rate, blood pressure and SPO2 level of the patients were not significantly different before and after the drug administration, which is consistent with the findings of our study[19]. In other words, neither administration method could significantly affect the heart rate, blood pressure and SPO2 level.

Kumar et al. found that, although patients with no important underlying diseases are less likely to be at the risk of SPO2 reduction during upper GI endoscopy, continuous monitoring of their oxygen saturation is recommended[20].

Karl et al. compared the effects of pre-endoscopic midazolam injections on the change of oxygen saturation in 60 patients. The results indicated the reduction of SPO2 to less than 90% in only five patients (8.3%). They concluded that the intravenous administration of low-dose midazolam is a safe method for an endoscopy procedure[21]. In a similar approach practiced in our study, no evidence has been found for SPO2 reduction to less than 95%, implying that both intravenous and sublingual administrations of midazolam are safe in terms of SPO2, as it was in Karl's study.

Due to its short half-life, the drug cannot have any significant effect on the stability of the cardiovascular system and the respiratory center. It is, thus, considered as an effective sedative drug for endoscopy procedures. In contrast, other sedative drugs such as diazepam are associated with more complications because their half-life is much longer. Midazolam proved to have no significant impact on the heart rate and the respiratory system of the patients in our study. This drug is highly preferred over other sedatives for its shorter half-life and higher clearance[22,23].

A double dose of sublingual midazolam is of a higher sedative effect than intravenously injected midazolam. The absorption of sublingual midazolam is, indeed, more than 50%. Therefore, it is recommended to compare the lower doses of sublingual and injected types of midazolam.

Conclusion

The results of this study showed that a double dose of sublingual midazolam is significantly more effective than intravenous administration for the sedation of patients during endoscopy. However, the patients' satisfaction level was not significantly different in the sublingual and intravenous groups. Finally, the two groups had no significant difference in terms of such complications as respiratory depression, hypotension and heart rate change.

Ethical consideration

The study was approved by Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran (AIR.SSU.MEDICINE.REC.1397.185). This study was also registered in Iranian Registry of Clinical Trials (IRCT20100102002963N36).

Abbreviations

GI: Gastrointestinal
SPO2: Oxygen Saturation
RS2: Ramsay Score
HR: Heart Rate

Conflict of Interest

The authors declare that there is no conflict of interest in the publication of this paper

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ORIGINAL

Aplicación del metaverso como técnica de aprendizaje en el grado de odontología. Estudio preliminar

Application of the metaverse as a learning technique in the degree of dentistry

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Resumen

Introducción: El metaverso es un entorno interactivo en 3D generado por un ordenador, en el que los seres humanos son representados por avatares que pueden interactuar entre sí y con el software del sistema. En referencia a los modelos y características del metaverso, podemos entenderlo como la convergencia de una realidad física virtualmente aumentada en un espacio virtual físicamente persistente. La utilidad del metaverso está ligada principalmente a los usuarios nativos digitales.
Hipótesis: El conocimiento del metaverso como herramienta de enseñanza, proporcionará un mayor nivel de rotación mental de la inteligencia espacial de los estudiantes de Odontología, evaluado mediante una Encuesta múltiple y el Test de Rotación Mental de Vandenberg.
Objetivo: Establecer en qué medida el conocimiento del metaverso influye en el nivel del factor de rotación mental de la inteligencia espacial en los estudiantes de Odontología.
Métodos: A través de una Encuesta múltiple se obtendrá una información referente al conocimiento o uso previo que los estudiantes universitarios de Odontología tienen sobre la tecnología virtual 3D y en especial del metaverso, para seguidamente realizar el Test de Rotación Mental de Vandenberg para determinar su inteligencia espacial.
Resultados: El 42% de los estudiantes encuestados dijo tener un alto nivel de conocimiento sobre el metaverso. Existe asociación entre el tipo de respuesta en el Test de Rotación Mental de Wandenberg y el curso del grado de Odontología.
Discusión: La Escuela Universitaria ADEMA, tras una actividad inmersiva parcial mediante simuladores hápticos y holográficos, abre un futuro sin retorno hacia una inmersión total mediante el metaverso. El metaverso estimula a los estudiantes con problemas de aprendizaje y conocerlo tiene un efecto positivo en la inteligencia espacial. Debemos convertir al estudiante en el verdadero protagonista del proceso de aprendizaje a través del metaverso, un aprendizaje que ya no se "entrega" sino que se "crea".

Palabras clave: Metaverso, Simulación Háptica, Inmersión, Educación Dental.

Abstract

Introduction: The metaverse is an interactive 3D environment generated by a computer, in which human beings are represented by avatars that can interact with each other and with system software. In reference to the models and characteristics of the metaverse, we can understand it as the convergence of a virtually augmented physical reality in a physically persistent virtual space. The usefulness of the metaverse is mainly linked to digital native users.
Hypothesis: Knowledge of the metaverse as a teaching tool will provide a higher level of mental rotation of the spatial intelligence of dentistry students, evaluated through a multiple Survey and the Vandenberg Mental Rotation Test.
Objective: To establish to what extent knowledge of the metaverse influences the level of the mental rotation factor of spatial intelligence in dentistry students.
Methods: Through a multiple Survey, information will be obtained regarding the knowledge or previous use that dental university students have about virtual technology in 3D and especially the metaverse, to then perform the Vandenberg Mental Rotation Test to determine their spatial intelligence.
Results: 42% of the students surveyed said they had a high level of knowledge about the Metaverse. There is an association between the type of response in the Wandenberg Mental Rotation Test and the course of the Dentistry degree.
Discussion: The ADEMA University School, after a partial immersive activity through haptic and holographic simulators, opens a future of no return towards a total immersion through the metaverse. The metaverse stimulates students with learning disabilities and knowing it has a positive effect on spatial intelligence. We must make the student the true protagonist of the learning process through the metaverse, a learning that is no longer "delivered" but "created".

Key words: Metaverse, Haptic Simulation, Immersion, Dental Education.

Introducción

El metaverso es un entorno interactivo 3D generado por un ordenador, en el que los seres humanos son representados por avatares que pueden interactuar entre sí y con el software del sistema[1,2]. El término proviene de la novela de ciencia ficción *Snow Crash*, escrita por Neal Stephenson[3].

Existen diferentes modelos de metaverso[4-6]:
- Juegos y Mundos Virtuales: permiten el contacto con otros usuarios y programas de software dentro de un mundo virtual 3D. (*World of Warcraft, SecondLife, Twinity*)
- Mundos en espejo: Permiten representaciones virtuales detalladas del mundo real.
- Realidad aumentada: representación virtual aumentada del mundo real con información adicional.
- *Lifelogging*: registro digital de la vida cotidiana mediante estadísticas.

Además de los entornos ya establecidos del metaverso como entretenimientos, teleeducación, telesalud y economía digital, avanzados por Zuckerberg[7], también comienzan a emerger nuevas formas en el arte, como los *No Fungibles Token* (NFT)[8].

En general, los metaversos presentan unas características comunes[4]:
- Interactividad: capacidad del usuario de comunicarse con otros usuarios y el ambiente tridimensional que lo rodea, con capacidad de generar comportamientos preestablecidos con su avatar de manera reciproca con otros.
- Corporeidad: es la representación del usuario a través de un avatar en el espacio tridimensional, sujeto a ciertas normas prestablecidas por recursos limitados.
- Persistencia: sigue desarrollándose a pesar de que algunos o todos sus usuarios no estén conectados. Las posiciones, conversaciones, objetos de propiedad, etc., siempre son guardados y permite recuperarlos al conectarse de nuevo.

En referencia a los modelos y características del metaverso, podemos entenderlo como la convergencia de una realidad física virtualmente aumentada en un espacio virtual físicamente persistente[9,10].

La utilidad del metaverso está ligada principalmente a los usuarios nativos digitales, los cuales, a diferencia de los inmigrantes digitales, pueden realizar varias tareas simultáneamente, como escuchar música, ver vídeos y hasta leer, convirtiendo su cerebro en un procesador multitareas[11,12].

Se cree que la exposición temprana y constante a la tecnología, es determinante para que los nativos digitales tengan una mayor familiaridad y comprensión de la tecnología que las personas que nacieron antes de que la tecnología fuera difundida, aunque no todos los niños que nacen actualmente son nativos digitales por defecto. Han crecido utilizando la tecnología como el Internet, las computadoras y los dispositivos móviles. Los nativos digitales son más informales y a la vez tienen un flujo de comunicación abreviado, es decir no utilizan palabras completas. Para ellos no existe una barrera de tiempo y espacio y exigen mayor interactividad tecnológica en la parte educativa.

Los inmigrantes digitales son las personas que nacieron antes de la adopción generalizada de la tecnología digital, son menos rápidos para acoger las nuevas tecnologías que los nativos digitales por la rutina y costumbres adoptadas[13].

Es preciso referirse a la Teoría de Inteligencias Múltiples para determinar qué tipo de inteligencia debemos valorar cuando queremos aplicar el metaverso en procesos de aprendizaje en estudiantes de Odontología. El sistema universitario ha entronizado la inteligencia lógico-matemática y la lingüística, pero en Ciencias de la Salud y especialmente en la Odontología debe preponderar la inteligencia cinestésico-corporal y sobretodo la inteligencia espacial[14].

Podríamos definir a la inteligencia espacial como la capacidad para procesar información 3D y poder percibir, reproducir, reconocer, anticipar, ver similitudes y aplicar habilidades en un mundo virtual, incluso la capacidad para imaginar objetos en movimiento[15], evaluada por el Test de Rotación Mental de Wandenberg[16]. De todo ello podemos deducir que el metaverso influye significativamente en el nivel del factor de rotación mental de la inteligencia espacial. A mayor capacidad de rotación mental como factor de inteligencia espacial, mejor aprendizaje procedimental, en donde el individuo genera imágenes mentales espaciales del procedimiento antes de realizarlo. La finalidad es crear haciendo y utilizar el instrumento adecuado para cada objetivo, mejorando el aprendizaje procedimental de técnicas operatorias sobre objetos 3D[17].

Los docentes universitarios de la carrera de Odontología se preocupan mucho por la parte procedimental de sus estudiantes ya que deben atender pacientes en los últimos cursos. El estudiante universitario a medida que desarrolla el factor de rotación mental de la inteligencia espacial, le permitirá adquirir una mejor habilidad en la parte procedimental de la carrera de Odontología.

Hipótesis de trabajo

De los conceptos expuestos podemos plantear la hipótesis de que el metaverso permite mejorar el factor de rotación mental de la inteligencia espacial en estudiantes universitarios de la carrera de Odontología. Creemos que los estudiantes que adquieran una capacitación

en metaverso mejorarán su factor de rotación mental de la inteligencia espacial. Las instituciones educativas deben pasar por un proceso de adaptación tanto en la realidad tecnológica de equipos como de metodologías que permitan su uso para mejorar las capacidades de los estudiantes. El estudiante universitario de la carrera de Odontología requiere tener inteligencia espacial en su factor de rotación mental para poder desenvolverse mejor en la capacidad procedimental tanto en asignaturas preclínicas como clínicas. Los estudiantes de Odontología de primeros cursos y nativos digitales son óptimos para la inmersión en el metaverso para el aprendizaje.

El conocimiento del metaverso como herramienta de enseñanza, proporcionará un mayor nivel de rotación mental de la inteligencia espacial de los estudiantes de Odontología, evaluado mediante una Encuesta múltiple y el Test de Rotación Mental de Vandenberg[16].

Objetivos

Tras la aplicación de los simuladores hápticos y holográficos en las prácticas preclínicas, y como paso previo a la incorporación del metaverso en la enseñanza de la Odontología en nuestra Escuela, hemos propuesto como objetivo de este estudio preliminar, conocer en qué grado los estudiantes de Odontología conocen el metaverso y qué nivel tienen sobre el factor de rotación mental de la inteligencia espacial. El estudiante universitario a medida que desarrolla el factor de rotación mental de la inteligencia espacial, le permitirá adquirir una mejor habilidad en la parte procedimental de la carrera de Odontología.

Este estudio preliminar nos permitirá conocer la situación actual en nuestro entorno sobre el conocimiento del metaverso y la capacidad de nuestros estudiantes y profesorado para asimilarlo como método de aprendizaje.

Objetivo Primario: Establecer en qué medida el conocimiento del metaverso influye en el nivel del factor de rotación mental de la inteligencia espacial en los estudiantes de Odontología.

Objetivos Secundarios:
1) Determinar el nivel del factor de rotación mental de la inteligencia espacial en los estudiantes de Odontología.
2) Determinar el nivel de conocimiento del metaverso en los estudiantes de Odontología.

Métodos

A través de una Encuesta múltiple se obtendrá una información referente al conocimiento o uso previo que los estudiantes universitarios de Odontología de la Escuela Universitaria ADEMA-UIB tienen sobre la tecnología virtual 3D y en especial de la herramienta del metaverso, para seguidamente realizar un test de rotación mental para determinar su inteligencia espacial.

Se trata de un estudio transversal, descriptivo y anonimizado:
1) Todos los participantes realizarán una Encuesta múltiple de autorrelleno de 11 items online con acceso libre, para determinar el nivel de conocimiento o uso previo del metaverso. Para ello deberán aceptar previamente el Consentimiento Informado.
2) Universo del análisis comprendido por todos los estudiantes matriculados del grado de Odontología de la Escuela Universitaria ADEMA-UIB (160 alumnos).
3) Todos los participantes realizarán el Test de Rotación Mental de Vandenberg para determinar su inteligencia espacial (valoración por puntos obtenidos).
4) Se observará si hay diferencias significativas en los resultados del Test de Rotación Mental de Vandenberg para determinar la inteligencia espacial de los participantes, en relación con su conocimiento o uso previo del metaverso, teniendo en cuenta las respuestas de la encuesta.

PARTE 1: ENCUESTA MÚLTIPLE

Consentimiento Informado SÍ NO
1. Edad 18 a 60
2. Género HOMBRE MUJER
3. Acceso a la Universidad SELECTIVIDAD FP CONVALIDACIÓN >25 >41OTROS
4. Curso del grado de Odontología que realizas 1º 2º 3º 4º 5º VARIOS
5. ¿Sabes en qué consiste la realidad virtual? SÍ NO NULO
6. ¿En qué campo utilizas la realidad virtual? JUEGOS EDUCACIÓN OTROS NULO
7. ¿Cómo calificarías tu conocimiento en cuanto al metaverso? ALTO MEDIO BAJO
8. ¿Has usado el metaverso? SÍ NO NULO
9. ¿Sabes en qué consiste la simulación háptica y holográfica? SI NO NULO
10. ¿Has utilizado la simulación háptica y holográfica en tus estudios de Odontología? SÍ NO NULO
11. ¿Crees necesario el metaverso como herramienta de aprendizaje en el grado de Odontología? SÍ NO NULO

La Encuesta múltiple permaneció abierta 30 días y sólo se pudo enviar una por participante.

PARTE 2: TEST DE ROTACIÓN MENTAL DE VANDENBERG.

El Test de Rotación Mental de Vandenberg permaneció abierto 30 días y el tiempo para responder se limitó a 6 minutos y sólo se pudo enviar un test por participante.

El Test de Rotación Mental de Vandenberg utiliza en cada línea cinco figuras, una sirve de modelo situada en el extremo izquierdo y cuatro situadas a la derecha del

modelo, entre las cuales el participante debe indicar las dos figuras que son idénticas al modelo. Implica veinte líneas distribuidas en 4 páginas, agrupadas en dos test independientes: Test A y Test B, los cuales deben llevarse a cabo independientemente con un tiempo máximo de 3 minutos cada uno.

Las figuras erróneas pueden ser, o rotaciones del modelo de la imagen en espejo, o rotaciones de una o varias de las partes que lo componen.

Es una prueba de visualización caracterizada por un grado de complejidad bastante elevado. Estas tareas exigen, a distintos niveles, la aplicación de múltiples operaciones mentales (translación, rotación…).

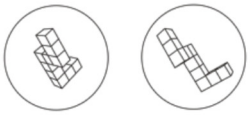
Valoración:

- Se asignan 2 puntos para cada línea que obtenga las 2 elecciones correctas.
- 1 punto si sólo es elegida una figura correcta.
- 0 puntos si las dos figuras elegidas son incorrectas.

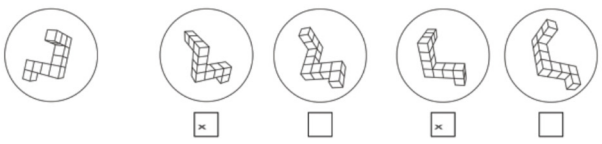
El Test de Rotación Mental de Vandenberg está destinado a medir la aptitud de reconocer un objeto determinado entre un conjunto de objetos diferentes. La única diferencia entre el objeto original y el objeto que debe identificar, consiste en una modificación del ángulo bajo el cual se ve.

A continuación se representa la misma figura en cinco posiciones distintas únicamente bajo un ángulo diferente de visión:

A continuación presentamos dos figuras que no pueden aparearse con los cinco dibujos anteriores, ya que son diferentes:



Para cada ejercicio hay un primer dibujo en la parte izquierda. Se debe indicar, entre los cuatro dibujos de la parte derecha, los dos que son iguales al modelo. En cada ejercicio hay siempre dos dibujos iguales al modelo.



Los formularios (Encuesta múltiple y Test de Rotación Mental de Vandenberg) se enviaron junto con la Hoja de Información al Participante (HIP) y el Consentimiento Informado (CI), aprobado por el Comité de Ética de la Investigación de las Islas Baleares (Código CEI: IB 4863/22 PI), el cual al ser aceptado, permite contestarlos a través de la aplicación Gsuit de Google Forms, facilitando retornar las respuestas en hoja de calculo y cuadros de gráficas que se obtienen de la aplicación, sin contener ningún dato identificativo, ni la dirección del correo electrónico que lo genera, por lo que la protección de datos queda garantizada y la encuesta anonimizada.

Los formularios son de autorelleno online con acceso libre, que se enviaron a través de los correos electrónicos corporativos de los estudiantes del grado de Odontología de la Escuela Universitaria ADEMA-UIB.

- Selección de los participantes:

Los formularios se enviaron a todos los alumnos de la Escuela Universitaria ADEMA-UIB matriculados en el grado de Odontología.

No existen criterios de exclusión puesto que la única condición es que estén matriculados, salvo que no acepten el consentimiento informado para participar en la Encuesta múltiple y en el Test de Rotación Mental de Vandenberg.

Los formularios se rellenaron sin los datos personales de los participantes, de modo que la prueba ha sido anónima y voluntaria, cuyo responsable del correcto funcionamiento del programa y su custodia ha sido a cargo del delegado de protección de datos de la Escuela Universitaria ADEMA-UIB.

- Hojas de recogida de datos:

Una vez aceptado el Consentimiento Informado (CI) por parte del participante, las respuestas requeridas en la Encuesta múltiple y en el Test de Rotación Mental de Vandenberg han quedado registradas de forma automática en el servidor del programa Gsuit de Google, una vez que se han rellenado los formularios y el participante ha clicado “enviar”. Por lo tanto, no ha habido una hoja específica de respuesta para cada participante, sino que las respuestas se han ido acumulando y una vez contestada la Encuesta múltiple y cerrado el período de 6 minutos para poder responder el Test de Rotación Mental de Vandenberg, todos los datos se han exportado posteriormente a las hojas de cálculo para proceder al análisis de los resultados, una vez cerrado el período de 30 días.

Resultados

PARTE 1. Encuesta múltiple

Los 53 participantes en la Encuesta dieron su consentimiento informado para que los datos

Table I: Encuesta múltiple.

VARIABLE	DISTRIBUCIÓN				
1. EDAD	Entre 15 y 20: 8(15%)	Entre 20 y 25: 30(57%)	Entre 25 y 30: 11(21%)	Entre 30 y 40: 3(5%)	Entre 40 y 50: 1(2%)
2. SEXO	Hombres: 14(26%)	Mujeres: 39(74%)			
3. VIA DE ACCESO A LA UNIVERSIDAD	EBAU_PAU_PAEU: 34(64%)	FP_CFGS: 14 (26%)	Más de 25 años: 1(2%)	Otros: 1(2%)	Reconocimiento de créditos: 3 (6%)
4. CURSO	Primero: 8(15%)	Segundo: 18(34%)	Tercero: 1(2%)	Cuarto: 19(36%)	Quinto: 7(13%)
5 ¿SABE EN QUÉ CONSISTE LA REALIDAD VIRTUAL?	Si: 49(92%)	No: 4(8%)			
6 ¿EN QUÉ CAMPO O CAMPOS UTILIZA LA REALIDAD VIRTUAL?	Juegos: 32(60%)	Educación: 25(47%)	Ocio: 19(36%)	Ninguno: 3(6%)	
7 ¿HA USADO EL METAVERSO?	Si: 20(38%)	No: 33(62%)			
8 ¿CÓMO CALIFICA SU CONOCIMIENTO EN RELACIÓN AL METAVERSO?	1: 8(15%)	2: 5(9%)	3: 16(30%)	4: 2(4%)	5: 22(42%)
9 ¿SABE EN QUÉ CONSISTE LA SIMULACIÓN 3D HÁPTICA Y HOLOGRÁFICA?	Si: 27(51%)	No: 26(49%)			
10 ¿HA UTILIZADO LA SIMULACIÓN 3D HÁPTICA Y HOLOGRÁFICA EN SUS ESTUDIOS DE ODONTOLOGÍA?	Si: 32(60%)	No: 21(40%)			
11 ¿CREE NECESARIO EL METAVERSO COMO HERRAMIENTA DE APRENDIZAJE DEL GRADO EN ODONTOLOGÍA?	Si: 32(60%)	No: 21(40%)			

proporcionados fuesen utilizados en la presente investigación. Como se puede ver en la tabla adjunta (**Tabla I**), la muestra obtenida está compuesta principalmente por sujetos con edades comprendidas entre 20 y 25 años (57%), con preponderancia de mujeres (74%), la mayoría de los cuales ingresó a la Universidad vía EBAU-PAU-PAEU (64%) y son cursantes del segundo o cuarto curso (70%). El 92% de los encuestados afirmó saber en qué consiste la realidad virtual y un 60% dijo usarla en juegos. Si bien un 62% respondió no haber usado el metaverso, un 42% afirmó tener un alto conocimiento del mismo (5). Poco más de la mitad (51%) de los encuestados sabe en qué consiste la simulación 3D háptica y holográfica, aunque el 60% la ha utilizado en sus estudios de Odontología. Finalmente, el 60% de los encuestados afirmó creer necesario el metaverso como herramienta de aprendizaje del Grado en Odontología.

PARTE 2: Test de Rotación Mental de Vandenberg

TEST A

Hay un total de 10 ítems y en cada uno de ellos los encuestados deben señalar dos imágenes de las cuatro existentes, con la intención de adivinar las dos idénticas al modelo situado en el extremo izquierdo. Si no hubo respuesta o si ninguna de las imágenes señaladas corresponde a las correctas, el puntaje asignado es 0. Si solo una de las imágenes es correcta el puntaje es 1 y, por último, si las dos imágenes son correctas el puntaje es 2. El tiempo máximo para realizar el Test A fue de 3 minutos.

En la **figura 1** podemos ver los porcentajes generales de respuestas incorrectas (0), parcialmente correctas (1) y correctas (2) diferenciado según el curso. Además, para determinar si existe asociación entre el tipo de respuesta y el curso se realizó el Test χ^2 y como el p-valor resultante es $p=4{,}98\cdot10^{-5}$, se puede concluir que, efectivamente, tal asociación existe.

Para ver si esta asociación está presente en todos los ítems por igual, en cada uno ellos se repitió el cálculo anterior. Sin embargo, aún cuando en los resultados que se pueden ver en las **figuras 9** a **11** (las correspondientes a los ítems 8 a10) los p-valores son menores de 0.05, no es correcto concluir que exista asociación debido a que hay categorías de las respuestas en las que no hay valores observados. Por ejemplo, en el ítem 8 todas las respuestas de los estudiantes del segundo curso fueron 1 y algo similar ocurre en los ítems 9 y 10, en los que todas las respuestas de los estudiantes del primer curso fueron 0.

En conclusión: existe una asociación entre las respuestas en los ítems del Test A y el curso. Sin embargo, por lo pequeño del volumen de observaciones, no es posible detectar cuál o cuáles de los ítems son mas relevantes al respecto.

Figure 1: TEST A, porcentajes generales de respuestas incorrectas (0), parcialmente correctas (1) y correctas (2) diferenciado según el curso.

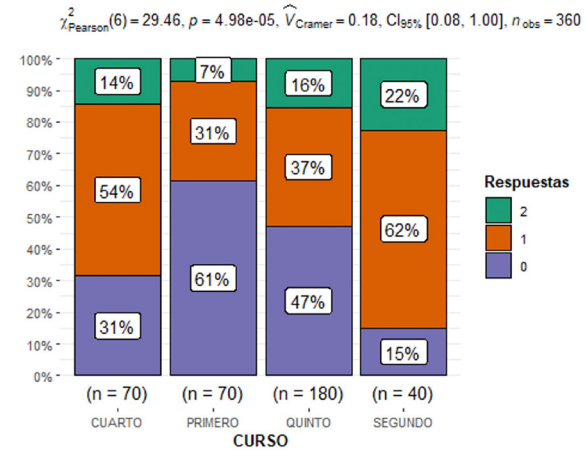


Figure 2: porcentajes del TEST A ítem 1 de respuestas incorrectas (0), parcialmente correctas (1) y correctas (2) diferenciado según el curso.

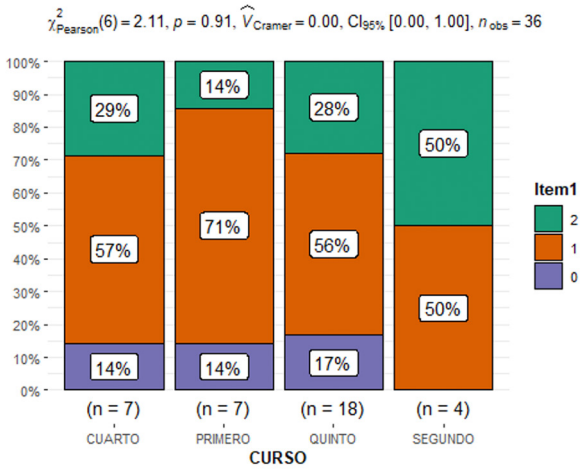


Figure 3: porcentajes del TEST A ítem 2 de respuestas incorrectas (0), parcialmente correctas (1) y correctas (2) diferenciado según el curso.

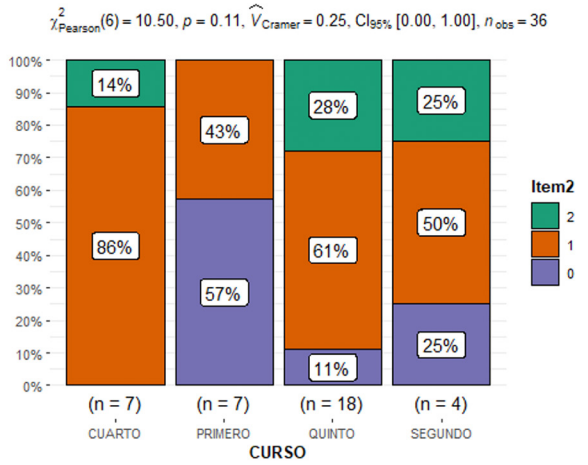


Figure 4: porcentajes del TEST A ítem 3 de respuestas incorrectas (0), parcialmente correctas (1) y correctas (2) diferenciado según el curso.

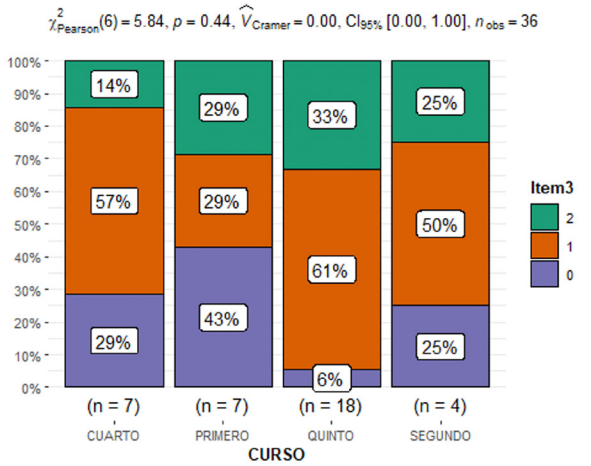


Figure 5: porcentajes del TEST A ítem 4 de respuestas incorrectas (0), parcialmente correctas (1) y correctas (2) diferenciado según el curso.

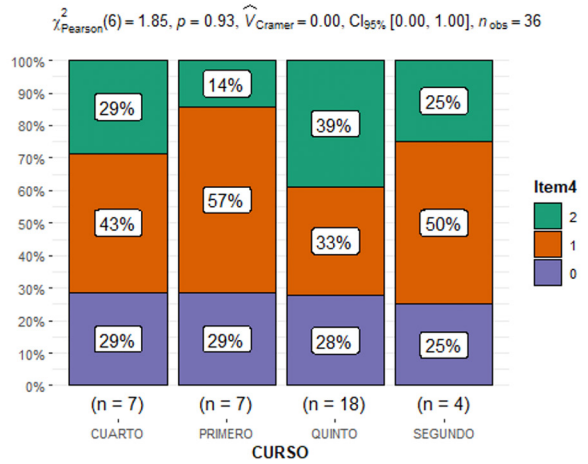


Figure 6: porcentajes del TEST A ítem 5 de respuestas incorrectas (0), parcialmente correctas (1) y correctas (2) diferenciado según el curso.

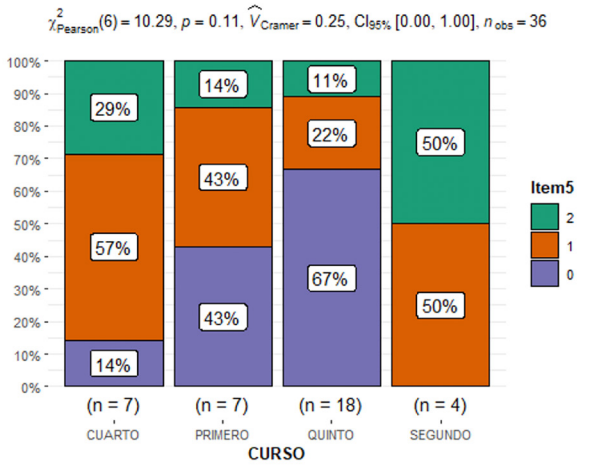


Figure 7: porcentajes del TEST A ítem 6 de respuestas incorrectas (0), parcialmente correctas (1) y correctas (2) diferenciado según el curso.

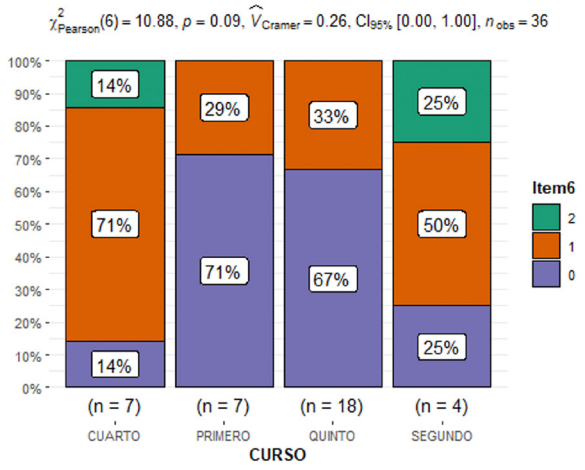


Figure 8: porcentajes del TEST A ítem 7 de respuestas incorrectas (0), parcialmente correctas (1) y correctas (2) diferenciado según el curso.

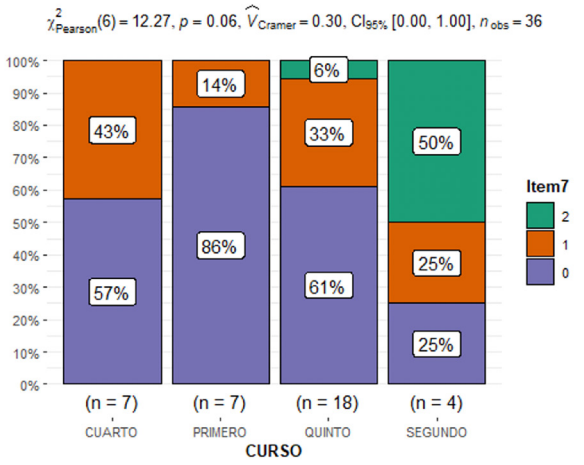


Figure 9: porcentajes del TEST A ítem 8 de respuestas incorrectas (0), parcialmente correctas (1) y correctas (2) diferenciado según el curso.

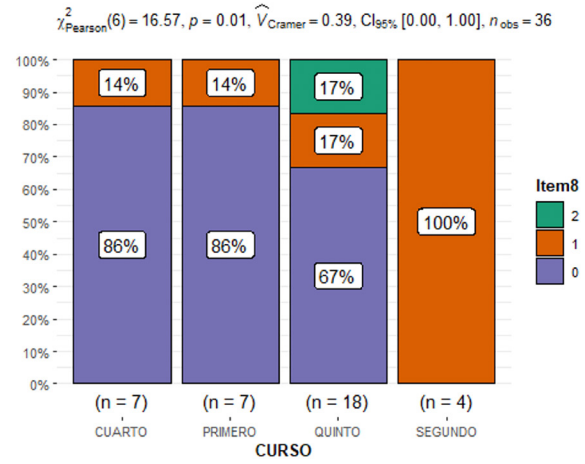


Figure 10: porcentajes del TEST A ítem 9 de respuestas incorrectas (0), parcialmente correctas (1) y correctas (2) diferenciado según el curso.

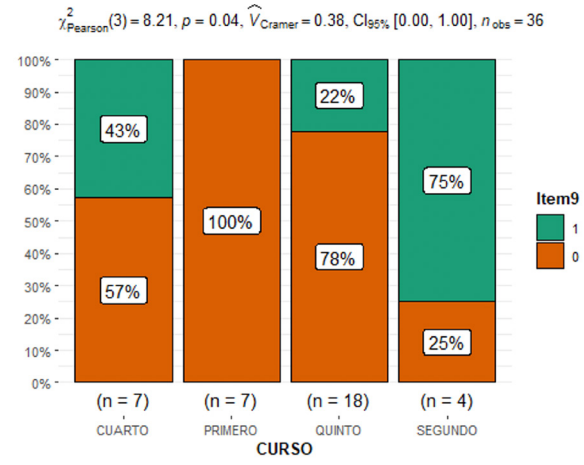


Figure 11: porcentajes del TEST A ítem 10 de respuestas incorrectas (0), parcialmente correctas (1) y correctas (2) diferenciado según el curso.

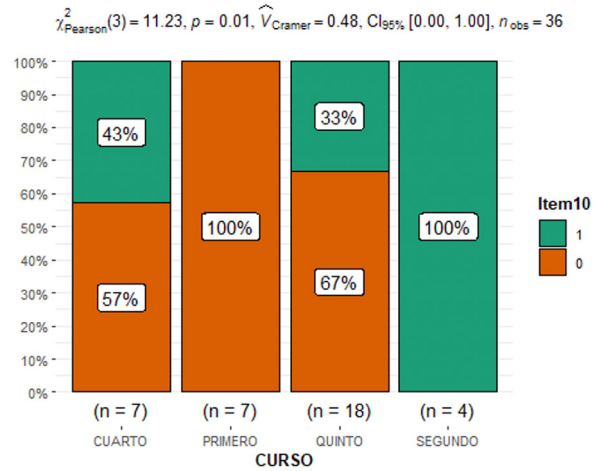
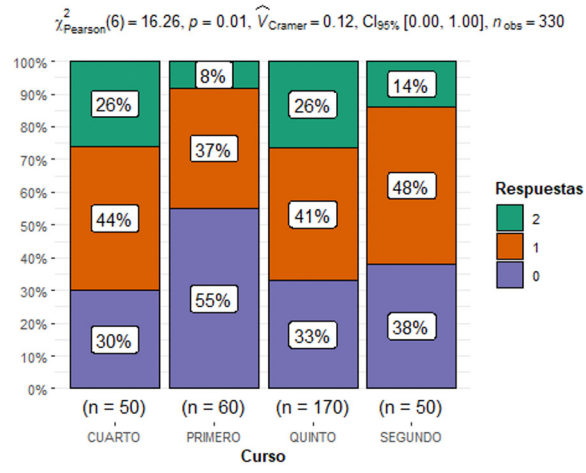


Figure 12: TEST B, porcentajes generales de respuestas incorrectas (0), parcialmente correctas (1) y correctas (2) diferenciado según el curso.



TEST B

Igual que en el Test A, hay un total de 10 ítems y en cada uno de ellos los encuestados deben señalar dos imágenes de las cuatro existentes, con la intención de adivinar las dos idénticas al modelo situado en el extremo izquierdo. Si no hubo respuesta o si ninguna de las imágenes señaladas corresponde a las correctas, el puntaje asignado es 0. Si solo una de las imágenes es correcta el puntaje es 1 y, por último, si las dos imágenes son correctas el puntaje es 2. El tiempo máximo para realizar el Test A fue de 3 minutos.

En la **figura 12** podemos ver los porcentajes generales de respuestas incorrectas (0), parcialmente correctas (1) y correctas (2) diferenciado según el curso. Además, para determinar si existe asociación entre el tipo de respuesta y el curso se realizó el Test χ^2 y como el p-valor resultante es $p=4{,}98 \cdot 10^{-5}$, se puede concluir que, efectivamente, tal asociación existe.

En cuanto al análisis por ítem los resultados se pueden observar en las **figuras 13** a **22**. Nuevamente, dado lo reducido del número de datos, el Test χ^2 no permite inferir en cual ítem es más significativa la asociación entre las respuestas y el curso del encuestado.

Figure 13: porcentajes del TEST B ítem 1 de respuestas incorrectas (0), parcialmente correctas (1) y correctas (2) diferenciado según el curso.

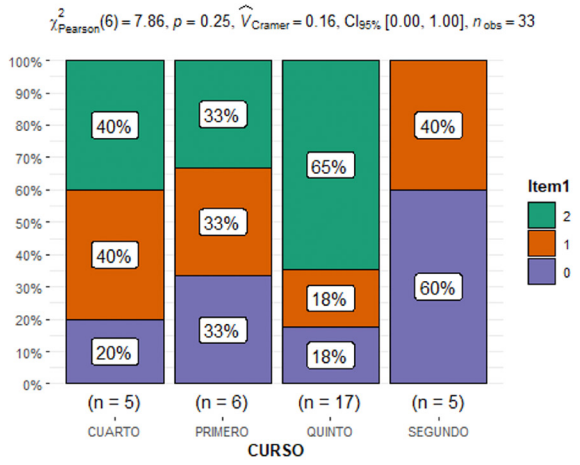


Figure 14: porcentajes del TEST B ítem 2 de respuestas incorrectas (0), parcialmente correctas (1) y correctas (2) diferenciado según el curso.

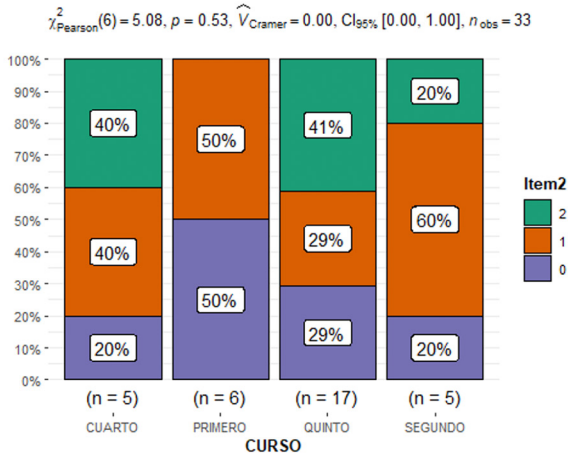


Figure 15: porcentajes del TEST B ítem 3 de respuestas incorrectas (0), parcialmente correctas (1) y correctas (2) diferenciado según el curso.

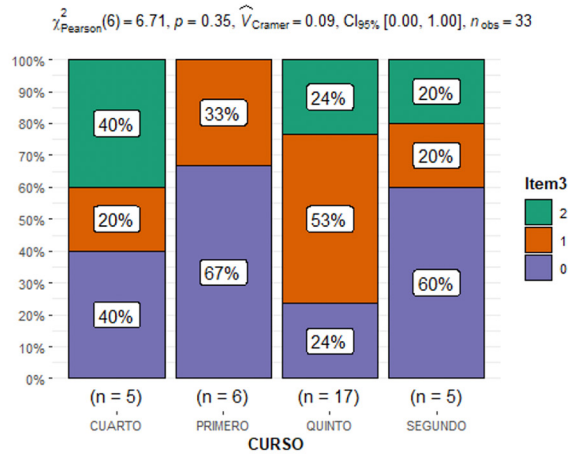


Figure 16: porcentajes del TEST B ítem 4 de respuestas incorrectas (0), parcialmente correctas (1) y correctas (2) diferenciado según el curso.

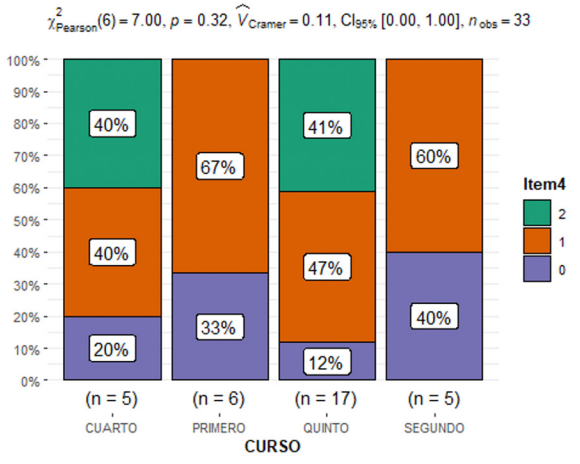


Figure 17: porcentajes del TEST B ítem 5 de respuestas incorrectas (0), parcialmente correctas (1) y correctas (2) diferenciado según el curso.

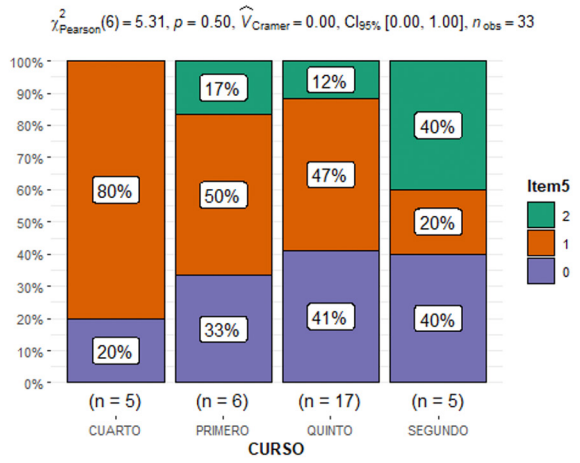


Figure 18: porcentajes del TEST B ítem 6 de respuestas incorrectas (0), parcialmente correctas (1) y correctas (2) diferenciado según el curso.

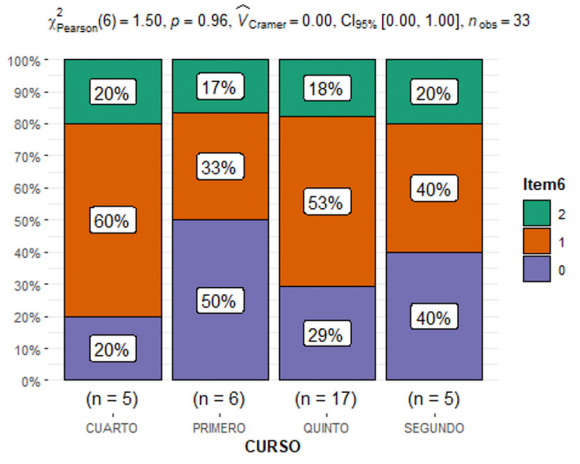


Figure 19: porcentajes del TEST B ítem 7 de respuestas incorrectas (0), parcialmente correctas (1) y correctas (2) diferenciado según el curso.

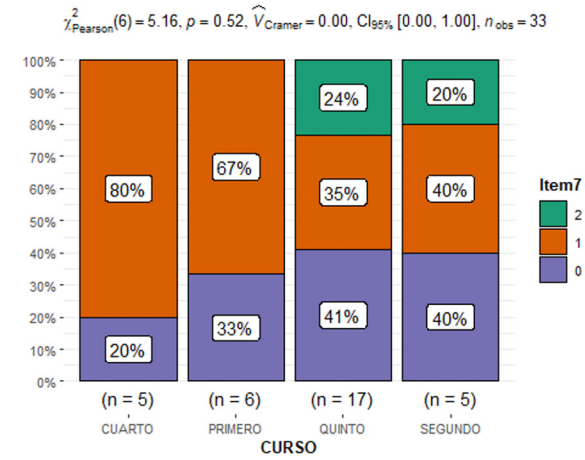


Figure 20: porcentajes del TEST B ítem 8 de respuestas incorrectas (0), parcialmente correctas (1) y correctas (2) diferenciado según el curso.

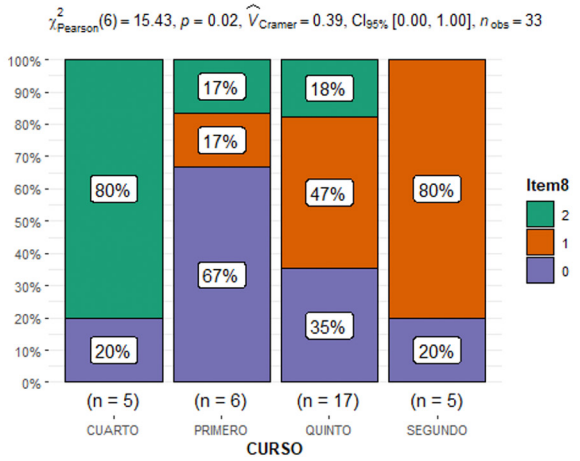


Figure 21: porcentajes del TEST B ítem 9 de respuestas incorrectas (0), parcialmente correctas (1) y correctas (2) diferenciado según el curso.

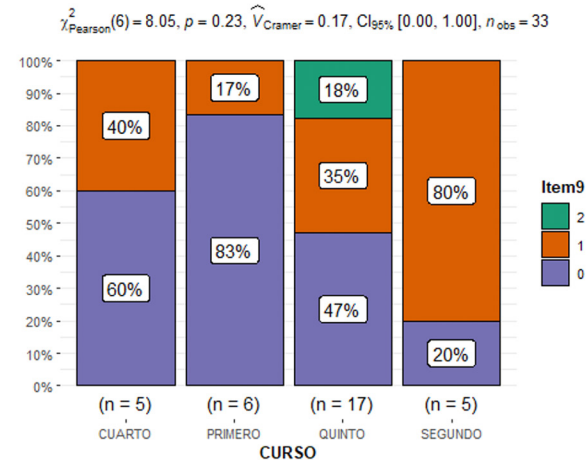
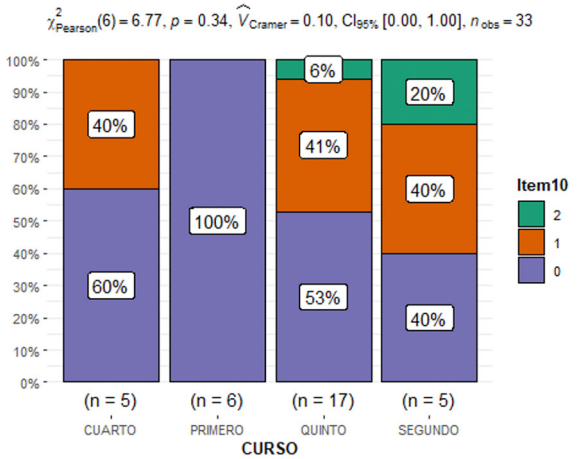


Figure 22: porcentajes del TEST B ítem 10 de respuestas incorrectas (0), parcialmente correctas (1) y correctas (2) diferenciado según el curso.



Discusión

Los estudiantes de Odontología de la Escuela Universitaria ADEMA han ido adquiriendo capacidades y habilidades en su proceso de aprendizaje preclínico mediante modelos analógicos o fantomas, para continuar su actividad inmersiva en simuladores hápticos y holográficos en prácticas desarrolladas en aulas, lo que entendemos como una inmersión parcial preclínica en el mundo virtual 3D.

Creemos que esta actividad inmersiva debe ser total mediante la introducción del metaverso en este proceso de aprendizaje, en donde la simulación pasará de un aula de prácticas a una clínica odontológica virtual donde entrarán en juego los diferentes modelos de metaverso, con el propósito de engañar y adiestrar al cerebro en las técnicas odontológicas y su entorno y consecuentemente con un aprendizaje más eficiente con posibilidades de repeticiones múltiples y poder incorporar casos más complejos en estas fases preclínicas.

La experiencia de la Escuela Universitaria ADEMA tras la incorporacióndesdesuiniciodelossimuladoreshápticos y holográficos en el flujo digital, presente en las técnicas aplicadas en las prácticas clínicas y preclínicas, abren un futuro hacia una Escuela Universitaria en metaverso. La tecnología actual lo permite y nos lleva al metaverso como una tendencia sin retorno.

Creemos que el nivel de conocimiento del metaverso es alto entre los estudiantes universitarios de Odontología, sobretodo en los nativos digitales. Ello implica la necesidad de cambiar la enseñanza para evitar las inasistencias a las clases teóricas y prácticas.

La inteligencia espacial es innata pero puede ser estimulada y desarrollada incluso en individuos que manifiestan limitaciones del aprendizaje mediante procedimientos técnicos en 3D[14]. El metaverso estimula a los estudiantes con problemas de aprendizaje y conocerlo tiene un efecto positivo en la inteligencia espacial[18,19].

Creemos preciso incluir el metaverso como asignatura en Odontología al ser una herramienta de enseñanza en la simulación de procedimientos preclínicos y clínicos, pudiéndose utilizar incluso como sala de conferencias virtual con participantes en forma de avatar.

En las aulas de la universidad las clases tradicionales son aburridas y muy poco atractivas; en ocasiones la misma información que el docente da en clase, los estudiantes la encuentran en internet en presentaciones de PowerPoint o incluso vídeos.

Si comparamos los resultados obtenidos en el presente estudio con otros estudios de grado més técnicos, observamos que el porcentaje de respuestas correctas en el Test de Rotación Mental de Wandenberg en los estudiantes de Odontología fue bajo en relación, por ejemplo, con el grado de arquitectura. Podemos encontrar como causas de estas diferencias, el motivo por el que los estudiantes de Odontología acceden a estos estudios, en parte por influencia familiar al querer
dar una continuidad generacional, en parte por ser una profesión bien remunerada y sólo en parte por tener una inteligencia espacial elevada a priori clave para adquirir las destrezas adecuadas, esta última motivación muy presente en estudiantes que optan por grados muy técnicos donde el diseño 3D es determinante, como es el caso de Arquitectura e Ingenierías[20].

Debemos convertir al estudiante en el verdadero protagonista del proceso de aprendizaje a través del metaverso, un aprendizaje que ya no se “entrega” sino que se “crea”[5,21].

Conclusiones

- El 60% de los encuestados ha utilizado simulación háptica en sus estudios de Odontología.
- El 60% de los encuestados afirmó que creía que el Metaverso era necesario como herramienta de aprendizaje para el grado en Odontología.
- Existe asociación entre el tipo de respuesta en el Test de Rotación Mental de Wandenberg y el curso del grado de Odontología

Conflicto de intereses: Ninguno.

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ORIGINAL

Evaluation of the Success Rate of Dental Implants in Oral Cavity Cancers: A Systematic Review and Meta-analysis

Evaluación de la tasa de éxito de los implantes dentales en los cánceres de cavidad oral: una revisión sistemática y un metanálisis

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Abstract

Objectives: There are many challenges and discussions about how and when Dental Implants and the survival rate of the implant are also very important. Therefore, the present study aimed to evaluate and determine the survival rate of implants in patients with Oral Cavity Cancers who received radiotherapy versus those who did not.
Methods: In this systematic review and meta-analysis study, all English-language full-text articles were published in international databases that listed the words Dental Implants, Oral Cavity Cancers in PubMed, Scopus, Science Direct databases, and Embase were reviewed between January 2012 and May 2022. Data analysis was performed using STATA.V16 software.
Results: The implant survival rate was 87.45% for non-irradiated jaws. The odds ratio for the survival rate of dental implants between irradiated and non-irradiated groups was 1.64 (OR, 1.64 95% CI 1.14, 2.15; p<0.01).
Conclusions: The present meta-analysis showed that in patients with Oral Cavity Cancers who were irradiated, the implant survival rate was 81.35%. In patients who were not irradiated, the survival rate of implants was high; it should be noted that this difference is not very significant

Key words: Dental Implants, Meta-Analysis, Survival Rate.

Resumen

Objetivos: Hay muchos desafíos y discusiones sobre cómo y cuándo los implantes dentales y la tasa de supervivencia del implante también son muy importantes. Por lo tanto, el presente estudio tuvo como objetivo evaluar y determinar la tasa de supervivencia de los implantes en pacientes con cáncer de cavidad oral que recibieron radioterapia versus aquellos que no la recibieron.
Métodos: En esta revisión sistemática y estudio de metanálisis, todos los artículos de texto completo en inglés se publicaron en bases de datos internacionales que enumeraban las palabras Implantes dentales, Cánceres de cavidad oral en PubMed, Scopus, bases de datos Science Direct y Embase se revisaron entre enero 2012 y mayo de 2022. El análisis de datos se realizó mediante el software STATA.V16.
Resultados: La tasa de supervivencia de los implantes fue del 87,45 % para los maxilares no irradiados. La razón de probabilidad para la tasa de supervivencia de los implantes dentales entre los grupos irradiados y no irradiados fue de 1,64 (OR, 1,64, IC del 95 %: 1,14; 2,15; p<0,01).
Conclusión: El presente metanálisis mostró que en pacientes con cáncer de cavidad oral que fueron irradiados, la tasa de supervivencia del implante fue del 81,35 %. En pacientes que no fueron irradiados, la tasa de supervivencia de los implantes fue alta; cabe señalar que esta diferencia no es muy significativa.

Palabras clave: Implantes Dentales, Metanálisis, Tasa de Supervivencia.

Introduction

According to reports, oral cavity cancers are one of the most common cancers caused by tobacco products; this type of cancer is prevalent in the Indian subcontinent. Surgery is used after the radiation therapy to treat this cancer, which can be done with or without chemotherapy[1,2]. Free fibular transplantation or reconstruction methods are usually used for segmental resection of the mandible. Transplants are performed after radiotherapy and after surgery[3]. It should be noted that the treatment methods for this type of cancer are very challenging, and patient safety is the most important goal of treatment; Secondly, dental rehabilitation is important[4]. This rehabilitation in patients improves chewing function and speaking and is also aesthetically important[5]. Osseointegrated implants are a rehabilitation method that is a gold standard[6,7]. Evidence suggests that about 85% of patients with this cancer receive radiotherapy after surgery[8,9]. Radiotherapy, in turn, reduces vascularization and impedes bone resorption and the ability to regenerate tissues[10]. After radiation, the effects on bone can be vascular, cellular, and metabolic. After radiation therapy, hyperemia is generally reported in the tissues, followed by vascular shrinkage, which leads to osteoradionecrosis of the bone[11,12]. There are many challenges and discussions about how and when dental implants, and the survival rate of the implant is also very important. Therefore, the present study aimed to evaluate and determine the survival rate of implants in patients with Oral Cavity Cancers who received radiotherapy versus those who did not.

Methods

The present study was a systematic review and meta-analysis. The PRISMA guide[13] was used for this study conducted in 2022. Searches in PubMed, Scopus, Science Direct databases, and Embase were conducted to identify related articles until May 2022. A review of more recent studies can provide stronger evidence[14], so the articles were reviewed over the last ten years in the present study.

The search terms ("Dental Health Services"[Mesh]) OR "Dental Implant-Abutment Design"[Mesh]) AND "Prostheses and Implants"[Mesh]) OR ("Dental Implants"[Mesh] OR "Dental Implants, Single-Tooth"[Mesh])) OR ("Dental Implants/adverse effects"[Mesh] OR "Dental Implants/classification"[Mesh] OR "Dental Implants/statistics and numerical data"[Mesh])) AND ("Electromagnetic Radiation"[Mesh] OR "Radiation"[Mesh])) AND "Neoplasms"[Mesh]) OR "Mouth Neoplasms"[Mesh]) AND ("Survival"[Mesh] OR "Mortality"[Mesh] OR "Survival Analysis"[Mesh] OR "Survival Rate"[Mesh])were used, which were adjusted based on the mesh term. All articles were reviewed, and the extracted data were categorized.

Inclusion and exclusion criteria

Inclusion criteria

Randomized control studies, retrospective, and prospective studies.
Oral cavity cancer patients
Reported survival of implants in studies
Only studies published in English

Exclusion criteria

Letter studies to the editor, review, laboratory, and in-vitro studies.

Studies without full text. **Table I** is based on the answer to the PICO strategy.

Table I: PICO strategy.

PICO strategy	Description
P	Population: Oral cavity cancer patients with implant treatment
I	Intervention: Radiation
C	Comparison: Irradiated vs. non-irradiated
O	Outcome: The survival rate

Data collection and data analysis

The "data extraction form" designed by the researchers based on the research purpose was used to review the articles. The form included sections such as author name, year of publication, type of study, number of patients, age, and number of implants.

The Newcastle-Ottawa Scale (NOS)[8] was used to determine the quality of cohort and case-control studies. With 9 items, this measure comprises three dimensions (selection, cohort comparability, and outcome). Any studies with NOS scores of 1-3, 4-6, or 7-9 were classified as low, medium, or high quality, respectively, in the analysis.

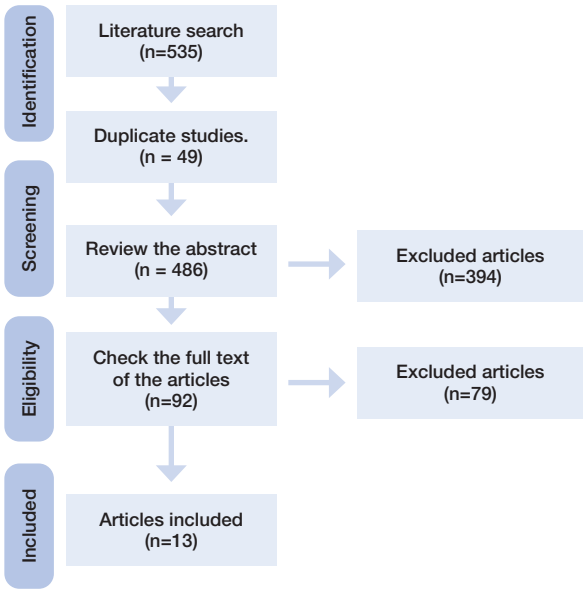
The STATA. V16 software was used to analyze data. I^2 index test was used to evaluate the level of heterogeneity (I^2< 50% = low levels, 50<I^2< 75% = moderate and I^2>75% = high levels). 95% confidence interval on the Odds ratio and effect size were done with the fixed-effect model and Mantel-Haenszel or in-variance method.

Results

The initial search result was 1535 articles, of which 821 were deleted due to lack of inclusion criteria; of the articles, 49 were deleted due to reprints in other journals and duplication. Of the remaining 665 articles, after deleting articles in accordance with the exclusion criteria (573 articles), the full text of 92 articles that met the inclusion criteria was prepared and reviewed, and 48 studies were inconsistent with the purpose of the present study, 31 studies presented incomplete data and were of very low quality and were excluded. Finally, 13 articles were included in the study. The flowchart of

the review and entry stages of the papers is shown in **Figure 1**.

Figure 1: PRISMA flowcharts.



Characteristics

Eleven studies and two studies that met the inclusion criteria for the present study were retrospective and prospective studies, respectively. The number of male and female participants was 473 and 253, respectively; the total was 726, and the number of implants was 2730. (**Table II**).

Bias assessment

According to the NOS tool, seven studies had a moderate risk of bias, whereas six studies had a low risk of bias. (**Table III**).

Survival rate

According to the findings of studies in patients with Oral Cavity Cancers, the implant survival rate was 81.35% for irradiated jaws and 87.45% for non-irradiated jaws. (**Figure 2**).

The odds ratio for the survival rate of dental implants between two groups was 1.79 (OR, 1.79 95% CI 1.36, 2.23; p<0.01) among nine studies with moderate heterogeneity I2=62.89%; P=0.01); there was a

Table II: Summary of patients' demographic data from selected studies.

Study. Years	Study design	Number of Patients		Number of Implants	Mean of Age (Years)
		Male	Female		
Sandoval et al., 2020[15]	Retrospective study	15	5	29	62.5
Menapace et al., 2018[16]	Retrospective study	6	7	121	62.4
Pellagrino et al., 2018[17]	Retrospective study	15	6	108	50
Woods et al., 2017[18]	Retrospective study	28	24	156	43.6
Kobayashi et al., 2016[19]	Retrospective study	27	14	134	61.3
Chang et al., 2016[20]	Retrospective study	166	80	1132	60
Jackson et al., 2016[21]	Retrospective study	31	15	15	58.1
Pompa et al., 2015[22]	Retrospective study	12	22	144	51
Dholam et al., 2013[23]	Retrospective study	18	12	85	46
Mancha et al., 2012[24]	Retrospective study	38	12	335	55.2
Sammartino et al., 2011[35]	Retrospective study	51	26	172	55
Katsoulis et al., 2011[36]	Retrospective study	31	15	104	57
Korfage et al., 2010[37]	Retrospective study	35	15	195	61

Table III: Bias assessment (NOS tool).

	Selection (5 scores)				Comparability (2 scores)	Outcome (2 scores)		
Number of Studies	Representative sample	Sample size	Non-respondents	Ascertainment of the exposure	Based on design and analysis	Assessment of outcome	Statistical test	Total Score
Sandoval et al., 2020[15]	*	*	*	*	*	*	*	7
Menapace et al., 2018[16]	*	*	*	-	*	*	*	6
Pellagrino et al., 2018[17]	*	*	*	-	*	-	*	5
Woods et al., 2017[18]	*	*	*	**	**	*	*	7
Kobayashi et al., 2016[19]	*	*	*	-	*	-	*	5
Chang et al., 2016[20]	*	*	*	*	*	*	*	7
Jackson et al., 2016[21]	*	*	*	*	**	*	*	8
Pompa et al., 2015[22]	*	*	*	*	*	*	*	7
Dholam et al., 2013[23]	*	*	*	*	**	*	*	8
Mancha et al., 2012[24]	*	*	*	-	*	*	*	6
Sammartino et al., 2011[35]	*	*	*	-	*	-	*	5
Katsoulis et al., 2011[36]	*	*	*	-	*	-	*	5
Korfage et al., 2010[37]	*	*	*	-	*	*	*	6

*=1 score, **=2 score, - = 0 score.

statistically significant difference between n irradiated and non-irradiated groups (p<0.01). **Figure 3** showed heterogeneity with binary data, and **Figure 4** showed graphical diagnostics of the small-study effect.

Figure 2: The Forest plot showed the survival rate of dental implants.

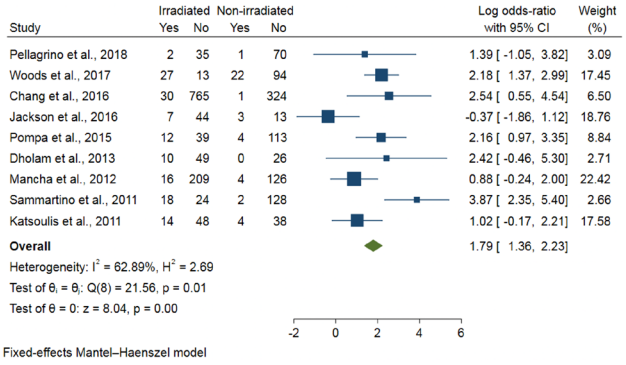


Figure 3: L'Abbe plot to check for heterogeneity with binary data.

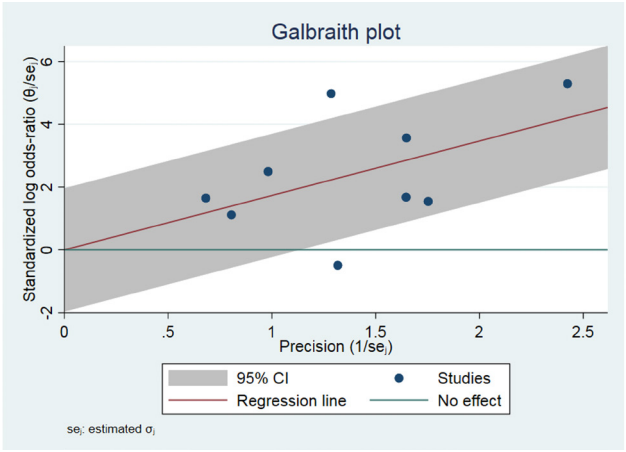
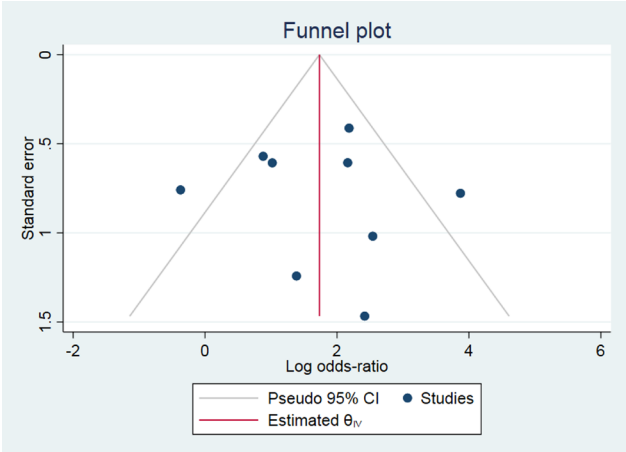


Figure 4: Funnel plot for graphical diagnostics of small-study effect.



Discussion

After surgical treatment and radiation therapy for patients with Oral Cavity Cancers, rehabilitation with dental implants has received much attention[25]. A study showed that dental rehabilitation with implants increases patients' quality of life undergoing radiotherapy[26]. According to the meta-analysis results, the failure rate of implants in irradiated people is about 15%. Based on the findings of the present meta-analysis, the survival rate of implants in irradiated patients and the control group was 81.35% and 87.45%, respectively[27]; these findings are consistent. Based on the present study's findings, a significant difference was observed between the survival rates in the two groups, although this difference is not very significant. Since the present study used articles from the last ten years and considered the quality of the studies to be high, moderate downward heterogeneity was also observed. The present study results could provide good evidence for implant rehabilitation in patients with Oral Cavity Cancers. RCT studies have shown that the survival rate of implants in patients who were not irradiated was much higher than in the irradiated group; However, the existing RCT studies did not meet the inclusion criteria of the present study. They were not included in the study, but their findings were in line with the present results[28-30]. Some RCT studies also reported the same survival rates in both groups; these findings are inconsistent with the present study[17,31]. One of the challenges in dental implants' survival is investigating the effect of radiation dose on the jawbone, which has not been investigated in the present study.

Further studies are needed in this field. According to a study with 50 Gray radiation, the failure rate of implants increases[32]. On the other hand, implant placement location may also affect the success and failure of implants. Evidence has shown no significant difference in the placement of implants in the upper and lower jaws. Some studies have shown that implant survival is higher in the mandible due to bone density and anatomy. Primary and secondary stability are two important points that increase the survival of implants. In irradiated patients, secondary stability is impaired, and survival is reduced because the arteries are affected[33]. Also, the distance between the definitive treatment of oral cancer and the installation of dental implants may contribute to the success or failure of osteointegration. Improving the quality of life of cancer patients is very important, and rehabilitation of implants can help speech, eating, and facial beauty[34]. The present study had limitations, the RCT study was not consistent with the purpose of the present study, and all selected studies were retrospective; On the other hand, the sample size of the studies was not high, and the follow-up period was not reported. Selected studies did not provide accurate information about the type of radiation therapy, which can be considered a confounding factor, and the severity of the disease; the studies that have

examined and compared the maxilla and mandible over the last ten years have been just one[19].

Conclusion

The present meta-analysis showed that in patients with Oral Cavity Cancers who were irradiated, the implant survival rate was 81.35%. There was a significant difference between the two groups regarding survival rate. In patients who were not irradiated, the survival rate of implants was high; it should be noted that this difference is not very significant. According to the findings of the study, the survival of implants in the mandible was higher.

Conflict of Interest

The authors declared that there is no conflict of interest.

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ORIGINAL

Evaluation of plasma levels of interleukin 6 and iron status of baseketball players in Madonna University, Elele, Rivers State, Nigeria

Evaluación de los niveles plasmáticos de interleucina 6 y del estado del hierro de los jugadores de baloncesto de la Universidad de Madonna, Elele, Estado de los Ríos, Nigeria

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Abstract

Aim: The study was done to determine the levels of interleukin 6 (IL-6) and iron status of basketball players in Madonna University, Elele, Rivers State, Nigeria.
Methods: A total number of 80 subjects were recruited for the study, comprising of 40 subjects before playing basketball (20 males and 20 females) and 40 subjects after playing basketball (20 males, 20 females) from Madonna University Nigeria, Elele Campus, Rivers State, Nigeria. The data obtained from the study were presented as Mean ± SD in tables and analysed using student t-test for parametric data using SPSS version 20. The level of significance was set at $p<0.05$.
Results: A significant increase ($p=0.002$) was found in interleukin 6 (IL-6) after playing basketball compared to before playing basketball and no significant change (0.276) in iron after playing basketball compared to before playing basketball respectively. It was also observed that there was no significant increase ($p=0.115$) in interleukin 6 (IL-6) of males compared to females and no significant change in iron ($p=0.770$) of males compared to females respectively. There was no significant increase ($p=0.115$) in interleukin 6 (IL-6) of basketball players aged 15 to 25 years compared to basketball players aged 26 to 35 years and no significant change in iron ($p=0.770$) of basketball players aged 15 to 25 years compared to volleyball players aged 26 to 35 years respectively.
Conclusions: The study showed increase in interleukin 6 (IL-6) of the basketball players after playing compared to the level before playing which shows that the physical activity increases the level of interleukin 6 and but has no effect on the iron level after basketball game.

Key words: Interleukin 6 (IL-6), Iron, basketball, sports, inflammation.

Resumen

Objetivo: El estudio se realizó para determinar los niveles de interleucina 6 (IL-6) y el estado del hierro de los jugadores de baloncesto de la Universidad Madonna, Elele, Estado de Rivers, Nigeria.
Material y métodos: Se reclutó un total de 80 sujetos para el estudio, que comprendía 40 sujetos antes de jugar al baloncesto (20 hombres y 20 mujeres) y 40 sujetos después de jugar al baloncesto (20 hombres y 20 mujeres) de la Universidad Madonna de Nigeria, Campus de Elele, Estado de Rivers, Nigeria. Los datos obtenidos en el estudio se presentaron en forma de media ± DE en tablas y se analizaron mediante la prueba t de student para datos paramétricos utilizando el SPSS versión 20. El nivel de significación se fijó en $p<0,05$.
Resultados: Se encontró un aumento significativo ($p=0,002$) en la interleucina 6 (IL-6) después de jugar al baloncesto en comparación con antes de jugar al baloncesto y ningún cambio significativo (0,276) en el hierro después de jugar al baloncesto en comparación con antes de jugar al baloncesto respectivamente. También se observó que no hubo un aumento significativo ($p=0,115$) en la interleucina 6 (IL-6) de los hombres en comparación con las mujeres y ningún cambio significativo en el hierro ($p=0,770$) de los hombres en comparación con las mujeres respectivamente. No hubo un aumento significativo ($p=0,115$) en la interleucina 6 (IL-6) de los jugadores de baloncesto de 15 a 25 años en comparación con los jugadores de baloncesto de 26 a 35 años y ningún cambio significativo en el hierro ($p=0,770$) de los jugadores de baloncesto de 15 a 25 años en comparación con los jugadores de voleibol de 26 a 35 años respectivamente.
Conclusiones: El estudio mostró un aumento de la interleucina 6 (IL-6) de las jugadoras de baloncesto después de jugar en comparación con el nivel anterior al juego, lo que demuestra que la actividad física aumenta el nivel de interleucina 6, pero no tiene ningún efecto sobre el nivel de hierro después del juego de baloncesto.

Palabras clave: Interleucina 6 (IL-6), hierro, baloncesto, deporte, inflamación.

Introduction

Exercise reduces the strain on muscles to perform contractions[1]. Muscles adapted to exercise by secreting interleukin-6 into the bloodstream. Interleukin-6 is a myokin important for muscle adaptation in sports, especially basketball[2]. It is involved in regulating inflammation, protein synthesis, lipid deposition, metabolism, and muscle building. Interluekin-6 was also associated with iron deposition, including ferritin, hepcidin and hemoglobin[3]. Interleukin-6 is a pro-inflammatory cytokine that can be increased after exercise[4]. Higher levels of interleukin-6 are associated with a stronger inflammatory response to exercise, such as soccer, which affects the whole body[5]. Interleukin-6 stimulates the synthesis of hepcidin, resulting in elevated blood levels of hepcidin during inflammation[6,7]. Reported by Cullen et al. the effect of exercise intensity and volume on interleukin-6 response was found to be increased in the high intensity group compared to the low intensity group[8]. Interleukin 6 (IL-6) is a cytokine involved in specific antigenic immune and acute inflammatory responses[9]. It is produced in a variety of cell types and acts in numerous tissues[10]. IL-6 plays an important role in defense responses and has pleiotropic properties that can determine multiple phenotypic traits[10,11]. Contraction of skeletal muscle is the stimulus for its release. Therefore, it is produced, expressed and released by muscle and is considered a myokine due to its paracrine and endocrine effects[12,13]. Reducing carbohydrate availability during exercise helps maintain serum glucose levels during exercise, thus stimulating IL-6 release[13].

IL-6 is an important marker. This is because its increased concentration is associated with increased concentrations of acute-phase inflammatory proteins such as C-reactive protein 14, the risk of cardiovascular events, and rupture processes[15].

Hepcidin plays a key role of ferroportin opening and iron transport via membrane regulation[16]. Hepcidin inhibits ferroportin opening so that iron fail to export across membrane of erythrocyte and macrophage[17].

The role of heme and non-heme iron in biological function and locomotion has been elucidated by human and animal studies, and several classic reviews have been published[18,19] and updated. However, because of the strong association between the ability to sustain submaximal exercise for prolonged periods and the activity of iron-dependent oxidase, endurance performance at reduced exercise intensity is more closely related to tissue iron concentrations. The study was done to determine the levels of interleukin 6 (IL-6) and iron status of basketball players in Madonna University, Elele, Rivers State, Nigeria

Materials and methods

Study Design

The project is a cross-sectional study involving subjects recruited from basketball players of Madonna University Nigeria, Elele Campus. The subjects encompass males and females football players age and sex-matched as the controls. The study is a quantitative research to assess the levels of interleukin 6 and iron status of the football players among the students of the University.

Study area

The research was carried out on basketball players in Madonna University Nigeria, Elele Campus, Rivers State, Nigeria. It is located in the South-South part of Nigeria.

Study population

A total number of 80 subjects were recruited for the study, comprising of 40 subjects before playing basketball (20 males and 20 females) and 40 subjects after playing basketball (20 males, 20 females) from Madonna University Nigeria, Elele Campus, Rivers State, Nigeria. They all gave consent to participate in this study.

Inclusion criteria

Students of Madonna University Nigeria, Elele Campus that are basketball players without any sign of disease and apparently healthy individuals were selected for the study.

Exclusion criteria

Any Student of Madonna University Nigeria, Elele Campus that is sick or showed s any sign of disease, pregnant, smoker, alcoholics or aged were excluded for the study.

Procurement of iron

A commercially prepared serum iron test kit product of BioSystems reagents and instruments company limited were used to assay the iron level.

Ethical consideration

The approval for the study was obtained from the Department of Medical Laboratory Science, Madonna University Nigeria, Elele Campus, Rivers State and written consent obtained from the subjects before commencement of the study.

Laboratory Investigations

Interleukin 6 (IL-6) determination using Elabscience

(Catalog No: E-EL-H0102)

Procedure

1. 100µL standard or sample was added to the wells and incubated for 90 min at 37°C
2. The liquid was discarded, immediately added 100µL Biotinylated Detection Ab working solution to each well and incubated for 60 min at 37°C.
3. The plate was aspirated and washed for 3 times

4. 100µL HRP conjugate working solution was added, incubated for 30 min at 37°C and aspirate d and washed the plate for 5 times
5. 90µL Substrate Reagent was added and incubated for 15 min at 37°C
6. 50µL Stop Solution was added
7. The plate was read at 450nm immediately and the results calculated.

Statistical analysis

The data obtained from the study were presented as Mean ± SD in tables and analysed using student t-test for parametric data using SPSS version 20. The level of significance was set at $p<0.05$.

Results

Table I showed that there was significant increase (p=0.002) in interleukin 6 (IL-6) after playing basketball (24.20±6.52 pg/ml) compared to before playing basketball (9.44±2.77 pg/ml) and no significant change (0.276) in iron after playing basketball (107.16±24.68 pg/ml) compared to before playing basketball (92.04±15.12 ug/dl) respectively.

Table I: Mean ± SD values of interleukin 6 (IL-6) and Iron status of the subjects before and after playing basketball.

Parameters	Before	After	t-value	P-value
IL-6 **(pg/ml)**	9.44±2.77	24.20±6.52	-4.658	0.002*
Iron **(ug/dl)**	92.04±15.12	107.16±24.68	-1.168	0.276

Table II showed that there was no significant increase (p=0.115) in interleukin 6 (IL-6) of males (18.59±0.50 pg/ml) compared to females (27.95±5.69 pg/ml) and no significant change in iron (p=0.770) of males (102.25±26.94 pg/ml) compared to females (110.43±28.55 ug/dl) respectively.

Table II: Mean ± SD values of interleukin 6 (IL-6) and Iron status of basketball players based on sex.

Parameters	Male	Female	t-value	P-value
IL-6 **(pg/ml)**	18.59±0.50	27.95±5.69	-2.204	0.115
Iron **(ug/dl)**	102.25±26.94	110.43±28.55	-0.320	0.770

Table III showed that there was no significant increase (p=0.115) in interleukin 6 (IL-6) of basketball players aged 15-25 Years (18.59±0.50 pg/ml) compared to volleyball players aged 26-35 Years (27.95±5.69 pg/ml) and no significant change in iron (p=0.770) of volleyball players aged 15-25 Years (102.25±26.94 ug/dl) compared to volleyball players aged 26-35 Years (110.43±28.55 ug/dl) respectively.

Table III: Mean ± SD values of interleukin 6 (IL-6) and Iron status of basketball players based on age brackets.

Parameters	15-25 Years	26-35 Years	t-value	P-value
IL-6 **(pg/ml)**	18.59±0.50	27.95±5.69	-2.204	0.115
Iron **(ug/dl)**	102.25±26.94	110.43±28.55	-0.320	0.770

Discussion

The results of **table I** showed that there was increase in interleukin 6 (IL-6) after playing basketball compared to before playing basketball and no significant change in iron after playing basketball compared to before playing basketball.

Table II showed that there was no significant increase in interleukin 6 (IL-6) of males compared to females and no significant change in iron of males compared to females. The study showed increase in interleukin 6 (IL-6) of basketball players after playing that was statistically significant. It is also known that sports enhance plasma levels of some cytokines[21]. Several studies demonstrated that tedious games like basketball is accompanied by an increase in circulating pro-inflammatory responsive cytokines along with other bioactive stress molecules having some similarities with the response to sepsis and trauma[22,23]. It has been shown that physical activity such as exercises help to the muscles increase the level of secretion and release of interleukin 6 form the muscles as well as from the lymphocytes. Despite the difficulties inherent in measuring plasma cytokines concentrations[24], studies of subjects exercising intensively reported conflicting results. Some authors reporting increase25 and others no changes[26] in IL-6 production after strenuous exercise. The stress and oxidation may increase the inflammatory process that will raise the levels of interleukin 6 and regulate iron production through hepcidin regulation. This study also shows a significant increase in IL-6 concentrations for volleyball players after playing. Thus, it has been demonstrated that plasma concentrations of IL-6 increases up to more than 100-fold during prolonged muscular exercise[27]. The augmented IL-6 plasma concentrations following football was associated with muscle damage in an earlier study[27], but today it is very clear that exercise without any muscle damage also induces marked production of IL-6 and that IL-6 is produced as a direct consequence of contraction per se[27]. **Table III** showed that there was no significant increase in interleukin 6 (IL-6) of volleyball players on age groups.

Conclusion

The study showed increase in interleukin 6 (IL-6) of the basketball players after playing compared to the level before playing which shows that the physical activity increases the level of interleukin 6 and but has no effect on the iron level after basketball game.

Recommendations

The levels of interleukin 6 should be monitored as accelerated increase of it will cause severe inflammatory

leading to tissue injury, unregulated immunological response and cardiovascular disease. Interleukin 6 should be monitored along with acute proteins and regulated in the players for their total fitness which will enhance their lifespan and productivity.

Conflict of interest

None

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ORIGINAL

Tratamiento con gentamicina aplicada localmente en úlceras infectadas de pie diabético. Una revisión sistemática

Locally applied gentamicin treatment in infected diabetic foot ulcers. A systematic review

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Resumen

Introducción: Las úlceras de pie diabético (UPD) son una de las complicaciones más comunes de la diabetes mellitus (DM) y generalmente son difíciles de cicatrizar, pudiendo provocar una amputación en los miembros inferiores (MMII). Las amputaciones relacionadas con la DM tipo 2 (DM2) han aumentado de forma alarmante en estos últimos años en nuestro país.
Objetivo: Evaluar el efecto terapéutico de la gentamicina administrada de forma local sola o en combinación, en el tratamiento de úlceras de pie diabético con signos y/o síntomas de infección.
Metodología: Revisión Bibliográfica sistemática mediante la búsqueda de artículos indexados en las bases de datos: PubMed®, EBSCO®, Web of Science y Science Direct, de los trabajos publicados en los últimos 13 años en todo el mundo.
Resultados: Se muestra que la gentamicina erradica los microrganismos que producen infección, es tolerada adecuadamente por los pacientes, disminuye el tiempo de curación y es activa frente a varios microorganismos como Psedomonas aeruginosas, E. coli, Enterobacter y Staphylococcus, incluidos los Staphylococcus resistentes a la meticilina.
Conclusión: La gentamicina aplicada localmente parece mostrar un efecto terapéutico positivo sobre úlceras infectadas de pie diabético, aunque no se puede concluir diciendo que la gentamicina es el tratamiento más adecuado ya que faltan muchas líneas de investigación en este ámbito.

Palabras clave: Pie diabético, úlcera de pie diabético, gentamicina.

Abstract

Introduction: Diabetic foot ulcers (DFUs) are the most common complications of diabetes mellitus (DM) and usually do not heal, leading to amputation of the lower limbs. Amputations related to type 2 diabetes mellitus (DM2) have increased alarmingly in our country in the recent years.
Aim: To evaluate the therapeutic effect of local gentamicin administered alone or in combination, in the treatment of diabetic foot ulcers with signs and/or symptoms of infection.
Materials and methods: Bibliographic Review by searching for indexed articles in the following databases: PubMed®, EBSCO®, Web of Science and Science Direct, of the works published in the last 13 years all over the world.
Results: Our bibliographic search in different databases and selected several articles for the study shows that gentamicin eradicates infection-producing microorganisms, it is well tolerated by patients, it decreases healing time and is sensitive to various microorganisms such as Psedomonas aeruginosas, E. coli, Enterobacter and Staphylococcus, including methicillin-resistant Staphylococcus.
Conclusion: Locally applied gentamicin appears to show a positive therapeutic effect in diabetic foot ulcers, although it cannot be concluded that gentamicin is the most appropriate treatment seeing as there are many lines of research lacking in this field.

Key words: Diabetic foot, diabetic foot ulcer, gentamicin.

Introducción

Las úlceras de pie diabético (UPD) son la principal causa de amputación no traumática, tienen un gran impacto en la calidad de vida del paciente y suponen un gran coste para la sociedad. La incidencia de amputaciones relacionadas con UPD ha ido aumentando a lo largo de estos últimos años[1]. Por tanto, la prevención de las lesiones del pie en las personas con Diabetes mellitus (DM) es fundamental para reducir su incidencia y la educación, junto con la atención podológica, puede favorecer el diagnóstico precoz y evitar así sus complicaciones[2]. Sin embargo, una vez aparecen, es necesario realizar un abordaje terapéutico multidisciplinario con descargas, diferentes tipos de curas y antibioterapia sistémica y local.

Desafortunadamente, los antibióticos sistémicos a menudo son ineficaces y, incluso después de un tratamiento intravenoso prolongado, son frecuentes las recurrencias[3,4]. Esta pérdida de eficacia puede estar relacionada con la alteración del flujo sanguíneo en el hueso infectado[5] y con la formación de biopelículas que provocan resistencias[6]. Asimismo, los tratamientos sistémicos se han visto asociados a efectos adversos graves incluidos la toxicidad hepática y renal[7]. Por ello, no es sorprendente que se haya utilizado la administración local de los antibióticos como tratamiento complementario[8]. Se ha demostrado que los sistemas de administración local de fármacos aumentan su concentración en el lugar de infección y minimizan los niveles sistémicos[1,5]. Sin embargo, en los últimos años, se están aislando bacterias resistentes a los antibióticos tópicos utilizados habitualmente en las UPD. Ello plantea la necesidad de valorar el efecto terapéutico de diferentes agentes.

En esta línea, los efectos de la aplicación local de gentamicina son poco conocidos. Por tanto, es interesante analizar su utilización sola o en combinación con otros tratamientos, sus posibles efectos adversos, y sus formas de aplicación. También, comparar las ventajas de su aplicación local en comparación su uso sistémico. Además, valorar si la gentamicina es una opción para tratar ulceras infectadas con microorganismos gram positivos resistentes a la meticilina, ya que su aislamiento implica una dificultad añadida para el tratamiento de este tipo de lesiones.

Por ello, nuestro objetivo ha sido evaluar el efecto terapéutico de la gentamicina administrada de forma local sola o en combinación, en el tratamiento de úlceras de pie diabético con signos y/o síntomas de infección, mediante una revisión sistemática de la literatura científica.

Métodos

Los objetivos específicos del estudio han sido evaluar si la aplicación de gentamicina de forma local disminuye el tiempo de erradicación de patógenos; analizar las ventajas de aplicar gentamicina de forma local en comparación con la antibioterapia sistémica; y finalmente, evaluar el efecto de la gentamicina frente diferentes tipos de microorganismos incluidos microorganismos resistentes a la meticilina.

Para investigar estos objetivos se planteó la siguiente pregunta PICO: ¿Qué efecto terapéutico tiene la aplicación local de gentamicina, sola o en combinación con otros métodos terapéuticos, como tratamiento de pacientes adultos con úlceras de pie diabético infectadas?

Las búsquedas necesarias se llevaron a cabo en bases de datos *Medline Pubmed, EBSCO Discovery Service (EDS), Web of Science (WOS)* y *ScienceDirect*.

Para realizar la búsqueda bibliográfica se seleccionaron las siguientes palabras clave: Diabetic foot, Diabetic foot ulcer, Gentamicin, Foot ulcer, Gentamicin treatment. Se escogieron todos los artículos de revista publicados en inglés o español publicados entre enero de 2009 y mayo de 2022. Los criterios de inclusión y exclusión utilizados se muestran en la **tabla I**.

Tabla I: Criterios de inclusión.

CRITERIOS INCLUSIÓN
Úlceras de pie diabético.
Presencia de infección.
Sexo de los pacientes: ambos incluidos.
Tratamientos monoterápicos y politerápicos.
Tamaño muestra: cualquiera.
Artículos *in vivo* e *in vitro*.

Las ecuaciones de búsqueda se detallan en la **tabla II**. Asimismo, para establecer el nivel de evidencia y rigor científico, de los artículos seleccionados se aplicaron los criterios de la Escala de Oxford (*Center for Evidence Based Medicine*)[9].

El diagrama de flujo que representa el algoritmo final de selección de artículos se muestra en la **figura 1**.

Por último, los artículos seleccionados se clasificaron en tablas en función de su contenido (**figura 2**).

Table II: Ecuaciones de búsqueda.

Bases de datos	Ecuaciones de búsqueda	Artículos encontrados	Artículos seleccionados
Medline Pubmed	Search (((“Gentamicins”[Mesh]) OR ((((((((((“gentamicins”[Title/Abstract]) OR “gentamicins/therapeutic”[Title/Abstract]) OR “gentamicins/therapeutic use”[Title/Abstract]) OR “gentamicins therapeutic use”[Title/Abstract]) OR “gentamicyn”[Title/Abstract]) OR “gentamicin/collagen”[Title/Abstract]) OR “gentamicin/collagen sponge”[Title/Abstract]) OR “gentamicin/collagen sponges”[Title/Abstract]) OR “gentamicin/day”[Title/Abstract]) OR “gentamicin/1”[Title/Abstract]) OR “gentamicin/cm 2”[Title/Abstract]))) AND ((“Diabetic Foot”[Mesh]) OR ((((((((((((((((((((“diabetic foot”[Title/Abstract]) OR “diabetic foot/ulcer”[Title/Abstract]) OR “diabetic foot care”[Title/Abstract]) OR “diabetic foot conditions”[Title/Abstract]) OR “diabetic foot classification system”[Title/Abstract]) OR “diabetic foot clinic”[Title/Abstract]) OR “diabetic foot amputation”[Title/Abstract]) OR “diabetic foot amputations”[Title/Abstract]) OR “diabetic foot disease”[Title/Abstract]) OR “diabetic foot/diagnosis”[Title/Abstract]) OR “diabetic foot examination”[Title/Abstract]) OR “diabetic foot infections”[Title/Abstract]) OR “diabetic foot ulcer infection”[Title/Abstract]) OR “diabetic foot ulcer treatment”[Title/Abstract]) OR “diabetic foot ulcer healing”[Title/Abstract]) OR “diabetic foot ulcer management”[Title/Abstract]) OR “diabetic foot ulceration”[Title/Abstract]) OR “diabetic foot ulceration”[Title/Abstract]) OR “diabetic foot wound”[Title/Abstract]) OR “diabetic foot wound care”[Title/Abstract]) OR “diabetic foot wounds”[Title/Abstract]))	27	12
Ebsco	((MH “Diabetic Foot”) OR TI ‘’diabetic foot ulcer” OR AB ‘’diabetic foot ulcer” OR TI ‘’diabetic foot” OR AB ‘’diabetic foot” OR TI ‘’diabetic foot infection” OR AB ‘’diabetic foot infection” OR TI ‘’diabetic foot care” OR AB ‘’diabetic foot care” OR TI ‘’diabetic foot wound” OR AB ‘’diabetic foot wound”) AND ((TI gentamicin OR AB gentamicin OR TI ‘’gentamicin treatment” OR AB ‘’gentamicin treatment” OR TI gentamycin OR AB gentamycin)	32	2
Web of science	TEMA: ((gentamicin) AND (‘’diabetic foot” OR ‘’foot ulcers”))	59	3
Science direct	Se buscó: gentamicin and ‘’diabetic foot” or ‘’foot ulcer”	319	2

Figura 1: Diagrama de flujo de la selección de artículos para el estudio.

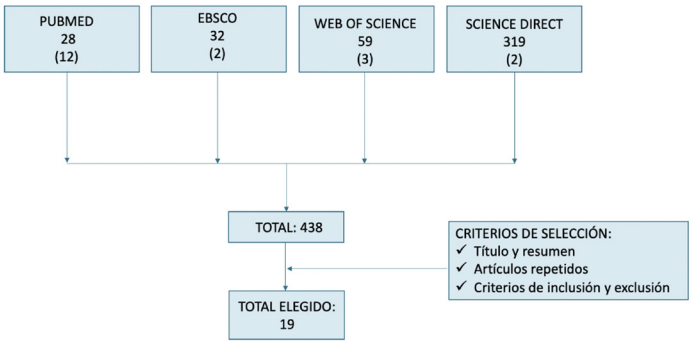
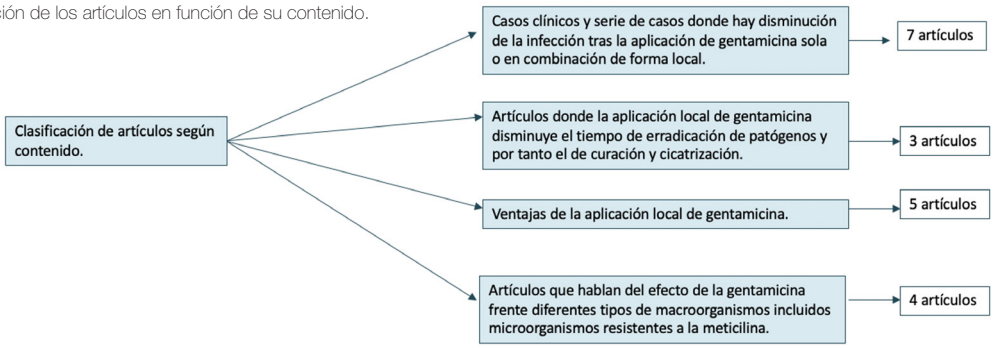


Figura 2: Distribución de los artículos en función de su contenido.



Resultados

El análisis de la evolución de la infección tras la aplicación de gentamicina sola o en combinación con otros tratamientos se detalla en las **tablas III** y **IV**. El estudio de los diferentes *case reports* parece indicar que la aplicación local de gentamicina sola o en combinación con otros tratamientos mejora la infección en las UPD y favorece la cicatrización. Por otra parte, las observaciones de Melamed EA et al., Jogia MR et al. y Drampalos E et al[10,11,12]. en series con más

de un paciente concuerdan con los resultados observados en pacientes únicos y apoyan el uso de la gentamicina tópica en UPD. Por tanto, la gentamicina aplicada localmente parece ser un tratamiento útil para las UPD si bien el nivel de evidencia es bajo y la necesidad de estudios más amplios y con un diseño más robusto es obvia.

Table III: Evolución de la infección por la aplicación de gentamicina local sola o en combinación con otros tratamientos Resultados obtenidos en artículos que tienen en cuenta a un paciente; GR: Grado de recomendación; NE: Nivel de Evidencia.

REFERENCIA	DISEÑO DEL ESTUDIO	CRITERIOS EVALUADOS	RESULTADOS	CONCLUSIONES	GR	NE
Iwakura (2014) (27)	Mujer de 57 años con diabetes mellitus no insulinodependiente con úlcera cutánea en el talón derecho con osteomielitis concurrente.	Valorar si el cemento de fosfato de calcio es un eficaz sistema local de administración de gentamicina y un material biocompatible para rellenar el espacio desnudo y facilitar la formación ósea. 1,5 g de imipenem/cilastatina. Gentamicina (40 mg) con 12 g del componente en polvo de fosfato cálcico.	La herida se cerró a los 5 días. Los antibióticos sistémicos se suspendieron a los 12 días al dar el recuento de glóbulos blancos que fue de 5900 /µl y el nivel de proteína C reactiva que fue de 0,1 mg/dl. Al año y medio no había evidencias de recurrencia.	El cemento de fosfato de calcio impregnado con gentamicina es un tratamiento eficaz para la osteomielitis crónica, ya que libera el antibiótico durante mucho tiempo y llena el espacio desnudo para facilitar la formación ósea.	4	D
Jeppesen (2015) (28)	Hombre de 52 años con DM tipo 2, con úlcera en el tercer dedo del pie derecho con osteomielitis.	Demostrar que determinados casos de osteomielitis causados por UPD pueden ser tratados con antibióticos para lograr una regeneración ósea completa y una recuperación funcional. Se trata con gentamicina local y flucloxacillin.	A la semana, no hubo contacto óseo en la base de la úlcera y el paciente reportó alivio del dolor. A los 3 meses de seguimiento, la paciente reportó una recuperación funcional completa y, en el examen clínico, la úlcera se había curado completamente y no se detectaron signos de infección residual.	Se combinaron antibióticos orales con gentamicina administrada localmente y esto podría haber tenido una influencia adicional en la resolución de la infección. El tratamiento conservador fue suficiente para resolver la infección.	4	D
Morley (2016) (29)	Paciente de 59 años con diabetes tipo 2 con una infección del pie complicada por osteomielitis.	Demostrar una ruta alternativa para la administración de antibióticos para superar algunas de las limitaciones de la administración sistémica, incluyendo la penetración en el sitio de la infección, la toxicidad sistémica, el ingreso hospitalario prolongado y el costo. Biocomposite de sulfato de calcio impregnado con gentamicina y vancomicina.	Tanto la úlcera plantar como la herida quirúrgica dorsal sanaron al poco más de un mes y tres meses respectivamente y se observó una recuperación completa a los cuatro meses. Once meses después de la cirugía el paciente permanece curado hasta la fecha.	Este caso demuestra que el sulfato de calcio como sistema de entrega de fármacos es un complemento eficaz para la infección profunda del pie diabético. La aplicación local produce una alta concentración de antimicrobianos en el lugar de la infección.	4	D
Costa Almeida (2016) (30)	Paciente masculino con úlcera neuroisquémica del pie diabético con exposición del tendón. Apósitos semanales con implante de colágeno impregnado con sulfato de gentamicina y se continuaron en un entorno ambulatorio.	Curación de la herida previamente tratada sin éxito con prostaglandina y varios tipos de apósitos durante 7 meses.	99% de epitelización en 9 meses. No ha habido dolor o infección desde el comienzo de este tratamiento.	Usando un implante de colágeno con sulfato de gentamicina, el colágeno es entregado al lecho de la herida ayudando en la formación de tejido de granulación, aumentará la microcirculación, y la gentamicina disminuirá la carga bacteriana, la producción de exudado y proteasas, aumentando la cicatrización.	4	D

Table IV: Resultados obtenidos en artículos que tienen en cuenta más de un paciente (serie de casos). GR: Grado de recomendación; NE: Nivel de Evidencia.

REFERENCIA	DISEÑO DEL ESTUDIO	CRITERIOS EVALUADOS	RESULTADOS	CONCLUSIONES	GR	NE
Melamed EA. et al. (2012) (10)	Serie de casos retrospectivos. Se reportan 23 casos de osteomielitis e infección severa asociada de las articulaciones del antepié en 20 pacientes consecutivos.	Resolución de la infección y cicatrización de la herida hasta el cierre total de la piel sin amputación.	De 23 casos, 21 (91.3%) sanaron y dos requirieron amputación del dedo del pie.	La infección grave asociada con la osteomielitis se trató con éxito con un desbridamiento extenso y el uso de cemento impregnado con gentamicina, que llenó el vacío creado por el desbridamiento. En la mayoría de los pacientes se evitó la amputación.	4	C
Jogia MR. et al. (2015) (11)	20 pacientes con úlceras en el pie diabético, edad media 59 años. Todos los pacientes tenían úlceras en el antepié con osteomielitis subyacente.	Valorar la experiencia del uso de sulfato de calcio mezclado con 1 g de clorhidrato de vancomicina y 80 mg de sulfato de gentamicina en el tratamiento de la osteomielitis en el antepié diabético.	Todos los pacientes lograron la curación con una media de tiempo de 5 semanas y sin recurrencia dentro de los 12 meses posteriores a la intervención.	Esta técnica parece ser segura y eficaz para el tratamiento de la osteomielitis diabética del antepié y se cree que esto ha evitado una cirugía más radical.	3	B
Drampalos (2018) (12)	12 pacientes diabéticos con úlcera asociada a osteomielitis calcánea crónica.	Valorar la técnica propuesta para la liberación local de gentamicina. Aplicación local de 175 mg de gentamicina en 10 ml de sulfato de calcio/hidroxiapatita.	La infección fue erradicada en los 12 pacientes en una media de 16 semanas.	La técnica Silo con la administración local de gentamicina puede aplicarse eficazmente en el tratamiento de osteomielitis calcánea ofreciendo mayor preservación ósea.	4	C

Por otro lado, el efecto de la gentamicina aplicada localmente sobre el tiempo de curación y erradicación del patógeno ha sido analizado en dos ensayos clínicos aleatorizados y una revisión sistemática (**Tablas V** y **VI**). Estos estudios muestran que una esponja de colágeno impregnada con gentamicina en comparación con un tratamiento estándar reduce el tiempo de curación y es más eficaz para la erradicación del patógeno. En este caso, al tratarse de ensayos aleatorizados, los resultados tienen un mayor nivel de evidencia y permiten establecer un mayor grado de recomendación.

Table V: Ensayos clínicos sobre el efecto del tratamiento de gentamicina con respecto al tiempo de eliminación del patógeno. GR: Grado de recomendación; NE: Nivel de Evidencia.

REFERENCIA	DISEÑO DEL ESTUDIO	CRITERIOS EVALUADOS	RESULTADOS	CONCLUSIONES	GR	NE
Lipsky (2012) (18)	Ensayo clínico aleatorio, controlado y multicéntrico. Se asignaron al azar 56 pacientes con úlceras del pie diabético con infección moderada. Grupo de tratamiento, n=38 con gentamicina-colágeno y grupo control, n= 18 con tratamiento estándar.	Determinar la seguridad y el beneficio potencial de agregar una esponja tópica de colágeno y gentamicina al tratamiento antibiótico sistémico para tratar las infecciones de pie diabético de gravedad moderada.	El grupo de tratamiento tuvo una proporción mayor de pacientes con curación clínica que el grupo de control (22 de 22[100.0%] versus 7 de 10[70.0%]. Además, el grupo de tratamiento obtuvo una mayor tasa y menor tiempo de erradicación de patógenos.	La aplicación tópica de la esponja de gentamicina-colágeno parece segura y puede mejorar los resultados clínicos y microbiológicos de las infecciones del pie diabético de gravedad moderada cuando se combina con el estándar de atención.	2	C
Varga (2012) (19)	Ensayo aleatorio propesctivo. 50 pacientes diabéticos indicados para amputaciones menores. Los pacientes fueron asignados al azar antes de la operación en dos grupos. 25 pacientes del grupo A fueron tratados con una esponja de colágeno impregnada con gentamicina aplicada en la herida perioperatoria, mientras que a 25 pacientes del grupo B se les realizó una amputación menor sin una esponja de gentamicina.	El objetivo de este ensayo aleatorio fue evaluar la influencia de la esponja de gentamicina-colágeno aplicada a una herida sobre los resultados quirúrgicos después de las amputaciones en pacientes diabéticos.	La mediana de la duración de la cicatrización de heridas en el grupo A fue de 3,0 semanas (rango: 1,7-17,1 semanas), comparada con 4,9 semanas (rango: 2,6-20,0 semanas) en el grupo control B. Esto fue con una diferencia estadísticamente significativa ($p < 0,05$).	Aplicación de esponja de colágeno impregnada con gentamicina durante un tiempo corto de cicatrización de heridas después de amputaciones menores en pacientes diabéticos durante casi dos semanas.	2	C

Table VI: Revisión sistemática sobre el efecto del tratamiento con gentamicina respecto al tiempo. GR: Grado de recomendación; NE: Nivel de Evidencia.

REFERENCIA	DISEÑO DEL ESTUDIO	CRITERIOS EVALUADOS	RESULTADOS	CONCLUSIONES	GR	NE
Marson . (2018) (20)	Revisión sistemática. Se realizaron búsquedas en las bases de datos para identificar los estudios elegibles y se identificaron 13 para su inclusión.	Analizar las pruebas disponibles del uso de sistemas locales de administración de antibióticos como complemento de la cirugía.	La esponja de colágeno impregnada de gentamicina se asoció con una disminución de 1,9 semanas en el tiempo medio de curación en comparación con el tratamiento habitual.	La cicatrización de heridas es más rápida cuando se implanta una esponja de colágeno impregnada de gentamicina. Se identificó una reducción en la incidencia de rotura de la herida.	2	A

Table VII: Revisiones sobre las ventajas de la aplicación local de la gentamicina. GR: Grado de recomendación; NE: Nivel de Evidencia.

REFERENCIA	DISEÑO DEL ESTUDIO	CRITERIOS EVALUADOS	RESULTADOS	CONCLUSIONES	GR	NE
Nandi (2009) (13)	Revisión.	Esta revisión introduce la osteomielitis: sus opciones actuales para la administración de fármacos y sus limitaciones, y la amplia gama de materiales portadores y opciones de fármacos eficaces.	Perlas de polimetilmetacrilato (PMMA) que contienen gentamicina, han sido aprobados para su uso en el tratamiento de la osteomielitis en Europa. Se ha comprobado que este producto es eficaz aplicado de forma local, pero tiene el inconveniente principal de requerir la remoción posterior de las perlas al completarse la liberación de los antibióticos.	Actualmente se está llevando a cabo una amplia investigación en el área de los sistemas locales de administración de medicamentos para tratar la osteomielitis.	2	A
Griffis (2009) (14)	Revisión.	Valorar si el implante de colágeno-gentamicina puede representar un medio seguro y económico de administrar gentamicina directamente al sitio de la infección con un riesgo mínimo de toxicidad sistémica. 130 mg de sulfato de gentamicina y colágeno bovino tipo 1.	El implante de colágeno-gentamicina es biocompatible y no requiere que el paciente incurra en el riesgo de otros procedimientos. Por lo tanto, el dispositivo es económico y clínicamente superior.	La gentamicina es más eficaz cuando se administra localmente, ya que proporciona una mayor concentración de fármaco sin aumentar el riesgo de morbilidad. El implante tiene numerosas ventajas y es muy versátil en su usabilidad.	2	A
Knaepler (2012) (15)	Revisión. 13 publicaciones de Pubmed con las palabras "gentamicin-conteniendo implante de colágeno" más "cirugía ortopédica", "osteomielitis", "osteítis", "amputación", "infección del sitio quirúrgico" e "infección de la herida".	Proporcionar una visión general de la eficacia de la aplicación profiláctica y terapéutica de los implantes de colágeno reabsorbibles que contienen gentamicina (ICCG) en la prevención de infección después de procedimientos quirúrgicos ortopédicos.	Cinco estudios han demostrado que el uso profiláctico del ICCG puede reducir la tasa de infección de la herida en procedimientos quirúrgicos ortopédicos. Ocho estudios han demostrado que el ICCG también puede desempeñar un papel en el tratamiento de la osteomielitis aguda y crónica.	Esta revisión demuestra que el uso profiláctico del ICCG puede tener un efecto positivo en la cicatrización de heridas en una variedad de procedimientos quirúrgicos ortopédicos y en pacientes de alto riesgo. El ICCG también puede tener un papel que desempeñar en el tratamiento de la osteomielitis.	2	A

Table VIII: Estudios sobre las ventajas de la aplicación local de gentamicina. GR: Grado de recomendación; NE: Nivel de Evidencia.

REFERENCIA	DISEÑO DEL ESTUDIO	CRITERIOS EVALUADOS	RESULTADOS	CONCLUSIONES	GR	NE
Gauland (2011) (16)	Estudio retrospectivo. Se evaluaron 354 pacientes con osteomielitis de la extremidad inferior clínicamente confirmada.	Determinar si el uso de tabletas de sulfato de calcio sintético implantado localmente, impregnadas de antibióticos, puede curar la osteomielitis de las extremidades inferiores. Cada encuentro quirúrgico, las tabletas de sulfato de calcio sintético se mezclaron con 500 mg de vancomicina en polvo mezclada en 240 mg de gentamicina.	Un total de 279 de 323 pacientes (86,4%) se curaron clínicamente sin el uso de antibióticos intravenosos después del desbridamiento quirúrgico y la implantación de tabletas. El 7,4% necesitó de antibióticos sistémicos y un 6,2% necesitó amputación.	El uso local de sulfato de calcio impregnado con vancomicina y gentamicina sin el uso de tratamientos intravenosos ha mostrado resultados alentadores.	2	B
Uçkay I. (2018) (17)	Estudio piloto. Asignó al azar (1:1) a pacientes adultos con una infección leve de úlcera del pie diabético al tratamiento con una esponja de colágeno de gentamicina con atención local versus atención local sola. N=22	Evaluar el beneficio potencial del tratamiento con un antibiótico tópico.	20 (91%) pacientes fueron categorizados como que lograron la curación clínica de la infección, y 2 (9%) como una mejoría significativa.	No hubo diferencias en los resultados clínicos o microbiológicos en los que recibieron o no la esponja de gentamicina-colágeno, aunque esta fue mejor tolerada.	2	C

Table IX: Estudios sobre el efecto de la gentamicina frente a diferentes tipos de microorganismos. GR: Grado de recomendación; NE: Nivel de Evidencia.

REFERENCIA	DISEÑO DEL ESTUDIO	CRITERIOS EVALUADOS	RESULTADOS	CONCLUSIONES	GR	NE
Perim (2015) (22)	Estudio prospectivo. 41 pacientes con lesiones del pie diabético.	Determinar las frecuencias de los aislados bacterianos cultivados a partir de infecciones del pie diabético y evaluar su resistencia y susceptibilidad a los antibióticos de uso común.	Las bacterias Grampositivas más comúnmente aisladas fueron Staphylococcus aureus. Las bacterias Gramnegativas más comúnmente aisladas fueron Proteus spp. y Enterobacter spp., seguidas por Escherichia coli, Pseudomonas spp. y Citrobacter spp. 9 casos de Staphylococcus aureus resistente a la meticilina (SARM). Escherichia coli (75%), Proteus spp. (70%) y Pseudomonas spp. (75%) fueron sensibles a la gentamicina.	Proteus spp. eran resistentes a todos los betalactámicos excepto el imipenem, la cefoxitina y la gentamicina. La gentamicina y el imipenem fueron los antibióticos más efectivos contra casi todas las bacterias de la familia Enterobacteriaceae.. Los aislados de Pseudomonas spp. eran regularmente sensibles sólo a la gentamicina.	2	B
Mottola (2016) (25)	Estudio de casos y controles. De un total de 53 estafilococos aislados de UPD, obtenidos de 49 muestras, se seleccionaron 23 aislamientos de Staphylococcus aureus productores de biopelícula.	Analizar los patrones de susceotibilidad antimicrobiana de las cepas Staphylococcus aureus productoras de biopelícula.	Se requieren concentraciones muy altas de los antibióticos más utilizados en tratamiento de UPD para inhibir las biopelículas de Staphylococcus aureus in vitro. Los únicos antibióticos capaces de inhibir la erradicación de biopelícula en el 50 % de las cepas aisladas fueron la ceftarolina y la gentamicina.	La gentamicina y la ceftarolina fueron los agentes más potentes contra las biopelículas de Staphylococcus aureus, alcanzando concentraciones clínicas que pueden ser aplicadas para inhibir y erradicar las biopelículas. Esto se observó incluso en las cepas aisladas de SARM.	3	B
Price (2016) (24)	Estudio de casos y controles. Cepas bacterianas, medios y condiciones de cultivo. Se utilizó la cepa PAO1 de tipo silvestre de *Nottingham Pseudomonas aeruginosa* y *Staphylococcus aureus* multirresistente (SARM).	Comparar el movimiento de diferentes antibióticos a través de la matriz de colágeno de tejido blando del modelo y evaluar la susceptibilidad a los antibióticos como la gentamicina y tobramicina de una biopelícula establecida formada por organismos susceptibles o multirresistentes Perlas de sulfato de calcio cargadas con el 100%, 50 % y 25% del CRC de gentamicina.	El modelo de tejido blando apoya el crecimiento de una biopelícula robusta de *Pseudomonas aeruginosa*, y que esto fue completamente erradicado por la introducción de perlas de sulfato de calcio cargadas con tobramicina o gentamicina. La biopelícula de *Staphylococcus aureus* multirresistente, mostró una disminución de casi 1 log en los recuentos viables cuando se expuso a perlas de sulfato de calcio combinadas con gentamicina.	Estos datos sugieren que los antibióticos aplicados localmente combinados con sulfato de calcio proporcionan una eficacia sorprendente en las infecciones del pie diabético y ofrecen un enfoque alternativo efectivo para el manejo de la infección.	3	B
Singh AK (2020) (23)	Este estudio prospectivo y observacional se llevó a cabo en un hospital docente de atención terciaria donde se reclutaron 105 pacientes de DFU que asistían a la clínica de pie diabético desde diciembre de 2018 hasta noviembre de 2019.	Este estudio tenía como objetivo determinar el perfil clínico y microbiológico de los pacientes con UPD, establecer el patrón de sensibilidad a los antibióticos de los microbios en los pacientes con UPD y formular un tratamiento antibiótico empírico.	Pseudomonas fue el aislado predominante (27,3%) sensible a imipenem (90%), amikacina (86,6%), gentamicina (83,3%) y cefotaxima (80%), seguido de Staphylococcus aureus (19,1%) sensible a amikacina y gentamicina (100%), y ofloxacina (90%).	Se recomendo la amikacina y la gentamicina como tratamiento empírico de elección para las UPD infectadas, especialmente en las zonas rurales, por parte de los médicos de atención primaria y los especialistas, hasta que se inicie el tratamiento definitivo basado en el patrón de sensibilidad	2	B

En cuanto a las ventajas de la aplicación local de gentamicina, estas han sido estudiadas en 3 revisiones (**Tabla VII**)[13,14,15], un análisis retrospectivo de 354 pacientes y un ensayo clínico con 22 pacientes (**Tabla VIII**)[16,17]. En general, estos estudios indican que la aplicación local de la gentamicina, incluso en aquellos casos con osteomielitis, obtiene concentraciones elevadas en el lugar de infección, puede erradicarla y se acompaña de la curación de la UPD en un porcentaje importante de casos. También, se aprecia que es bien tolerada y tiene menos efectos graves que los tratamientos sistémicos.

Por último, en referencia al efecto de la gentamicina local sobre los diferentes tipos de microorganismos, incluidos aquellos resistentes a la meticilina (SARM), se han publicado 2 estudios de casos y controles y 2 estudios observacionales prospectivos sin comparador (**Tabla IX**). Estos trabajos muestran que tiene efecto sobre cepas aisladas de diferentes microrganismos como el *Staphylococcus aureus* (incluso aquellos resistentes a la meticicilina), Pro*teus spp., Enterobacter spp., Escherichia coli, Pseudomonas spp.* y *Citrobacter sp*. Estos resultados, apoyan el concepto de que la gentamicina puede ser un tratamiento útil y seguro en UPDs producidas por microorganismos resistentes a los antibióticos usados habitualmente.

Discusión

Nuestro trabajo ha estudiado, mediante una revisión sistemática, el efecto terapéutico de la aplicación local de gentamicina sobre las UPD infectadas. Para ello se realizaron varias búsquedas con el objetivo de valorar si la gentamicina sola o en combinación, de forma local, erradicaba la infección en un menor tiempo en comparación a otros tratamientos, así como las ventajas de aplicar este tratamiento de forma local y su actividad frente diferentes tipos de microorganismos incluidos los resistentes a la meticilina.

Con respecto al efecto terapéutico de la gentamicina en el tratamiento de UPD, existen diversos estudios que demuestran que el uso de este antibiótico reduce la infección en las UPD y por tanto ayuda a la cicatrización. Según el estudio realizado por Gauland et al.[16], que contaba con 323 pacientes, encontraron que 279 respondieron favorablemente al tratamiento llegando a su curación total, es decir, un 86,4% de los tratados consiguieron eliminar la infección. Por otra parte, en el estudio de Uçkay et al.[17] se trataron aleatoriamente pacientes adultos que presentaban UPD con gentamicina local o con atención local sola en proporción 1:1. Los resultados obtenidos mostraron que el 91% de los pacientes fueron capaces de eliminar la infección tras el tratamiento con gentamicina, no hallándose diferencias significativas con el resultado obtenido mediante tratamiento estándar. Sin embargo, sí que observaron diferencias en cuanto a la tolerancia a los antibióticos, presentando la gentamicina ventajas en este sentido.

En cuanto al tiempo de curación, según el estudio realizado por Lipsky et al.[18] el grupo de tratamiento con gentamicina local tuvo una mayor proporción de pacientes con curación clínica además de un menor tiempo en la erradicación de patógenos. Por otra parte, otros estudios como el de Varga et al[19] o el de Marson et al.[20] mostraron una disminución del tiempo de hasta 1,9 semanas con el tratamiento de gentamicina local en relación con el comparador. Todo esto parece indicar que la gentamicina puede ser una alternativa útil a los tratamientos actuales, ya que parece eliminar las infecciones disminuyendo el tiempo de tratamiento y por tanto reduciendo el tiempo de exposición al fármaco.

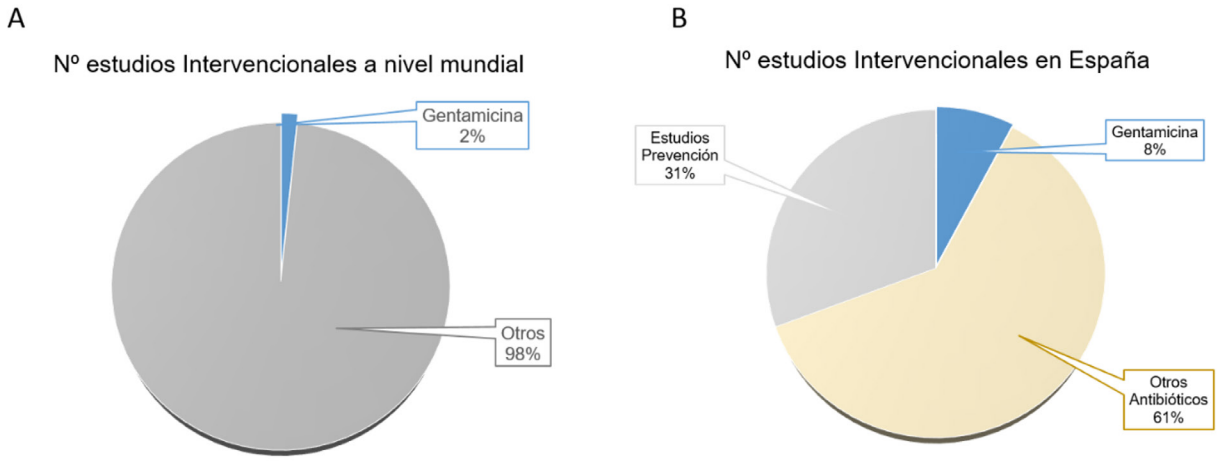
Con respecto a la toxicidad por parte de la gentamicina aplicada de forma sistémica, se sabe que produce nefrotoxicidad, neurotoxicidad y ototoxicidad[21]. Sin embargo, cuando se aplica de forma local, hemos observado que es bien tolerada. En el estudio de Nandi et al[13], se vio que la aplicación de perlas de gentamicina de forma local fue eficaz y sin efectos adversos graves, aunque cabe destacar que tiene el inconveniente de requerir la retirada posterior tras la liberación del antibiótico. El trabajo de Griffins et al[14] muestra que el implante de gentamicina es suficiente y por tanto, no requiere que el paciente se someta al riesgo de otros tratamientos. Estos autores, observaron que la gentamicina era más eficaz administrada de forma local. Esto podría estar relacionado con la obtención de una mayor concentración local de fármaco en comparación con tratamientos sistémicos.

La emergencia y propagación de bacterias patógenas resistentes a los antibióticos se ha convertido en un importante problema de salud pública en los últimos 50 años. La aparición de cepas de SARM, ha ocasionado brotes de infecciones nosocomiales en diferentes pacientes del mundo. Estudios descritos en este trabajo, han visto que la gentamicina tiene efectividad frente a diferentes tipos de microorganismos incluidos los resistentes a la meticilina. En los estudios de Perim et al[22] y Singh AK[23], por ejemplo, se observaron que la gentamicina local era efectiva frente a casi todas las bacterias de la familia *Enteriobacteriaeae* además de *pseudomonas spp*. Por otra parte, en el estudio de Price et al[24], tras la aplicación de gentamicina, se evidenció una disminución de casi 1 log en los recuentos viales de la biopelícula de *Staphylococcus aurerus* metilresistente. También, es destacable que Mottola et al[25], objetivaron efectividad incluso en las cepas aisladas de SARM, produciendo una erradicación del 50% de la biopelícula. Todo esto, hace pensar que la gentamicina local sea una buena alternativa a los tratamientos actuales o que sirva de apoyo para los casos más resistentes.

La escasa disponibilidad de resultados estadísticamente significativos ha sido un problema a la hora de responder a algunos de nuestros objetivos, ya que, en muchos casos, solo se disponía de información a partir de casos clínicos con un único sujeto (*case report*). Por ello, adicionalmente a las búsquedas realizadas de trabajos publicados, también investigamos en la base de ensayos clínicos *Clinical Trials*[26] ,de la Biblioteca Nacional de Medicina de los Estados Unidos (NIH), con la esperanza de encontrar más información. Sin embargo, pese a que detectamos algunos ensayos en la base de datos que habían concluido, ninguno de ellos presentaba los resultados y a fecha de hoy, aún no han sido publicados.

Además, según *Clinial trials*[26], actualmente hay 7 ensayos activos que investigan el efecto de la gentamicina sobre las úlceras infectadas. Esto supone únicamente un 1,6% de los estudios de intervención sobre el tratamiento de UPD (**Figura 3A**). Si tenemos en cuenta, únicamente los estudios que se realizan en nuestro país, solo 1 estudia los efectos de la gentamicina (**Figura 3B**).

Figura 3: (A) Número de estudios intervencionales no observacionales para el tratamiento o prevención de las UPD a nivel mundial. **(B)** Numero de estudios intervencionales no observacionales para el tratamiento o prevención de las UPD en España. En este caso, la proporción de ensayos clínicos viene desglosada en tratamiento con gentamicina, estudios que utilizan otros antibióticos o compuestos con carácter bactericida o tratamientos preventivos. Datos obtenidos de la base de ensayos clínicos *Clinical Trials*.



Como conclusión, las UPD son una de las lesiones más habituales en el entorno hospitalario. Además, con frecuencia se producen en pacientes pluripatológicos y polimedicados, por lo que es de vital importancia el individualizar el tratamiento. la aplicación de gentamicina a nivel local en UPDs, podría ser una buena opción terapéutica, debido a su alta eficacia y baja toxicidad en comparación con otras alternativas. Además, es útil frente a bacterias metilresistentes que con frecuencia dificultan la curación.

Por otra parte, es destacable la escasez de ensayos clínicos aleatorizados que impliquen un alto grado de evidencia y permitan establecer una recomendación firme. Por ello, en el momento actual, no podemos concluir que la gentamicina local deba ser el tratamiento de primera elección. Es bien sabido que la escasez de evidencia se asocia a variabilidad clínica y falta de fundamento al escoger entre diferentes opciones terapéuticas. Por tanto, parece obligada la realización de más estudios para poder posicionar adecuadamente el uso local de gentamicina en el tratamiento de las UPD infectadas.

ÍNDICE DE ABREVIATURAS

AGE= Glicación avanzada
CEBM= Centre for Evidence-Based Medicine
DM1=Diabetes mellitus tipo I
DM2: Diabetes mellitus Tipo II
ECCD= Enfermedad cardiovascular arterosclerótica
EDS= EBSCO Discovery Service
EVP= Enfermedad vascular periférica
GR= Grado de recomendación
IDB= Índice dedo brazo
ICCG=Implantes de colágeno reabsorbibles que contienen gentamicina
ITB= Índice tobillo brazo
MMII= Miembro inferior
NCBI= Centro Nacional sobre Biotecnología
NE= Nivel de evidencia.
NLM= Biblioteca Nacional de Medicina
NPD= Neuropatía diabética periférica
SARM= *Staphylococcus aureus* resistente a la meticilina

Conflicto de intereses: Ninguno.

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ORIGINAL

How to categorize a panoramic images database for automatically detection of dental treatments

Cómo categorizar una base de datos de imágenes panorámicas para la detección automática de tratamientos dentales

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Abstract

Objectives: The objective is to provide a methodology to obtain a categorized database without segmentation by sex or age that can be used in dental object detection applications and that may help in the diagnosis and usual clinical practice.
Methods: A total of 10,677 panoramic images were analyzed by four examiners. In each tooth, the examiner indicated if the tooth exists or not and the position on FDI notation. After that, and for each tooth that exists, the examiner detailed whether or not there were the variables analyzed. Those variables were filled teeth, crown, implant, endodontic treatment, caries, and prosthetic. A descriptive study of inter-observer and intra-observer concordance-consistency was performed.
Results: The results were statistically significant. Both teams obtained for all variables an almost perfect concordance k = 0.9 except in filled teeth where the kappa was k=0.8 and caries where a moderate agreement was obtained. The intra-examiner agreement was poor in caries variable and almost perfect in the rest of variables.
Conclusions: A correctly categorized database is essential to obtain correct results in applications with artificial intelligence and neural networks. This study shows how to categorize a database of dental images for use in object detection applications in the field of dentistry.

Key words: image dataset; panoramic image; categorization; dental application.

Resumen

Objetivos: El objetivo de este estudio es proporcionar una metodología para categorizar imágenes dentales que serán usadas para detectar objetos dentales sin que exista segmentación por sexo o edad y la cual ayude en el diagnóstico y la práctica clínica.
Métodos: 10.677 imágenes panorámicas fueron examinadas por 4 examinadores. En cada diente, los examinadores indicaron la existencia de dicho diente y la posición del mismo de acuerdo a la notación FDI. Posteriormente, para cada diente existente, se detalló la existencia o no de las variables analizadas. Dichas variables son: empastes, coronas, implantes, endodoncias, caries y prótesis. Se realizó un estudio de la concordancia inter e intra examinador.
Resultados: Los resultados alcanzados son estadísticamente significativos. Ambas parejas obtuvieron una concordancia casi perfecta, k=0.9, en todas las variables excepto en los empastes, donde kappa toma un valor de k=0.8 y en las caries, donde la concordancia fue moderada. La concordancia intra-examinador fue pobre para las caries y casi perfecta para el resto de variables.
Conclusiones: Una correcta categorización es esencial para obtener buenos resultados en las aplicaciones en las que se emplean las redes neuronales y la inteligencia artificial. Este estudio muestra cómo categorizar una base de datos de imágenes panorámicas que vayan a ser empleadas para detectar objetos en el campo de la odontología.

Palabras clave: base de datos; imagen panorámica; categorización; odontología.

Background

Medical practice in general, and dentistry in particular, generates massive data from sources such as high-resolution medical imaging, biosensors with continuous output and electronic medical records[1].

We nowadays require more than ever to provide healthcare which, together with the large amount of data generated, makes the use of algorithms increasingly necessary[1]. Diagnostic mistakes and errors in treatment cause loss of resources and time both for patients and clinicians[2]. This is one of the reasons why artificial intelligence is being an increasingly used tool in the field of medicine and dentistry.

Several studies have employed different computer techniques to obtain dental information from X-ray images. Lin et al.[3] employed bitewing images to automatically classify teeth, Miki *et al*.[4] proposed a neural network to classify teeth for forensic identifications.

To reduce errors on machine predictions, artificial intelligence can be trained to recognize some patters from several data inputs[5]. The results provided by the automatic algorithms and artificial intelligence have a great dependence on the data with which they learn and are training, that is, on the input data.

On the other hand, caries is one of the most common chronic diseases in the oral field with a great impact on the patient's health[6]. Clinical examination is the main method for caries detection being radiographic examination a complementary diagnostic tool[7]. Panoramic radiographies are very common in dentistry practice to make a general diagnosis of the patient[8] but intraoral bitewings images are more effective in detecting caries lesions than dental panoramic tomographies[9]. Previous studies compared the effectiveness of panoramic and bitewing radiographs for the detection of caries but with opposed results on inter-examiner agreement[10,11].

The objective is to provide a methodology to obtain a categorized database without segmentation by sex or age that can be used in dental object detection applications and that may help in the diagnosis and usual clinical practice.

Method

Four dentists with at least three years of experience in general dentistry was divided into two groups (Team 1: E.A., MF.S. and Team 2: B.S., I.J.).

Image dataset

Panoramic images were taken from Asisa Dental S.A.U. centers in the Community of Madrid (Spain). These images were completely anonymized by CareStream® Health Spain SA (Pozuelo de Alarcón, Madrid, Spain). No additional information such as name, gender, age, or when the image was taken was used to for the database. Data collection was ethically approved (Ethics Committee of Research with Regional Medicines of the Community of Madrid (CEIm-R)) in June 15th, 2018. The requirement to obtain informed consent from patients was waived by the ethics committee.

The radiographies included in the study were those that correspond to adults older than 18 years. Images with poor definition, repeated, patients with only presence of implants, edentulous, with mixed dentition or with removable prostheses (metallic or acrylic) were excluded. Periapical radiographies were also excluded.

Data collection methodology

For each non-rejected radiograph, the variables detailed in **table I** must be evaluated:

In each tooth, the examiner indicated if the tooth exists or not and the position on FDI notation. After that, and for each tooth that exists, the examiner detailed whether or not there were the variables detailed in the previous table. A program created for this propose was employed by the examiners to collect information on each of the variables. **Figure 1** details the main page of the visualization program and **Figure 2** how the variables are selected in each tooth.

This visualization program has the possibility of increase the size of the panoramic image, but it does not allow to modify brightness or contrast.

Before beginning the evaluation, the four examiners were instructed through an informational meeting where they were administered a guide manual and use of the interface. This manual met the criteria that each evaluator should consider making the diagnosis of the radiograph in detail.

Statistical analysis

The analysis was done using Stata® version 14.2 (StataCorp LLC, Texas, USA) and results were obtained with a 95% confidence interval. The interpretation was made with the classification proposed by Landis and Koch[12]. Intra- and inter-examiner agreement was evaluated by calculating Cohen's Kappa. According to Bulman and Osborn[13], values of Cohen's Kappa below 0.40 were considered as poor agreement, between 0.41 and 0.60 as moderate agreement, between 0.61 and 0.80 as substantial agreement, and between 0.81 and 1.00 as almost perfect agreement.

To perform the intra-examiner statistics, each evaluator re-analyzed 50 images.

Table I: Variables definition.

Presence	Absence
Tooth	
There is root and crown	There is no type of crown
Filling	
There is a filling of any material in the crown of the tooth Overlays (until 2/3 of the occlusal part of the clinical crown)	There is no type of obturation or overlay in the crown
Crown	
There is a total covering of any material in the crown of the vital tooth There is a total coating of any material in the crown of the root canal There is a total coating of any material in the crown of the implant	There is no total coating of any kind in the clinical crown.
Implant	
There is a dental implant on the bone	There is no dental implant
Endodontic treatment	
Presence of radiopacity in the roots of a tooth (clinical crown + root)	There is no type of radiopacity in any of the roots of the tooth.
Prosthetic	
There is a prosthetic crown, of any material, without being supported by any tooth or implant.	There is no prosthetic crown without support.
Caries	
Radiolucency may extend to the dentinoenamel junction or outer one third of the dentin. Radiolucency extends into the middle one-third of the dentin Radiolucency extends into the inner one-third of the dentin Recurrent caries lesion: irregularly shaped radiolucency below a restoration or next to it.	No radiolucency

Figure 1: Visualization program employed to collect data by the examiners.

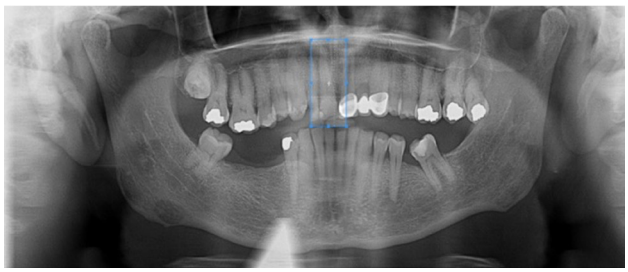
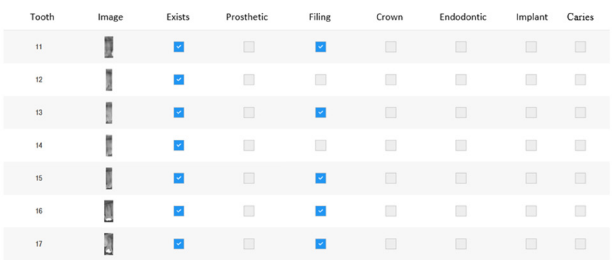


Figure 2: Detail of how variables are collected.



Results

Inter-observer agreement

The four examiners needed 30 weeks to complete the process of visualization and analysis of the images. A total of 10,684 radiographs were categorized, and after the elimination of duplicates, the final result was 10,677 panoramic radiographs.

Table II details the concordance obtained from each variable by each team with the Cohen Kappa statistic.

Table II: Concordance obtained from the total of categorized images.

	Team 1	Team 2
	kappa	kappa
Exists	0.9	0.9
Filling	0.8	0.8
Caries	0.4	0.5
Prosthetic	0.9	0.9
Crown	0.9	0.9
Endodontic	0.9	0.9
Implant	0.9	0.9

Panoramic images categorized with an ideal concordance k=1 in the variable exists were a total of 7,390. Both teams obtained for all variables an almost perfect concordance k=0.9 except in filling and caries. For filling variable, a substantial concordance k=0.8 in both teams. For the caries variable, team 1 obtained a moderate agreement k=0.4 and team 2 also a moderate agreement k=0.5.

Evaluation of sex and age of the analyzed sample

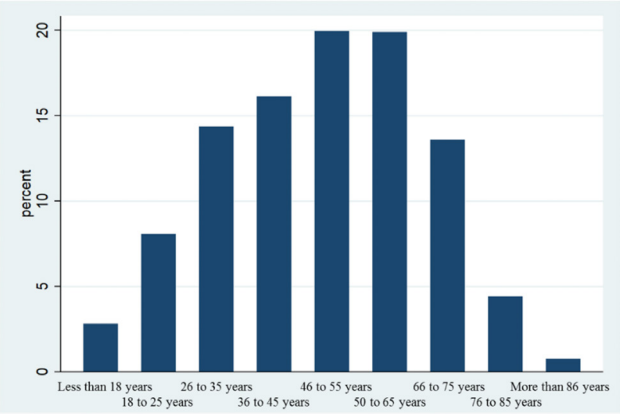
In the total of the sample analyzed (10,677 radiographs) the minimum age was 0 years and the maximum was 114. The average age was 48.93 years with a standard deviation of 17.39 years. **Table III** details the descriptive statistic of age.

Table III: Descriptive statistic of age.

Variable	N	Min	Max	p25	p50	p75	Mean
Age	10,677	0	114	35	50	62	48.92826

Figure 3 shows the distribution by age intervals.

Figure 3: Age range percentage.



Regarding the variable sex, the distribution of men represented 52.72% and women 47.28%. **Table IV** details the descriptive statistic of sex.

Table IV: Descriptive statistic of sex.

Sex	Frequency	Percentage	Cumulative
Man	5,629	52.72	52.72
Woman	5,048	47.28	100.00
Total	10,677	100.00	

Intra-observer agreement

Each examiner re-analyzed a total of 50 images. **Table V** details the intra-examiner concordance obtained from each variable with the Cohen Kappa statistic.

The results of the intra-examiner statistic for endodontic, implant, prosthetic and crown variables was an almost perfect agreement. Examiners 2 and 3 a poor agreement in caries variable while examiners 1 and 4 obtained a moderate agreement. An almost perfect agreement was obtained by all examiners in exists variable.

Table V: Intra-examiner concordance.

	Examiner 1 (E.A.)	Examiner 2 (MF.S)	Examiner 3 (B.S.)	Examiner 4 (I.J.)
	kappa	kappa	kappa	kappa
Exists	0.8194	0.8039	0.9065	0.8637
Filling	0.8553	0.6907	0.7893	0.7861
Caries	0.5176	0.3036	0.1555	0.5329
Prosthetic	0.9438	0.9467	0.9784	0.8183
Crown	0.9617	0.9602	0.9358	0.9205
Endodontic	0.9425	1	0.9876	0.9750
Implant	0.8921	1	0.9224	0.8132

Discussion

This study proposed a methodology to categorize a panoramic images database for dental object detection applications. Four examiners randomly divided into two groups analyzed 10,677 images and in each of the radiographs they selected the existence or absence of tooth and, in case of existence, if on that tooth there were filling, crown, implant, endodontic treatment, caries or prosthetic. Finally, a descriptive study of inter-observer and intra-observer concordance-consistency was performed.

One of the limitations that automatic object detection is related to the number of images used to build the algorithm. For example, Wang *et al*. employed 400 cephalometric X-ray image in different object detection algorithms[14], or Miki et al. employed fifty-two images[4]. In our study, a database of 10,677 images is prepared and categorized.

The trustworthy interpretation of dental images, such as, radiographs, can be affected by several factors like training, the experience of the observer or the quality of the image[15]. Therefore, it is important to control these potential factor sources of examiner bias. Regarding the experience of the examiner, Fortes *et al*. evaluated the possible differences when selecting an implant for dental treatment between junior and senior experienced dentists[16]. Pakbaznejad Esmaeili *et al*. compared the differences on caries detection between an expert in oral radiologists and general dentists and concluded that caries remained mainly unobserved by general dentists[9]. In our study, to avoid the possible introduction of bias in data collection, the four examiners had the same experience in general dentistry.

The main advantages of this study are, first, in the number of categorized images that could be used for the use of artificial intelligence techniques and, secondly, that the categorized database is not biased by the experience of observers.

Francio *et al*. analyzed the inter- and intra-examiner agreement to detect tooth-restoration in panoramic images. Excellent and good levels of intra-examiners agreement were obtained in detecting tooth restoration[17]. These results are in accordance with the results obtained in our study. One of the reasons for obtaining a lower concordance for the "filling" variable can be found in the noise generated in the radiographic images, which refers to an artifact that can mask a factor[17].

Interpretation of X-ray images is subjective and difficult on the occlusal surface to detect caries, therefore, to obtain lower values of kappa statistic is understandable. Thomas *et al*. compared the concordance of caries detection between bitewing and panoramic radiographies and concluded that the intra-examiner reproducibility was low[8]. Our results agree with this study. Kamburoglu *et al*. also compared proximal caries detection using intraoral bitewing, extraoral bitewing and panoramic radiography and concluded that inter-observer agreements for the panoramic images were between 0.477 and 0.740, less agreement than intraoral bitewing radiographies[18]. Our results in caries variable are closed to the range obtained in that study.

Conclusions

A correctly categorized database is essential to obtain precise results in applications with artificial intelligence. This study shows a methodology to categorize a database of dental images for use in object detection applications in the field of dentistry. As future studies are the detection of variables by artificial intelligence from the analyzed images.

Declarations

Ethics approval and consent to participate: Ethics Committee of Research with Regional Medicines of the Community of Madrid (CEIm-R)) in June 15th, 2018. The requirement to obtain informed consent from patients was waived by the ethics committee.
We confirm that all methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication: "Not applicable"

Availability of data and materials: The datasets generated and/or analysed during the current study are not publicly available due they have been obtained from patients of from Asisa Dental S.A.U. centers but are available from the corresponding author on reasonable request.

Competing interests: "The authors declare that they have no competing interests"

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Authors' contributions: M.P-P, J.G.V, R.R and A.B. designed the study, C.H.M-M and C.I revised critically the content, M.P-P drafted the manuscript and all authors approved the final version.

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ORIGINAL

Impact of COVID-19 Lockdown on cardiometabolic risk scales in Adults: A before and after Pandemic Lockdown Longitudinal Study

Impacto del confinamiento por COVID-19 en las escalas de riesgo cardiometabólico en adultos: un estudio longitudinal antes y después del confinamiento por la pandemia

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Abstract

Introduction: In December 2019 the first cases of SARS-CoV-2 virus infection were detected, with the months it became pandemic and forced most countries to establish a state of lockdown. The aim of this study is to evaluate the influence of unhealthy lifestyles during lockdown on different cardiometabolic parameters.
Methods: A prospective study was performed in 6.236 workers in a Spanish population between March 2019 and March 2021. Different cardiometabolic parameters were determined before and after pandemic lockdown.
Results: An increase in all the parameters analyzed in the post-lockdown period compared to the pre-lockdown period was observed. Conclusions. Lockdown has had a negative impact on cardiometabolic parameters in both sexes.

Key words: Covid-19, cardiometabolic parameters, confinement, disease.

Resumen

Introducción: En diciembre de 2019 se detectaron los primeros casos de la infección por el virus SARS-CoV-2, con el paso de los meses se transformó en pandemia y obligo a la mayoría de países a establecer el confinamiento de la población. El objetivo de este estudio es evaluar cómo influían los estilos de vida poco saludables que se produjeron durante el confinamiento en diferentes parámetros cardiometabólicos.
Material y métodos: Se realizó un estudio prospectivo en 6.236 trabajadores de una población española entre marzo de 2019 y marzo de 2021. Se determinaron diferentes parámetros cardiometabólicos antes y después del cierre por la pandemia.
Resultados: Se aprecia un incremento de todos los parámetros analizados en el periodo post-confinamiento frente al periodo pre-confinamiento. Conclusiones. El confinamiento ha tenido un efecto negativo sobre los parámetros cardiometabólicos en ambos sexos.

Palabras clave: Covid-19, parámetros cardiometabólicos, confinamiento, enfermedad.

Introduction

In January 2020, COVID-19 was classified as a Public Health Emergency of International Importance (PHEIC). In March of the same year, the World Health Organization (WHO) declared it a global pandemic[1]. Its rapid spread and the high severity of the virus made it a major public health problem worldwide. This, together with the shortage of effective drugs and vaccines, forced countries to establish restrictive measures in order to prevent the spread of the pandemic[2,3]. Enclosures, quarantines and even total isolation of some populations were established, which in April 2020 affected one out of every three people in the world[4]. In Spain, the Royal Decree 463/2020 of 14 March was published, declaring a state of emergency[5]. This decree forced the abandonment of work and educational tasks with the consequent increase in boredom that ended in loss of appetite or food binges[6,7]. Consumption of fish, fruits and vegetables decreased and consumption of sweet or salty snacks increased[8,9]. Sleep disorders also increased[10,11] and physical activity decreased, which caused a significant weight gain, which in Spain was estimated at 12.8%-44%[12]. This weight gain related to COVID-19 may lead to an increased risk of developing metabolic disorders in the future in the population with a previous diagnosis of the disease[13], but also in the population that had not previously suffered from it[14]. It is known that the population with previous pathology is more likely to present more severe symptoms if infected by the virus.

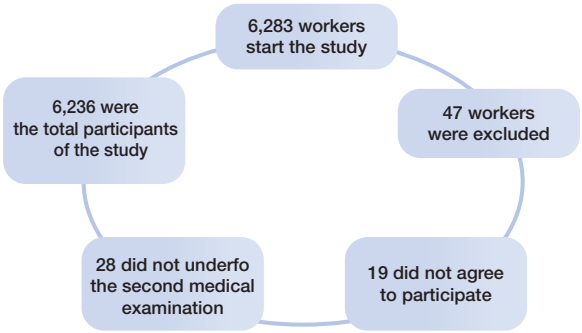
The aim of our study is to evaluate how lockdown and the unhealthy lifestyles associated with it can influence the values of different cardiometabolic parameters in a group of 6,236 workers in Spain, so that if at some point in the future a similar situation occurs, we can take appropriate preventive measures in order to reduce its side effects on people's health and the development of disease.

Methods

A prospective study was carried out in workers of the Autonomous Community of the Balearic Islands and the Valencian Community. The population of our study was made by workers who attended occupational medical examinations between March 2019 and March 2021; both included.

A total of 6,283 workers were selected, of which 47 were excluded (19 of them because they did not want to participate in the study and the remaining 28 because they did not attend the second examination), so the study was conducted on a final sample of 6,236 workers. (See **Figure 1**).

Figure 1: Flowchart of participants.



Inclusion criteria:

- Age between 18-69 years.
- Having undergone a medical check-up.
- Belonging to one of the companies collaborating in the study.
- Accepting to participate in the study and ceding the data for study and analysis.

The analytical and anthropometric determinations were performed by the health personnel of the occupational health units. Uniformity in taking these measurements was previously standardized to avoid interobserver bias.

The determination of weight (kilograms) and height (centimeters) was obtained with a SECA 700 stadiometer with a SECA 220 telescopic stadiometer with millimeter divisions. Height was obtained with the person standing upright, back against the stadiometer and feet together.

Waist circumference was measured with a SECA model tape measure. The tape was placed parallel to the ground at the height of the last floating rib with the person standing with feet together, arms resting on both sides of the body and abdomen relaxed.

The hip circumference was measured with the same tape and the person in the same previous position. The measuring tape was placed horizontally at hip height.

Blood pressure was determined with the patient seated and using a sphygmomanometer.

The patient was placed in the supine position, and a calibrated automatic sphygmomanometer type OMRON M3 was used. Three measurements were taken at one-minute intervals and the mean was calculated.

The analytical determinations were performed after fasting for at least 12 hours. Samples were processed within 48-72 hours. Automated enzymatic methods were used to determine cholesterol, glucose and triglycerides. HDL was determined by precipitation with dextran sulfate. LDL levels were calculated using Friedewald's formula (LDL = total cholesterol-HDL-triglycerides/5).

All these parameters were expressed in mg/dL.

Metabolic syndrome (MS) was assessed using three different criteria: the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP-III), the Joint Interim Statement (JIS) and the International Diabetes Federation (IDF) update[15].

Metabolic age is obtained from bioimpedance results obtained using a TANITA model monitor.
The following formulas were used to calculate the different atherogenic indexes[16]:
Castelli's atherogenic index=CT/cHDL.
Kannel atherogenic index=cLDL/cHDL.
Triglycerides/cHDL atherogenic index.

For each index, different cutoff points were established according to the existing data in the literature. The Castelli index was considered low risk[17] if the values were less than 4.5% in women and less than 5% in men, moderate risk between 4.5-7% in women and 5-9% in men, and high risk if they were higher than 7% and 9%, respectively. The Kannel index was low risk if it was less than 3% and high above that value. The triglyceride/HDL-CHDL index was considered elevated at 3% or higher.

The normalized weight-adjusted index (NWAI)[18] is calculated by applying the formula:

[(weight/10) – (10x height) + 10] with weight measured in kg and height in m.

Body Surface Index (BSI)[19]. BSA is calculated using the DuBois formula where w (weight) represents weight in kg and h (height) represents height in cm.

$$BSI = \frac{WEIGHT}{\sqrt{BSA}} \quad \text{and} \quad BSA = w^{0,425} * h^{0,725} * 0,007184$$

Visceral adiposity index (VAI) is calculated using different formulas for males and females[20].

Females:

$$VAI = \left(\frac{WC}{36,58 + (1,89 \times BMI)}\right) \times \left(\frac{TG}{0,81}\right) \times \left(\frac{1,52}{HDL}\right)$$

Males:

$$VAI = \left(\frac{WC}{39,68 + (1,88 \times BMI)}\right) \times \left(\frac{TG}{1,03}\right) \times \left(\frac{1,31}{HDL}\right)$$

Body adiposity index (BAI)[21] and abdominal volume index (AVI) are calculated using this formulas[22]:

AVI = [2 cm (waist) 2+0.7 cm (waist-hip)2]/1000
BAI = ((hip circumference)/ ((height)$^{1.5}$)-18),

A smoker was considered to be a person who had regularly consumed at least one cigarette each day during the previous month or who had quit smoking less than one year ago.

Physical activity was determined by means of the International Physical Activity Questionnaire (IPAQ), a self-administered questionnaire of seven questions that assesses the type of physical activity performed in the previous seven days[23].

Social class was determined by applying the proposal of the social determinants group of the Spanish Society of Epidemiology[24]. Three categories were considered: Class I: directors/managers, university professionals, sportsmen and artists; Class II: intermediate occupations and skilled self-employed workers; Class III: unskilled workers.

Statistical Analysis

A descriptive study was carried out using the different categorical variables by calculating both the frequency and distribution. For the analysis of the quantitative variables, the mean and standard deviation were determined, and for the qualitative variables, the percentage was obtained. For the bivariate analysis, the X2 test (with Fisher's exact correction if necessary) and Student's t test were used when the samples were independent. Statistical analysis was performed with SPSS 28.0 (IBM, New York, NY, USA), accepting a statistical significance level of 0.05.

Ethical Considerations and Aspects

The study was approved by the Clinical Research Ethics Committee of Balearic Islands Health (Aproval Code: IB 4383/20). The participants received the information regarding the study and signed the informed consent before being included in the study. All procedures were performed in accordance with the ethical standards of the institutional research committee and with the 2013 Declaration of Helsinki.

Results

Table I shows the mean values of different anthropometric and clinical parameters in the periods between pre-lockdown and post-lockdown COVID-19. Statistically significant differences can be observed in all cases. Of the sample studied, 51.9% were women and 48.1% men.

There was an increase in all the anthropometric parameters (weight, BMI, waist and hip circumference and body fat) between both pre-lockdown and post-lockdown periods. Something similar occurred with the analytical parameters (hepatic and lipid profile) and the clinical parameters (systolic and diastolic blood pressure). In all cases the differences obtained were statistically significant.

For the qualitative variables, there was a statistically significant decrease of 11% in the percentage of people who regularly exercise and an increase of 2% in tobacco consumption. Both situations show that, during the months of lockdown and in both genders, a more sedentary lifestyle was adopted, probably due to the restrictive measures imposed by the authorities during the state of lockdown.

Table I: Characteristics of the population.

N=6236	Year 2018 Mean ± SD	Year 2019 Mean ± SD	Year 2020 Mean ± SD	p-value
Age (years)	41.1 ± 9.9	42.1 ± 9.9	43.1 ± 9.9	<0.001
Weight (kg)	71.7 ± 16.3	72.2 ± 16.4	73.8 ± 16.5	<0.001
BMI (kg/m²)	25.1 ± 4.7	25.3 ± 4,7	25.9 ± 4.7	<0.001
Waist circumference (cm)	82.8 ± 14.0	84.6 ± 14.1	87.6 ± 14.1	<0.001
Hip circumference (cm)	98.7 ± 9.4	99.8 ± 9.4	101.5 ± 9.5	<0.001
Waist to Height ratio	0.49 ± 0.08	0.50 ± 0.08	0.52 ± 0.08	<0.001
Waist to hip ratio	0.84 ± 0.10	0.85 ± 0.09	0.86 ± 0.09	<0.001
Body fat (%)	24.5 ± 9.1	25.3 ± 8.7	26.9 ± 8.8	<0.001
SBP (mmHg)	120.0 ± 16.8	121.3 ± 16.3	124.6 ± 16.3	<0.001
DBP (mmHg)	76.9 ± 10.7	78.2 ± 10.5	82.8 ± 10.6	<0.001
Glycaemia (mg/dL)	90.5 ± 16.4	91.9 ± 15.7	95.4 ± 15.8	<0.001
Total cholesterol (mg/dL)	190.7 ± 37.3	194.3 ± 35.3	202.8 ± 35.7	<0.001
HDL-c (mg/dL)	53.9 ± 13.7	53.1 ± 13.4	50.7 ± 13.7	<0.001
LDL-c (mg/dL)	117.4 ± 40.3	121.4 ± 38.5	131.0 ± 39.0	<0.001
Triglycerides (mg/dL)	96.8 ± 79.2	98.7 ± 78.5	105.8 ± 78.9	<0.001
ALT (U/L)	24.1 ± 28.5	25.7 ± 28.7	28.4 ± 28.7	<0.001
AST (U/L)	21.7 ± 15.5	22.7 ± 15.6	24.0 ± 15.7	<0.001
GGT (U/L)	25.8 ± 27.4	26.8 ± 27.4	28.9 ± 27.4	<0.001
	N (%)	N (%)	N (%)	p-value
Women	3236 (51.9)	3236 (51.9)	3236 (51.9)	
Men	3000 (48.1)	3000 (48.1)	3000 (48.1)	
Smokers	1176 (18.9)	1202 (19.3)	1302 (20.9)	<0.001
Physical exercise	2732 (43.8)	2600 (41.7)	2044 (32.8)	<0.001
Social class I	3664 (58.8)	3664 (58.8)	3664 (58.8)	
Social class II	812 (13.0)	812 (13.0)	812 (13.0)	
Social class III	1760 (28.2)	1760 (28.2)	1760 (28.2)	

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL: high density lipoproteins; LDL: low density lipoproteins; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma glutamyl transpeptidase.

When analyzing the cardiometabolic risk scales (metabolic age, metabolic syndrome, waist triglyceride index, waist weight index, atherogenic index, normalized weight adjusted index, body surface index, visceral adiposity index, body adiposity index and abdominal volume index) a statistically significant increase in the mean results of all of them is observed during lockdown. If we focus on the pre-lockdown and post-lockdown differences, the worsening of all of the percentages of the different scales studied stands out, with the NWAI scale being the worst: going from values of 0.05% pre-lockdown to values of 0.16% post-lockdown; the VAI also stood out, with an increase of 0.1% to 0.5% compared to pre-lockdown values, as can be seen in **table II**.

Table II: Changes in mean values of different cardiometabolic risk scales in 2018, 2019, and 2020.

	Year 2018 Mean (SD)	Year 2019 Mean (SD)	Year 2020 Mean (SD)	p-value	Difference 2018-2019 Value (%)	Difference 2019-2020 Value (%)	p-value
ALLY metabolic age	-4.3	-3.6	-2.0	<0.001	0.7 (16.4)	1.7 (45.7)	<0.001
Nº factors MS ATPIII	1.0	1.2	1.6	<0.001	0.2 (17.3)	0.4 (27.9)	<0.001
Cholesterol/HDL-c	3.8	3.9	4.3	<0.001	0.1 (3.4)	0.4 (10.8)	<0.001
LDL-c/HDL-c	2.4	2.5	2.8	<0.001	0.1 (4.8)	0.3 (14.6)	<0.001
Triglycerides/HDL-c	1.9	2.0	2.3	<0.001	0.1 (3.6)	0.3 (13.9)	<0.001
Cholesterol-HDL-c	136.7	141.2	152.1	<0.001	4.5 (3.2)	10.9 (7.8)	<0.001
NWAI	0.32	0.37	0.53	<0.001	0.05 (14.7)	0.16 (43.6)	<0.001
Body surface index	38.9	39.0	39.4	<0.001	0.1 (0.3)	0.4 (1.1)	<0.001
Visceral adiposity index	2.9	3.0	3.5	<0.001	0.1 (5.5)	0.5 (16.4)	<0.001
Body adiposity index	27.3	27.8	28.6	<0.001	0.5 (1.9)	0.8 (2.8)	<0.001
Abdominal volume index	28.5	29.7	31.7	<0.001	1.2 (4.2)	2.0 (6.7)	<0.001

ALLY Avoidable lost life years. MS ATPIII Metabolic syndrome Adult Treatment Panel III. HDL-c High density lipoprotein-cholesterol. LDL Low density lipoprotein-cholesterol. NWAI Normalized Weight Adjusted Index.

Table III assesses the changes in the prevalence of the different values of the insulin resistance and non-alcoholic fatty liver disease scales analyzed pre-lockdown and post-lockdown due to the COVID-19 pandemic, revealing statistically significant results with a difference of more than 2% between the years before and after pandemic in both groups as well as between patients with type 2 diabetes and non-diabetic patients. However, the highest variations in both groups are found in the lipid accumulation product scale and in the fatty liver disease scale, with a greater worsening in the NAFLD prevalence scales compared to the insulin resistance scales. It is noteworthy that all the formulas experienced greater worsening in the non-diabetic group compared to in the diabetic group. The worst values of the different analyzed scales occurred in the metabolic score for insulin resistance (METS-IR) followed by the lipid accumulation product scale and the fatty liver disease scale. These alterations are affected in the same order in diabetic patients; however, their percentage scores are much lower.

Table III evaluates the changes in the prevalence of the different values of the cardiometabolic risk scales analyzed before and after COVID-19 pandemic, showing statistically significant differences between both groups in all cases. The greatest variations were found in diabesity, Triglycerides/HDL-c high, Cholesterol/HDL-c moderate-high and lipid triad.

Table III: Changes in prevalence of high values of different cardiometabolic risk scales in 2018, 2019, and 2020.

	Year 2018	Year 2019	Year 2020		Difference 2018-2019	Difference 2019-2020	
	Mean (SD)	Mean (SD)	Mean (SD)	p-value	Value (%)	Value (%)	p-value
ALLY metabolic age >5	30.1	31.6	34.5	<0.001	1.5 (5.0)	2.9 (9.2)	<0.001
MS ATPIII	9.9	13.9	20.9	<0.001	4.0 (40.4)	7.0 (50.4)	<0.001
MS IDF	12.4	17.0	25.0	<0.001	4.6 (37.1)	8.0 (47.1)	<0.001
Cholesterol/HDL-c moderate-high	16.4	18.2	29.5	<0.001	1.8 (11.0)	9.3 (62.1)	<0.001
LDL-c/HDL-c high	23.4	26.6	37.5	<0.001	3.2 (13.7)	10.9 (41.0)	<0.001
Triglycerides/HDL-c high	16.8	17.1	21.9	<0.001	0.3 (1.8)	4.8 (28.1)	<0.001
Cholesterol-HDL-c high	56.2	62.3	72.1	<0.001	6.1 (10.9)	9.8 (15.7)	<0.001
Atherogenic dyslipidemia	3.4	4.2	6.6	<0.001	0.8 (23.5)	2.4 (57.1)	<0.001
Lipid triad	0.6	0.9	2.4	<0.001	0.3 (50.0)	1.5 (66.7)	<0.001
Diabesity	0.6	0.6	1.0	<0.001	0.0 (0.0)	0.4 (66.7)	<0.001

ALLY Avoidable lost life years. MS ATPIII Metabolic syndrome Adult Treatment Panel III. MS IDF Metabolic syndrome International Diabetes Federation. HDL-c High density lipoprotein-cholesterol. LDL Low density lipoprotein-cholesterol.

Discussion

Changes in lifestyle have been observed in recent decades, with an increase in sedentary lifestyle and a worsening of eating and sleeping patterns. Due to the pandemic and the state of lockdown, this situation has been aggravated[25].

In our study, we observed a decrease in physical activity and an increase in tobacco consumption associated with lockdown, which can be translated into an increase in the cardiometabolic parameters analyzed. These data corroborate our previous studies26,27 and the data obtained by Cicero et al28 and Khan et al29. Lockdown has affected both the health of previously healthy individuals and those with previous pathologies by increasing cardiovascular risk factors and metabolic diseases[30,31].

Low HDL cholesterol levels, increased waist circumference, elevated triglycerides and blood glucose and high blood pressure values constitute what is known as the metabolic syndrome, which is considered a global measure of cardiometabolic disease. In our studies all these parameters have worsened during lockdown as seen in our results, which can be translated into an increase in the prevalence of metabolic syndrome and other cardiometabolic scales; these data agree with those found by other authors such as Cinque et al[32]. This situation is important since studies such as the one by Ghoneim et al[33] show that people with cardiometabolic disorders are more susceptible to being infected by COVID-19 and also present more complications in case of infection. Furthermore, these cardiometabolic complications have led to an increase in morbidity and mortality as well as a higher risk of infection by COVID-19 and a worse prognosis in the event of infection and requiring hospitalization[34,35].

The results obtained in this study show that the state of lockdown led to a statistically significant deterioration of different health indicators, causing a worsening of cardiometabolic risk factors and the presence of new pathologies that have led to an increase in morbidity and mortality. These data agree with those obtained by other authors[36].

It is important to be aware of the effects of lockdown on health, since, due to globalization, it is necessary to be alert to the risk of new pandemics that may force the health authorities to impose new lockdowns. The reduction in cardiometabolic diseases is important not only because of its effect on cardiovascular health but also because it increases the risk of infection by COVID-19.

There are studies that compare the effects of the pandemic and COVID-19 infection on cardiometabolic parameters, but we have not found any study that compares as many parameters in the same population as in our study. In addition, all the studies consulted had smaller sample sizes than ours.

Strengths and limitations

As limitations, we highlight the fact that the study corresponds to a specific geographical area, in a Caucasian working population, which could limit the generalization of the results to other areas where lifestyles may be different. Selection bias is another limitation of our study, since it is limited to workers who voluntarily attended company medical check-ups during those years. Therefore, the results are not applicable to other populations, and it would be necessary to carry out specific studies.

Conclusions

The state of lockdown due to COVID-19 has caused a worsening of different health parameters, with a negative influence on cardiometabolic risk factors as well as a worsening of healthy lifestyle habits, thus worsening the health of the population. This situation should alert us to the fact that, as a consequence of globalization, new lockdowns associated with new pandemics could occur.

Conflict of Interest

The authors declare that no competing interests exist.

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ORIGINAL

Prevalence of prediabetes among first degree relatives of type 2 diabetes individuals in Abakaliki, Ebonyi State Nigeria

Prevalencia de prediabetes entre familiares de primer grado de personas con diabetes tipo 2 en Abakaliki, Estado de Ebonyi, Nigeria

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Abstract

Aim: This study was aimed at determining the prevalence and factors of pre-diabetes (PD) among first degree relatives, (FDRs) of type 2 diabetes, (T2D) subjects in Abakaliki Metropolis, Ebonyi State, Nigeria.
Methods: 100 participants (70 men and 30 women) were selected through respondent-driven sampling and interviewed about their knowledge, common symptoms and family history of T2D. Venous blood samples were collected after an overnight fast and 2 hours after a 75g oral dose of 75g anhydrous glucose. Samples were collected into fluoride-oxalate bottles, kept at 40ºC and analyzed within 1 hour of collection by the glucose oxidase method. Data were analyzed using SPSS 20.0 and summarized as mean and standard deviation.
Results: Twenty-two FDRs – (17 male and 5 females) had PD giving prevalence rates of 22%, 24.3% and 16.7% respectively for the entire study, males and females populations respectively. 13 (11 male, 2 females; 84.6% and 6.7%) of FDRs with PD had IFG only while 3 each – (4.3 and 10% respectively) - had IGT only. 3 males only (4.3%) had both IFG and IGT. The BMI of subjects with IGT (23.80 ± 2.68 kg/m^2) was significantly higher than IFG (22.09 ± 1.94 kg/m^2) (p = 0.028). Female subjects with PD had significantly higher BMI (21.8 ± 3.38 vs 21.73 ± 3.15 kg/m^2; p = 0.035) than the male FDRs. Almost 25% of FDRs of T2D subjects in Abakaliki have PD and are at risk of developing diabetes.
Conclusion: More men than women were affected. Body mass, among others, may be a contributing factor.

Keywords: Pre-diabetes, impaired fasting glycaemia, impaired glucose tolerance, first degree relatives.

Resumen

Objetivo: El objetivo de este estudio era determinar la prevalencia y los factores de la prediabetes (PD) entre los familiares de primer grado (FDR) de los sujetos con diabetes tipo 2 (T2D) en la metrópolis de Abakaliki, estado de Ebonyi, Nigeria.
Material y métodos: Se seleccionaron 100 participantes (70 hombres y 30 mujeres) mediante un muestreo dirigido por los encuestados y se les entrevistó sobre sus conocimientos, síntomas comunes e historia familiar de la T2D. Se recogieron muestras de sangre venosa después de un ayuno nocturno y 2 horas después de una dosis oral de 75g de glucosa anhidra. Las muestras se recogieron en frascos de oxalato de flúor, se mantuvieron a 40C y se analizaron en la hora siguiente a la recogida por el método de la glucosa oxidasa. Los datos se analizaron con el programa SPSS 20.0 y se resumieron como media y desviación estándar.
Resultados: Veintidós FDR (17 hombres y 5 mujeres) tenían EP, lo que arroja unas tasas de prevalencia del 22%, 24,3% y 16,7%, respectivamente, para la totalidad de la población del estudio, los hombres y las mujeres. 13 (11 hombres y 2 mujeres; 84,6% y 6,7%) de los FDR con EP tenían sólo IFG, mientras que 3 (4,3 y 10% respectivamente) tenían sólo ATG. Sólo 3 varones (4,3%) tenían tanto IFG como ATG. El IMC de los sujetos con ATG (23,80 ± 2,68 kg/m^2) fue significativamente mayor que el de los sujetos con ATG (22,09 ± 1,94 kg/m^2) (p = 0,028). Los sujetos femeninos con EP tenían un IMC significativamente mayor (21,8 ± 3,38 vs 21,73 ± 3,15 kg/m^2; p = 0,035) que los FDR masculinos. Casi el 25% de los sujetos FDR de T2D en Abakaliki tienen EP y están en riesgo de desarrollar diabetes.
Conclusiones: Hay más hombres que mujeres afectados. La masa corporal, entre otros, puede ser un factor contribuyente.

Palabras clave: Prediabetes, glucemia alterada en ayunas, tolerancia alterada a la glucosa, familiares de primer grado.

Introduction

Pre-diabetes (PD) is a health condition with blood glucose level above normal but lower than the defining limits for T2D. A person with PD, has blood glucose levels consistently high but not yet high enough to be classified as type 2 diabetes[1]. The presence of PD is considered a risk factor rather than a clinical entity in its own right[2]. Individuals with PD may have one of these conditions- impaired fasting glycaemia (IFG), impaired glucose tolerance (IGT) or both. The risk factors for PD include: being overweight. being 45 years or older, having a parent, brother, or sister with type 2 diabetes and being physically active less than 3 times a week.

According American Diabetes Association, PD can be defined by a glycated hemoglobin (HbA1c) between 5.7 and 6.4%. Individuals with PD may be euglycemic in their daily lives as shown by normal or near normal HbA1c[1]. IGT manifests hyperglycaemia only when standard oral glucose tolerance test is performed and it may be directly involved in cardiovascular diseases[3]. Subjects with PD have increased risk of progressing to diabetes and macro-vascular complications.

Not all individuals with PD progress to T2D []. 50% remain in their abnormal glycemic state, 25% revert to normal glucose tolerance leaving 25% to progress to T2D,[4]. Aging, high total cholesterol, high LDL-cholesterol, high conicity index and longer urban residence after migration were significantly associated with pre-diabetes, were associated with prediabetes[5]. IGT and IFG have heterogeneous pathogenesis and different rates of progression to diabetes[6]. Both present with IR but the sites of IR differ. Elevated hepatic insulin resistance is a typical finding in IFG, with almost normal skeletal muscle sensitivity. Individuals with IFG have moderate hepatic IR and impaired early (1=30 minutes) exocytosis of insulin from secretory vesicles during OGTT,[6,7]. Because the late phase plasma insulin response is intact and muscle sensitivity is normal or near-normal, the 2 hour glucose returns to the initial FPG level[6]. Those with IGT have moderate to severe muscle insulin resistance with small changes in liver sensitivity [DeFronzo and Abdul-Ghani, 2011] and impaired early and late insulin (60-120 minutes) response during OGTT[8]. Although FPG is not elevated, there is a progressive and sustained PG rise during OGTT and 2 hour level remain above the fasting level[6]. Individuals with IFG have normal 2 hour PG but their 1 hour PG level may be elevated. Similarly, the 1 hour level in those with IGT exceeds those with NGT and is higher than the 2 hour values during OGTT. The 1 hour PG concentration during OGTT correlates more strongly with insulin secretion, insulin resistance and insulin secretion/insulin resistance index than the 2 hour PG concentration. Subjects with both of the conditions have approximately double the rate of developing diabetes compared with subjects with just one. Both conditions are associated with metabolic syndrome and manifest insulin resistance and impaired insulin secretion[2,9]. However, there are differences in the nature of these defects between these conditions[10]. Because PD is not a clinical entity, it progress to T2D without the sufferer being aware of it. Early detection and control of PD will lead to delay in the development of the condition and/or its complications[9,10]. To the best of our knowledge, no studies have reported the prevalence of PD in Abakaliki adult population.

Materials and Methods

This case-control study enlisted 100 FDRs of T2D subjects and 100 apparently healthy non relative of diabetes subjects as control. Sample size was calculated using the formula by Cochram[11]. The subject were not receiving any drug treatment at the time of sample collection. The FDRs had first degree relatives with clinical diabetes or family history of diabetes to qualify for inclusion in the study. The control subject had no FDR with diabetes or family history of diabetes. Ethical approval was obtained from the Ethic Committee of Ebonyi State University Teaching Hospital and informed consent was obtained before sample collection.

Anthropometric measurements were taken for the calculation of BMI using standard methods. Two milliliters of blood was collected from the ante cubital vein using standard method. Thereafter each of the FDRs received 75g of oral anhydrous glucose powder in 250ml of clean cold water and a second blood sample was collected 2 hours post glucose load. Collected samples were kept at 40C until analyzed usually within 3 hours of collection using the Glucose oxidase method of Trinder as described by Cheesbrough[12].

Data were entered in MS Excel 2007 sheet and analyzed using SPSS for Social Science software version 20.0 (SPSS Inc. Chicago, IL, USA) and summarized as means and standard deviations for quantitative variables. Differences between continuous variables were analyzed using Student's "t" test and statistical significance was placed at $p<0.05$.

Prediabetes was diagnosed as FPG between 5.6 and 6, 1 mmol/l and/or 2hppG between 7.8 and 11.0 mmol/l[9].

Results

22 FDRs – (17 male and 5 females) had PD. These gave prevalence rates of 22%, 24.3% and 16.7% respectively for the entire study, males and females populations respectively. 13 (11 male, 2 females) of FDRs with PD had IFG only (84.6 and 6.7%) while 3 each – (4.3 and 10%) - had IGT only. 3 males (4.3%) had both IFG and IGT.

Table I: Showing comparison of the characteristics of the subjects with and without PD.

Group/Parameter	BMI (kg/m²)	FPG (mmol/l)	2hppG (mmol/l)	Age (years)
FDRs (100) Controls (100) p-value	21.77 ± 3.24 20.66 ± 2.73 0.017	4.73 ± 1.01 4.33 ± 0.67 0.028	5.55 ± 1.29 4.77 ± 0.39 0.030	25.44 ± 4.44 24.56 ± 2.73 0.046
Male FDRs (70) Female FDRs (30) p-value	21.73 ± 3.15 21.8 ± 3.38 0.035	4.53 ± 0.95 4.24 ± 1.15 0.058	5.58 ± 1.23 5.47 ± 1.45 0.572	22.42 ± 3.25 23.51 ± 2.54 0.056
IFG (16) IGT (3) p-value	22.09 ± 1.94 23.80 ± 2.68 0.028	6.20 ± 0.47 5.00 ± 1.73 0.073	6.66 ± 1.31 9.50 ± 1.35 0.049	23.09 ± 2.64 24.08 ± 1.74 0.052

The FDRs of T2D subjects with or without PD had significantly higher FPG, (4.73 ± 1.01mmol/l vs 4.33 ± 0.67; p = 0.028), 2hppG, (5.55 ± 1.29mmol/l vs 4.77 ± 0.39; p = 0.030) and BMI, (21.77 ± 3.24 kg/m^2 vs 20.66 ± 2.73 kg/m^2; p = 0.017). (**Table I**).

Male subjects with PD had higher FPG, (4.53 ± 0.95mmol/l, vs 4. 24 ± 1.15 P =0.014) and higher 2hppG, (5.58 ± 1.23mmol/l vs 5.47 ± 1.45mmol/l; p = 0.572) than the female FDRs. However, the female FDRs had significantly higher BMI than their male counterpart, (21.8 ± 3.38 vs 21.73 ± 3.15 p = 0.035) (**Table I**).

FDRs with IFG had significantly higher FPG, (6.20 ± 0.47 mmol/l vs 5.00 ± 1.73; p = 0.073). However, IGT subjects had significantly higher BMI (23.8 ± 2.68 kg/m^2 vs 22.09 ± 1.94 kg/m^2) and 2hppG (vs 9.50 ± 1.35 vs 6.66 ± 1.31 mmol/l; p = 0.049; p = 0.028) than those with IFG, (**Table I**).

Discussions

This study recorded a prevalence of PD of 22% among the FDRs of T2D. In a study.in the general population of the same geographical zone as this, Ezeala-Adikaibe et al. [13] reported a prevalence of 7.6%. Majority of the FDRs with PD (19 out of 22) were males giving a prevalence of 27% and 10% for male and female FDRs. Much higher figures than these have earlier been reported for Nigeria and sub-Saharan Africa with projected increases worldwide by 2035[14,15]. Ogbu *et al*.[16] reported a prevalence of 15.5% for apparently healthy subjects within the same age range in Owerri Municipality in Imo State in the same geographical zone as the current studies. The prevalence of PD among the male FDRs was significantly higher than among the females, (27% vs 10%). This agrees with the report of Ogbu *et al*.[16] but there does not seem to be any explanation for this yet.

According to Tirosh *et al*.[17], individuals with glucose levels approximating 5.2 mmol/l, considered as normal and below the IFG threshold, are at increased risk for developing diabetes. In this study several of the FDRs but none of the control had FPG above this threshold. It is conceivable that postprandial glucose levels below 7.8 mmol/l, the cut off point for defining IGT, also confer increased risk for developing T2D[18]. Curiously none of the FDRs in this study attained this level of postprandial glucose level. According to Weir and Bonner-Weir[19], the level of plasma glucose that define IGT occurred rather late just before conversion to diabetes. This is in line with the concept that total body glucose disposal can gradually worsen from normal tolerance to IFG to IGT and then to T2D. Consequently, there are more FDRs with IFG (16; 16%) than IGT (3; 3%) or IFG plus IGT (3; 3%). This is not in agreement with Ogbu *et al*.[16] who recorded, 30.6%, 62.4% and 7.0% respectively. The later 2 stages, IGT and IFG plus IGT, are terminal stages of PD and individuals do not remain long in them before entering clinical diabetes. However, individuals can live with IFG for much longer time before progressing to IFG plus IGT and then diabetes. IGT and IFG have heterogeneous pathogenesis and different rates of progression to diabetes[20]. Subjects with both conditions, IFG plus IGT, have approximately double the rate of developing diabetes compared with subjects with just one.

From the result of this study, it would appear that being FDR predisposes to presence of metabolic syndrome, (MetS). The FPG, 2hppG and BMI of the FDRs with or without PD were significantly higher than those of the controls though not yet in the range for the definition of MetS[21]. One of disposing factors for PD and MetS is age. The subjects used for this study were all above 35 years of age so it is not possible to predict from this study at what age factors of MetS and PD started to manifest in them. To confirm this, it is would be necessary to study younger FDRs. From the results of the current study, it is apparent that BMI is a factor in the different plasma glucose concentrations recorded. Though within the range considered normal, 18-23 kg/m^2, significant differences exist along with PG of groups as can be seen from **table I**. One study reported that weight did not influence the development of overt diabetes or prediabetes conditions[22].

Not adequate attention is given to PD in the prevention of diabetes. This is evident from the paucity of current literature on the topic. However, individuals at risk of

developing T2D when diagnosed at the PD stage can be saved from the scourge of diabetes. With lifestyle changes, the progression to clinical diabetes can be delayed or even prevented and even when diabetes eventually results, the complications will not be as severe as otherwise[23]. The long period of time it takes to progress to diabetes should be taken advantage of to stop PD subjects progressing to diabetes. This is possible if people at risk do their blood glucose, fasting and 2hpp, annually and are followed up to ensure the glucose concentration is not rising even within the range considered normal. PD subjects are prone to cardiovascular events and macro-vascular complications[5,24].

Conclusion

One quarter of the population of FDRs of type 2 diabetes subjects in Abakaliki have PD and are at risk of developing diabetes. More men than women were affected. Body mass, among others, is a contributing factor. Because the work was carried out in the capital city only, the results may not be representative of the entire state. It is recommended that PD be accorded the status of clinical entity to prevent, by simple life-style changes, sufferers progressing to diabetes.

Authors Contributions'

ISIO conceived and supervised the project; EEJ, OEI, OCC, UUA and EIO took part in the identification, collection and analysis of samples.

Authors' Declaration of Conflict of Interests

The authours declared that there is no conflict of interest.

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ORIGINAL

Awareness and Practice of Caregivers toward Type 1 Diabetes Among Children in Khartoum State 2021

Conciencia y práctica de los cuidadores hacia la diabetes tipo 1 entre los niños del estado de Jartum 2021

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Abstract

Background: Type 1 diabetes, also known as juvenile diabetes or insulin-dependent diabetes, is a chronic autoimmune disease in which the pancreas produces very little or no insulin due to autoantibodies against the β-cell of the pancreas. Insulin is a hormone that is required for sugar (glucose) to enter cells and produce energy. Knowledge of disease and socioeconomic status (SES) of family, mother, and caregiver plays an important role in the management of diabetes, especially type 1 diabetes in children.
Objective: To assess the Awareness and Practice of caregivers toward Insulin dependent diabetic children in Khartoum State 2021.
Methodology: It was a descriptive, cross-sectional hospital-based study conducted at Sudan's childhood diabetes center. Data were collected through interviewer-administered data collection sheets on the children's caregivers (Google form).
Results: A total of 93 caregivers of type 1 diabetic children participated in this study; according to the demographic data of the children; their age range from 4 to 14 years, 51 (55%) children were aged from 5-10 years, and 33 (36%) were aged more than 10 years, and 9 (10%) were aged less than 5 years with an average age of 9 years. According to the maternal educational level; most of the mothers 57 (61%) graduated from university. Of most of the fathers 36 (39%) were employees, and 30 (32%) were free workers. According to the awareness and attitude, type 1 diabetes; all (100%) of them were aware of to use of insulin (ideal dose, site of injection, storage of insulin, injection with supervisor or alone), 81 (87%) of the caregivers were aware to types of diabetes, 81 (87%) of them were aware to Hb A1C, 78 (84%) of them were aware to home blood glucose monitoring (HBGM), and FBG, 78 (84%) of the participants were aware to types of diet (number of meal/day, types of meals/day, sugar content or not, exercise or not on exercise), and 78 (84%) of the participants were aware symptoms of hypoglycemia and hyperglycemia. However, some of the participants had poor awareness regarding diabetes retinopathy and nephropathy.
Conclusion: According to our findings, caregivers with more diabetes awareness and education were able to keep their children's glycemic control better regardless of socioeconomic status. In addition, in the routine questions asked of the diabetic patient and the care provider, a method of assessing socioeconomic changes such as loss of income, divorce, and disability must be incorporated. The majority of the participants in the study had a positive outlook on type 1 diabetes.

Key words: Type 1 diabetes mellitus, Awareness, Practice of Caregivers, Children, Khartoum, Sudan.

Resumen

Antecedentes: La diabetes de tipo 1, también conocida como diabetes juvenil o diabetes insulinodependiente, es una enfermedad crónica autoinmune en la que el páncreas produce muy poca o ninguna insulina debido a los autoanticuerpos contra la célula β del páncreas. La insulina es una hormona necesaria para que el azúcar (glucosa) entre en las células y produzca energía. El conocimiento de la enfermedad y el estatus socioeconómico (SES) de la familia, la madre y el cuidador juegan un papel importante en el manejo de la diabetes, especialmente de la diabetes tipo 1 en los niños.
Objetivo: Evaluar el conocimiento y la práctica de los cuidadores hacia los niños diabéticos dependientes de la insulina en el Estado de Jartum 2021.
Metodología: Se trata de un estudio hospitalario descriptivo y transversal realizado en el centro de diabetes infantil de Sudán. Los datos se recogieron mediante hojas de recogida de datos administradas por un entrevistador a los cuidadores de los niños (formulario de Google).
Resultados: Un total de 93 cuidadores de niños diabéticos tipo 1 participaron en este estudio; según los datos demográficos de los niños; su edad oscila entre los 4 y los 14 años, 51 (55%) niños tenían entre 5 y 10 años, y 33 (36%) tenían más de 10 años, y 9 (10%) tenían menos de 5 años con una edad media de 9 años. Según el nivel educativo materno, la mayoría de las madres, 57 (61%), tenían estudios universitarios. De la mayoría de los padres 36 (39%) eran empleados y 30 (32%) eran trabajadores libres. Según el conocimiento y la actitud, la diabetes tipo 1 todos (100%) conocían el uso de la insulina (dosis ideal, lugar de inyección, almacenamiento de la insulina, inyección con supervisor o sola), 81 (87%) de los cuidadores conocían los tipos de diabetes, 81 (87%) conocían la Hb A1C, 78 (84%) conocían la monitorización de la glucosa en sangre en casa (HBGM) 78 (84%) de los participantes conocían los tipos de dieta (número de comidas al día, tipos de comidas al día, contenido de azúcar o no, ejercicio o no ejercicio), y 78 (84%) de los participantes conocían los síntomas de la hipoglucemia y la hiperglucemia. Sin embargo, algunos de los participantes tenían poco conocimiento sobre la retinopatía y la nefropatía diabéticas.
Conclusión: Según nuestros hallazgos, los cuidadores con mayor conocimiento y educación sobre la diabetes fueron capaces de mantener mejor el control glucémico de sus hijos, independientemente del nivel socioeconómico. Además, en las preguntas rutinarias que se hacen al paciente diabético y al cuidador, debe incorporarse un método para evaluar los cambios socioeconómicos, como la pérdida de ingresos, el divorcio y la discapacidad. La mayoría de los participantes en el estudio tenían una visión positiva de la diabetes tipo 1.

Palabras clave: Diabetes mellitus tipo 1, Conciencia, Práctica de los cuidadores, Niños, Jartum, Sudán

Introduction

Type 1 diabetes (T1D) is a multifactorial disease in which both genetic predisposition and environmental factors promote the triggering of autoimmune responses against pancreatic beta cells, which ultimately result in beta cell destruction and severe impairment of insulin secretion[1]. The incidence of type 1 diabetes is increasing at a rate of 3% to 5% per year based on studies reviewed from the United States, Germany, Poland, and Italy[2]. Type 1 diabetes mellitus (T1DM) results from the destruction of pancreatic β-cells that is mediated by the immune system. Multiple genetic and environmental factors found in variable combinations in individual patients are involved in the development of T1DM. Genetic risk is defined by the presence of particular allele combinations, which is the major susceptibility locus (the HLA region) that affects T cell recognition and tolerance to foreign and autologous molecules. Multiple other loci also regulate and affect features of specific immune responses and modify the vulnerability of β-cells to inflammatory mediators[3].

A variety of presenting symptoms has been described, the most common being the classical triad of polyuria, polydipsia, and weight loss. In addition, the frequency of presentation in the life-threatening condition of diabetic ketoacidosis (DKA) reported in the literature is variable from 10 to 80%[4].

The effects of glycemic extremes on the developing human brain's structure and function are of increasing interest to both diabetes and clinical neuroscience communities[5]. Severe hypoglycemia is a significant and relatively common complication of insulin treatment in children with type 1 diabetes[6]. The long-term cognitive effects of such episodes have been debated. One hypothesis is that severe hypoglycemia occurring early in development is more harmful to cognitive function than severe hypoglycemia later in development, but few data address this issue directly. If this hypothesis was correct, it could explain the consistent finding that early onset of type 1 diabetes predicts poorer cognitive function[7,8].

Treatment of individuals with type 1 diabetes in the acute care setting often differs greatly from the care required by type 2 diabetics. Clinicians should be aware that type 1 diabetics may have difficulty with fasting requirements and may need more intensive glucose monitoring and modifications to existing insulin therapy. Patients with type 1 diabetes are considered at high risk for hypoglycemia during periods of fasting and diabetic ketoacidosis if their basal insulin is not administered. Nurses and all members of the care team should be aware that basal insulin should not be held without specific indications[9].

The ADA applies the general diabetes nutrition principles to patients with type 1 or types 2 diabetes. The current recommendation includes a focus on healthy food patterns rather than strict diets. Nutrient-dense foods and high quality are recommended, such as whole grains, fruits, vegetables, low-fat dairy, and lean proteins. Highly processed foods with added sugar are discouraged. The ADA also recommends an individualized medical nutrition therapy program provided by a registered dietician[10]. These interventions have been shown to decrease hemoglobin A1c values by nearly 1% in type 1 diabetics, particularly when carbohydrate counting is a primary focus[11]. Patients who ask about nutritional supplements should be advised that without evidence of underlying deficiency, no benefit has been seen from additional herbal or non-herbal supplementation, such as cinnamon[12].

Materials and methods

Study design

It was a descriptive, cross-sectional hospital-based study.

Study area

This study conducted at the Sudanese childhood diabetes center is an independent charitable voluntary non-profit based in coordination between volunteers and families of children with diabetes are directly intended Boamah that those who work in the organization of Aatkadon salaries and allowances of any Aatkadon any party.

Study duration

This study was conducted during the period from May 2021 to January 2022.

Study population

All caregivers with an adiabatic child were in the study area during the study period.

Data collection tools and methods

Data were collected through interviewer-administered data collection sheets on the children's caregivers (Google form). A specially designed questionnaire was prepared for this purpose and filled by the principal investigator and trained registrars of pediatrics specialty in Sudanese childhood diabetes detailed information will be collected from the hospital records.

Study variables

Dependent variables, Knowledge of the mother about her child's illness and emergencies. Independents Variables, demographic age, residence, occupation, and education level.

Data analysis and interpretations

Dara analyzed Statistical Package for Social Sciences SPSS. The data will be calculated as numbers, and % frequencies. The Chi-square test was used for categorical variables and to find an association among them. Statistically, the mean value is accepted as $P<0.05$, which was considered a significant difference.

Ethical considerations:

Ethical approval will be obtained from SMSB counsel of the Council of Pediatrics and Child Health. Ethical approval will be obtained from SMSB ethical research committee and EDC. Ethical approval will be obtained from the Ministry of Health Ethical approval will be obtained from the selected hospital. A verbal informed consent and personal data confidentiality will be provided to participants by using serial codes instead of names.

Results

It was a cross-sectional hospital-based study conducted in Khartoum state the estimated sample size was 113; 10 patients were excluded due to other co-morbidities. A total of 93 caregivers of insulin-dependent diabetic children participated in this study; according to the demographic data of the children; their age ranges from 4 to 14 years, 51 (55%) children were aged from 5-10 years, 33 (36%) were aged more than 10 years, and 9 (10%) were aged less than 5 years with an average age of 9 years. Most of them 69 (74%) were females, and 24 (26%) were males.

Despite the residence, the majority of the population 39 (42%) live in Khartoum north (Bahri), and 36 (39%) live in Khartoum, followed by 12 (13%) living in Omdurman. According to the maternal educational level; most of the mothers 57 (61%) graduated from university, 18 (19%) studied secondary school, and 15 (16%) were postgraduates. Most of the studied population 78 (84%) had a moderate income, 9 (10%) had a low income, and 6 (7%) had a high income. Most of the fathers 36 (39%) were employees, 30 (32%) were free workers, and 9 (9.7%) were doctors, while most of the mothers 48 (52%) were housewives, 15 (16%) were employees, and 6 (7%) were doctors (**Table I**).

Moreover, almost half 48 (52%) of the studied population had a positive family history of DM, among them, 30 (63%) had a history from the father's side, 9 (19%) had a history from the mother's side, and 9 (19%) had a history from both sides. The majority of the population 69 (74%) had type 1 DM, while 24 (26%) had type 2 DM. According to the awareness and attitude insulin-dependent diabetes; all of them were aware of to use of insulin, 81 (87%) of the caregivers were aware of types of diabetes, 81 (87%) of them were aware of Hb A1C, 78 (84%) of them were aware to RBG, and FBG, and 72 (77%) of them aware to hypoglycemia, hyperglycemia, and dietary needs of diabetic patients. furthermore, they have poor awareness of diabetic retinopathy, diabetic nephropathy, and diabetic ketoacidosis (**Table II**). There was no significant association between income and awareness of insulin-dependent diabetes *P-value*>0.05 Some variables were significantly associated with *P-value*<0.05 (**Table III**). There was a significant association between the educational/cognitive performance and awareness of insulin-dependent diabetes *P-value*<0.05 while there was no significant association between RBG & FBG and awareness of insulin-dependent diabetes *P-value*>0.05 (**Table IV**).

Table I: The distribution of caregivers of type 1 diabetic children according to their occupation (N=93).

Fathers' occupation	Frequency	Mothers' occupation	Frequency
Doctor	9 (10%)	Doctor	6 (7%)
Employee	36 (39%)	Employee	15 (16%)
Engineer	6 (7%)	Housewife	48 (52%)
Free worker	30 (32.3%)	Teacher	9 (10%)
Other	12 (13%)	Other	15 (16%)
Total	93 (100%)	Total	93 (100%)

Table II: The awareness and attitude of caregivers regarding type 1 diabetes (N=93).

Awareness and attitude variables	Frequency	
	Yes	No
Types of diabetes	81 (87%)	12 (13%)
Use of insulin	93 (100%)	0 (0%)
Dietary needs of diabetic patients	72 (77%)	21(22.6%)
Hypoglycemia	72 (77%)	21 (23%)
Hyperglycemia	72 (77%)	21 (23%)
Diabetic retinopathy	45 (48%)	48 (51%)
Diabetic nephropathy	48 (52%)	45 (48%)
Diabetic ketoacidosis	63 (68%)	30 (32%)
Hb A1C	81 (87%)	12 (13%)
RBG	78 (84%)	15 (16%)
FBG	78 (84%)	15 (16%)

Table III: The association between the income and awareness toward type 1 diabetes. (N=93).

Awareness and attitude variables		Income				P-value
		High	Low	Moderate	Total	
Types of diabetes	No	0	3	9	12	0.11
	Yes	6	6	69	81	
Use of insulin	No	0	0	0	0	-
	Yes	6	9	78	93	
Dietary needs of diabetic patients	No	0	6	15	21	0.01
	Yes	6	3	63	72	
Hypoglycemia	No	1	4	15	21	0.01
	Yes	6	3	63	72	
Hyperglycemia	No	0	5	16	21	0.01
	Yes	6	3	63	72	
Diabetic retinopathy	No	3	6	39	48	0.64
	Yes	3	3	39	45	
Diabetic nephropathy	No	3	6	36	45	0.51
	Yes	3	3	42	48	
Diabetic ketoacidosis	No	0	6	24	30	0.02
	Yes	6	3	54	63	
Hb A1C	No	0	0	12	12	81
	Yes	6	9	66	81	
RBG	No	3	0	12	15	0.03
	Yes	3	9	66	78	
FBG	No	2	1	12	15	0.03
	Yes	3	9	66	78	

Table IV: The association between the educational/cognitive performance and awareness toward type 1 diabetes.

Awareness and attitude variables		Educational/cognitive performance				Total	P-value
		Excellent	Good	Moderate	Weak		
Types of diabetes	No	3	3	6	0	12	0.001
	Yes	27	45	6	3	81	
Dietary needs of diabetic patients	No	3	9	6	3	21	0.001
	Yes	27	39	6	0	72	
Hypoglycemia & Hyperglycemia	No	3	6	9	3	21	0.001
	Yes	27	42	3	0	72	
Diabetic retinopathy	No	12	21	12	3	48	0.001
	Yes	18	27	0	0	45	
Diabetic nephropathy	No	9	21	12	3	45	0.001
	Yes	21	27	0	0	48	
Diabetic nephropathy	No	9	21	12	3	45	0.001
	Yes	21	27	0	0	48	
Diabetic ketoacidosis	No	6	12	9	3	30	0.001
	Yes	24	36	3	0	63	
Hb A1C	No	3	6	3	0	12	0.81
	Yes	27	42	9	3	81	
RBG & FBG	No	3	9	3	0	15	0.50
	Yes	27	39	9	3	78	

Discussion

The current study included 93 caregivers of insulin-dependent diabetic children ranging in age from 4 to 14 years, with the most common age group being 5-10 years, with 51 (54.8 percent) children with an average age of 9 years. Females outnumbered males. Iversen et al. conducted another study on children with type 1 diabetes aged 1 to 7 years[13]. Their research sheds light on what it's like for mothers and fathers to have a child with T1D. We'll discuss the following key findings: Sub-themes: A life-changing situation, always on guard, and struggling to let go considering existential dimensions involved; lived body, lived time, lived space, and lived relations to others[14]. This is consistent with the study's phenomenological foundation. According to Saad et al., the peak incidence age was between 11 and 15 years (15.9/100,000). The incidence rates in children under the age of five and between the ages of 16 and 19 were 8.4 and 7.7/100,000, respectively. There was no statistically significant difference between men and women[15]. The study reported a different peak age than the current study. According to the current study's maternal educational level, 57 (61 percent) of the mothers had completed university. The majority of those in the study, 78 (84 percent), earned a middle-class income. The majority of fathers (38.7 percent) worked, while the majority of mothers (48.6 percent) stayed at home with their children. A Sudanese study reported that 32.3% of caregivers were primary/ intermediate level of education, while 34.3% were post graduated. Regarding the study of Alboushi et al, there was an improvement in the awareness of caregivers which was noticed by a change in knowledge, attitudes, and practice toward improving the control of diabetes among their children[16]. Higher-educated caregivers perform better on knowledge tests, which leads to improved glycemic control[15,17]. Based on this information, interventions such as knowledge assessments and appropriate education may help to reduce any knowledge disparities based on income, which, while not significant in our study, may help to improve glycemic control in all children. With a *P-value* of 0.01 in this study, there was a significant relationship between socioeconomic income and knowledge of diabetic patients' dietary needs. According to the findings, caregivers' awareness is strongly related to their socioeconomic status. However, due to a lack of data on the relative contribution of diabetes complications in many African countries, estimates of diabetes costs may be understated[18]. In this study hypoglycemia and hyperglycemia are two diverse types of blood sugar levels. Hb A1C level *P-value*=0.04 and *P-value*=0.01. Alboushi et al, informed that health education had a significant effect, on regularly done HbA1C before intervention the percentage was 51.6%, but after the post-intervention 75.3%[19]. Al-Odayani et al. reported in a similar study that the socio-demographic data of mothers was recorded through self-report. It was discovered that there was a significant difference in diabetes knowledge among mothers of various ages (p>0.05). Mothers in their eighties and widowed mothers were more informed, but the difference was not statistically significant (p>0.05). There were no significant findings between family income and diabetes knowledge (p>0.05). Higher-income and knowledge, on the other hand, were found to have a positive relationship. There was a significant relationship between the mother's diabetes knowledge and HbA1C level (r=-0.1739, p0.05), indicating that greater knowledge leads to better HbA1c control [48]. Both studies agreed that having a good socioeconomic

and educational level will have a positive impact on mothers' awareness of diseases. These findings are in line with previous studies and support the effectiveness of diabetes education in assisting mothers who are caring for a child with diabetes to achieve better glycemic control. Only 2.4% of the children had HbA1c levels that were in the optimal glycemic control range, 31.32 percent were in the suboptimal glycemic control range, and 66.26 percent were in the poor glycemic control range, according to this pediatrics clinic[18-20].

Conclusion

Regardless of socioeconomic status, caregivers with more diabetes awareness and education were able to maintain better glycemic control of their children, according to our findings. In addition, a method of assessing socioeconomic changes such as loss of income, divorce, and disability must be incorporated into the routine questions asked of the diabetic patient and the care provider. The majority of the people in the study had a positive attitude toward type 1 diabetes mellitus (T1DM).

Recommendations

The current levels of diabetes knowledge in Sudanese mothers were only marginally better, indicating the need for additional educational assessments and supplemental diabetes education as needed such as social network support and first aid training centers. Further studies on a large scale are needed to obtain more generalized and accurate findings. Increase awareness regarding diet control by providing nutritional centers and nutritionists among the diabetic pediatric population and their caregivers. More diabetic care centers, and pediatric endocrinologists, should be provided for all social and economic differences. And health insurance should be available as a basic health care service for the population and should be taken seriously. Finally, this study backs up previous findings linking age, knowledge, and education levels to HbA1c profiles, revealing who is most at risk for poor glycemic control.

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Conflict of Interest

The author has declared that no competing interests exist.

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Tendencias en la hospitalización de complicaciones neurológicas de diabetes mellitus en el área de Palencia en el periodo 1993-2017

Trends in hospitalization for neurological complications of diabetes mellitus in Palencia between 1993 and 2017

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Resumen

Introducción: Se analiza el comportamiento de los ingresos hospitalarios en el área de salud de Palencia en el periodo 1993-2017 de pacientes con complicaciones neurológicas (CN) de Diabetes Mellitus (DM), basándose en la información registrada en el Conjunto Mínimo Básico de Datos (CMBD).

Material y métodos: Estudio de asociación cruzada de las altas hospitalarias del Complejo Asistencial Universitario de Palencia entre 1993-2017, a partir del CMBD, con los diagnósticos de DM y las subcategorías de DM con manifestaciones neurológicas. Análisis descriptivo general, bivariante, multivariante y análisis de regresión lineal de Joinpoint para comprobar cambios de tendencia.

Resultados: El CMBD consistió en 410218 registros; 48225 (11,8%) incluían los códigos 249.xx y 250.xx (CIE-9), y 969 (2%) presentaban CN. La hospitalización de pacientes con DM creció anualmente un 9,4 entre 1993-2008, un punto de ruptura en 2008, y se redujo anualmente el -0,3 entre 2008-2017. La hospitalización de pacientes con CN de DM creció anualmente un 3,4 entre 1993-2014, un punto de ruptura en 2014, y se redujo anualmente un -23.9 entre 2014-2017.

Conclusiones: El CMBD aporta información valiosa y extrapolable a la del conjunto de la población. Los modelos de regresión logística de joinpoint permiten cuantificar tendencias, comprobar cambios en las mismas, planificar recursos para atender demandas futuras de salud, y evaluar efectos de actividades preventivas. La publicación entre 2004 y 2008 de distintas guías de práctica clínica puede explicar la posterior reducción en las hospitalizaciones de pacientes diabéticos. Sin embargo, existe una infraestimación en las CN de DM en el CMBD.

Palabras clave: Diabetes mellitus; Neuropatía diabética; Ingreso hospitalario; Sistemas de información médicas

Abstract

Introduction: Trends of hospital admissions in the health area of Palencia in the period 1993-2017 of patients with neurological complications (NC) of Diabetes Mellitus (DM) is analyzed, based on the information recorded in the Minimum Basic Data Set (MBDS).

Methods: Cross-association study of hospital discharges from the Palencia University Assistance Complex between 1993-2017, based on the MBDS, with the diagnoses of DM and the subcategories of DM with neurological manifestations. General descriptive, bivariate, multivariate analysis and joinpoint regression analysis to check trend changes.

Results: The MBDS consisted of 410218 records; 48225 (11.8%) included the codes 249.xx and 250.xx (CIE-9), and 969 (2%) had NC. Hospitalization of patients with DM grew annually by 9.4 between 1993-2008, with a breaking point in 2008, and decreased annually by -0.3 between 2008-2017. Hospitalization of patients with NC of DM grew by 3.4 annually between 1993-2014, with a break point in 2014, and decreased annually by -23.9 between 2014-2017.

Conclusions: The MBDS provides valuable information that can be extrapolated to that of the population as a whole. Joinpoint logistic regression models make it possible to quantify trends, check changes in them, plan resources to meet future health demands, and evaluate the effects of preventive activities. The publication between 2004 and 2008 of different clinical practice guidelines may explain the subsequent reduction in hospitalizations of diabetic patients. However, there is an underestimation in the NC of DM in the MBDS.

Key words: Diabetes mellitus; Diabetic neuropathy; Hospitalization; Health information systems.

Introducción

En 2017 se estimaba que el número de diabéticos en el rango de edad de 18 a 99 años en el mundo ascendía a 451 millones (el 8,4% de la población mundial mayor de 18 años), y que en 2045 la cifra alcanzaría los 693 millones (el 9,9% de la población)[1]. La diabetes mellitus (DM) no sólo supone una importante causa de hospitalización, sino que condiciona una mortalidad hospitalaria 3,4 veces superior a la de pacientes no diabéticos[2]. Además, la presencia de DM es uno de los principales factores que influyen en una tasa de reingresos y unos costes de hospitalización más elevados[3]. Dichos costes se incrementan significativamente en presencia de complicaciones crónicas de DM, que llegan a ocasionar en torno al 30% del gasto hospitalario de los pacientes diabéticos[4]. De todas ellas, las complicaciones neurológicas (CN) prevalecen en aproximadamente el 8% de los pacientes en el momento del diagnóstico de la DM, pero pueden alcanzar hasta el 50% trascurridos varios años[5,6].

No obstante, a pesar de estas previsiones desfavorables, en los últimos años se advierte un cambio de tendencia en algunos países, con una reducción en el porcentaje de pacientes ingresados con angiopatía diabética y en la mortalidad por enfermedad cardiovascular entre la población con DM[3,7]. Sin embargo, son escasos los estudios en nuestro entorno que analicen la evolución de los ingresos hospitalarios de pacientes diabéticos con otro tipo de complicaciones, y su estudio puede ser importante para predecir la evolución natural de la enfermedad y los efectos que las distintas medidas realizadas ocasionan en la frecuentación, el gasto y la mortalidad[2].

Las bases de datos administrativas, como la de altas hospitalarias, han demostrado su utilidad en la obtención de información de procesos de alta prevalencia a lo largo del tiempo a falta de registros específicos[8]. El objetivo del presente estudio es el de, basándose en la información registrada en el Conjunto Mínimo Básico de Datos (CMBD), analizar el comportamiento de los ingresos hospitalarios en el área de salud de Palencia en el periodo 1993-2017 de pacientes con CN de DM, determinar cambios de tendencias y evaluar así el impacto de las intervenciones preventivas y terapéuticas aplicadas en los últimos años.

Material y métodos

Diseño y variables

Estudio de asociación cruzada de las altas hospitalarias del Complejo Asistencial Universitario de Palencia (CAUPA) entre los años 1993 y 2017, a partir del CMBD, que incluyeron, según la Clasificación Internacional de Enfermedades, 9ª revisión, modificación clínica (CIE-9-MC) desde 1993 hasta 2015, y según la CIE-10 los años 2016 y 2017, los siguientes diagnósticos, principales o secundarios, al alta (entre paréntesis, los códigos correspondientes a CIE-9):

- Diabetes mellitus secundaria (249.xx)
- Diabetes mellitus (250.xx)

Posteriormente se seleccionaron las subcategorías 249.6 (DM secundaria con manifestaciones neurológicas) y 250.6 (DM con manifestaciones neurológicas). Y se asociaron los códigos de la neuropatía diabética específica:

- Neuropatía autonómica periférica en trastornos clasificados bajo otros conceptos (337.1)
- Mononeuritis de miembro superior y mononeuritis múltiple (354)
- Mononeuritis de miembro inferior y sitio no especificado (355)
- Polineuropatía en diabetes (357.2)
- Síndromes miasténicos en enfermedades clasificadas bajo otros conceptos (358.1)
- Trastornos funcionales del estómago. Gastroparesia (536.3)
- Artropatía asociada con trastornos neurológicos (713.5)

Se incluyeron en el estudio variables como la fecha de nacimiento (edad en años), fecha de ingreso y fecha de alta (estancia en días), sexo, año, ámbito de residencia (Rural/Urbano), tipo de ingreso (Urgente/Programado) y tipo de alta (Domicilio/Traslado/Éxitus). Finalmente se registraron las comorbilidades más relevantes, de acuerdo a los siguientes códigos: Enfermedades infecciosas y parasitarias (001-139), neoplasias (140-239), enfermedad cardiaca (390-429), enfermedad cerebrovascular (430-438), enfermedades de las arterias, arteriolas y capilares (440-449), enfermedades de venas y linfáticos, y otras enfermedades del aparato circulatorio (451-459) y enfermedad renal (580-589)

Análisis estadístico

Se realizó un análisis descriptivo general de todas las variables demográficas y clínicas recogidas en el CMBD, considerando como nivel de confianza el 95%. Posteriormente se realizó un análisis bivariante entre los dos subgrupos (DM con CN y DM sin CN) utilizando tablas de contingencia y test de chi-cuadrado de Pearson o la prueba exacta de Pearson para las variables categóricas, t de Student para comparar dos grupos de variables continuas con distribución normal, y test de Mann-Whitney en caso de distribución no normal. Un análisis multivariante de regresión logística binaria por pasos evaluó la asociación de la CN con el resto de variables de interés. Para el cálculo de las tasas de hospitalización por habitantes se emplearon los datos poblacionales de la provincia de Palencia procedentes del Instituto Nacional de Estadística.

Y finalmente, para comprobar los cambios de tendencia del número de hospitalizaciones por 100.000 habitantes se utilizó el análisis de regresión lineal de Joinpoint, que comprueba la existencia de cambios estadísticamente significativos en el tiempo, detectando puntos de inflexión (o joinpoints). En cada segmento articulado por un joinpoint se calculó un porcentaje anual de cambio en la tendencia mediante modelos lineales generalizados, asumiendo una distribución de Poisson y mostrando su nivel de significación estadística asociado, con intervalos de confianza del 95% (IC95%). Se consideraron diferencias estadísticamente significativas los valores de p<0,05. Se utilizó el software de acceso libre del Programa de Investigación y Vigilancia del Instituto Nacional del Cáncer de Estados Unidos.

El diseño ha sido aprobado por el Comité Ético de Investigación Clínica del CAUPA.

Resultados

El CAUPA representa la totalidad de la atención especializada pública del Área de Salud de Palencia, coincidente con la provincia del mismo nombre más algunos municipios de la provincia de Burgos, y que en 2017 contaba con 163390 tarjetas sanitarias individuales. Desde 1993 hasta 2017 el CMBD de altas hospitalarias del CAUPA consistió en 410218 registros, de los que 48225 (11,8%) incluían los códigos 249.xx y 250.xx y fueron seleccionados para el presente estudio. En la **tabla I** se describen sus características generales y las diferencias entre los pacientes con CN y sin CN. El análisis multivariante que se muestra en la **tabla II** detalla estas diferencias. La **tabla III** muestra las frecuencias de los distintos subgrupos de las CN. Los servicios responsables del alta de estos pacientes fueron principalmente: Medicina Interna (35%), Cardiología (12%), Cirugía general (11%), Traumatología (7%) y Neumología (6%).

En el análisis de tendencias de la tasa de hospitalización de pacientes con DM en el CAUPA ajustada por edad (**Figura 1**), se observó una evolución ascendente desde 1993 hasta 2008 con un porcentaje anual de cambio de 9,4 (IC al 95%: 11,1 a 12,6; p<0,01), un punto de ruptura en el año 2008 (p<0,05), y posteriormente un porcentaje anual de cambio decreciente en el periodo 2008-2017 de -0,3 (IC al 95%: -2,4 a 1,8; p=0,7).

Respecto a la tasa de hospitalización de pacientes con CN asociada a DM (**Figura 2**), el porcentaje anual de cambio en el periodo 1993-2014 fue ascendente de 3,4 (IC al 95%: 1 a 5,8; p<0,01), evidenciándose un punto de ruptura en el año 2014 (p<0,05), y posteriormente un porcentaje anual de cambio decreciente en el periodo 2014-2017 de -23,9 (IC al 95%: -45,4 a 6,1; p=0,1).

Tabla I: Características generales de las altas hospitalarias de pacientes con DM en el Área de Salud de Palencia entre 1993 y 2017.

	Total	Con CN	Sin CN	p
Número de casos	48225	969 (2%)	47256 (98%)	
Edad (años)*	73,6±13,1	72,3±12	73,6±13	0,002
Sexo H M	 51,60% 48,40%	 528 (54,5%) 441 (45,5%)	 24364 (51,6%) 22892 (48,4%)	 0,07
Ámbito geográfico Urbano Rural	 53% 47%	 499 (51,5%) 470 (48,5%)	 25041 (53%) 22170 (47%)	 0,3
Tipo de ingreso Urgente Programado	 83;8% 16,20%	 865 (89,3%) 104 (10,7%)	 39561 (83,7%) 7725 (16,3%)	 <0,001
Tipo de alta Domicilio Traslado Alta voluntaria Éxitus	 87;8% 2,50% 0,20% 9,40%	 846 (87,3%) 21 (2,2%) 8 (0,8%) 94 (9,4%)	 41518 (87,9%) 1178 (2,5%) 108 (0,2%) 4452 (9,4%)	 0,03 0,8
Días de ingreso**	9±10	9,4±8,6	9±10	0,2
Tipo de DM Tipo 1 Tipo 2	 4,10% 95.9%	 68 (7%) 901 (93%)	 1888 (4%) 45368 (96%)	 <0,001
Infección	9,80%	80 (13%)	33 (9,4%)	0,09
Neoplasia	17%	60 (9,7%)	33 (9,4%)	0,86
Afectación cardiaca	76,20%	521 (84,4%)	268 (76,1%)	0,002
Afectación cerebrovascular	12%	106 (17,2%)	48 (13,6%)	0,14
Afectación vasos arteriales	8,40%	119 (19,3%)	78 (22,2%)	0,29
Afectación vasos venosos	5,60%	31 (5%)	15 (4,3%)	0,59
Enfermedad renal	17,90%	283 (45,9%)	86 (24,4%)	<0,001

*Media ±´desviación estándar. **Mediana ± rango intercuartil

Tabla II: Análisis multivariante. Diferencias entre los casos de DM con CN y sin CN.

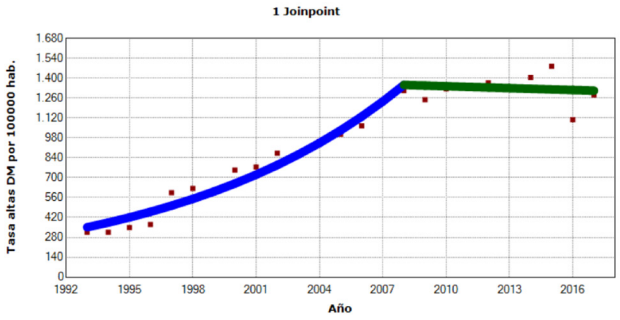
	p	OR cruda (IC al 95%)	p	OR ajustada (IC al 95%)
Edad en años	0,002	0,993 (0,988 a 0,997)	<0,001	0,989 (0,983 a 0,995)
Mujer vs varón	0,071	0,889 (0,782 a 1,010)	0,12	0,9 (0,79 a 1,03)
Ámbito rural vs urbano	0,340	1,064 (0,937 a 1,208)	0,197	1,09 (0,96 a 1,24)
Ingreso programado vs urgente	<0,001	0,615 (0,501 a 0,755)	0,05	0,81 (0,65 a 1,0)
Estancia en días	0,231	1,003 (0,998 a 1,009)	0,52	1,002 (0,996 a 1,008)
DM tipo 2 vs tipo 1	<0,001	0,55 (0,4 a 0,71)	0,85	0,97 (0,72 a 1,32)
Infección vs no infección	0,045	1,225 (1,005 a 1,494)	0,35	1,1 (0,9 a 1,36)
Neoplasia vs no neoplasia	<0,001	0,514 (0,415 a 0,638)	<0,001	0,6 (0,49 a 0,75)
Alteración cardiaca vs no alteración	<0,001	1,375 (1,168 a 1,619)	0,87	1,03 (0,74 a 1,4)
Alteración cerebrovascular vs no alteración	<0,001	1,400 (1,176 a 1,666)	0,059	1,2 (0,993 a 1,44)
Alteración de la circulación arterial vs no alteración	<0,001	2,882 (2,456 a 3,382)	<0,001	2,01 (1,8 a 2,5)
Alteración de la circulación venosa vs no alteración	0,225	0,831 (0,617 a 1,121)	0,18	0,81 (0,6 a 1,1)
Alteración renal vs no alteración	<0,001	2,903 (2,545 a 3,313)	<0,001	1,97 (1,7 a 2,28)

Variable dependiente: CN.
Variables independientes: Edad en años, sexo (mujer vs varón), ámbito geográfico (rural vs urbano), tipo de ingreso (programado vs urgente), estancia en días, tipo de diabetes (tipo 2 vs tipo 1), infección (si vs no), neoplasia (si vs no), alteración cardiaca (si vs no), alteración cerebrovascular (si vs no), alteración circulación arterial (si vs no), alteración circulación venosa (si vs no), alteración renal (si vs no).

Tabla III: Frecuencias de los distintos subgrupos de las CN.

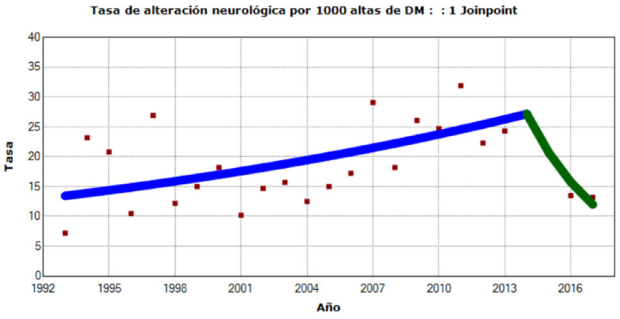
	Número de casos	Porcentaje sobre el total de casos con CN	Porcentaje sobre el total de casos de DM
Neuropatía autonómica periférica	157	16,2%	0,3%
Mononeuritis miembro superior y múltiple	90	9,2%	0,2%
Mononeuritis miembro inferior y NEOM	44	4,5%	0,1%
Polineuropatía en DM	617	63,6%	1,3%
Síndromes miasténicos	3	0,3%	0%
Gastroparesia	53	5,4%	0,1%
Artropatía	5	0,5%	0%
TOTAL	969		

Figura 1: Análisis de Joinpoint. Tasas de hospitalización de pacientes con diabetes mellitus en el CAUPA ajustadas por edad.



Punto de ruptura en el año 2008 (p<0,05). Porcentaje anual de cambio en el periodo 1993-2008: 9,4 (IC al 95%: 11,1 a 12,6; p<0,01). Porcentaje anual de cambio en el periodo 2008-2017: -0,3 (IC al 95%: -2,4 a 1,8; p=0,7).

Figura 2: Análisis de Join point. Tasas de hospitalización de pacientes con alteración neurológica asociada a diabetes mellitus por cada 1000 pacientes ingresados con diabetes mellitus en el CAUPA.



Punto de ruptura en el año 2014 (p<0,05). Porcentaje anual de cambio en el periodo 1993-2014: 3,4 (IC al 95%: 1 a 5,8; p<0,01). Porcentaje anual de cambio en el periodo 2014-2017: -23,9 (IC al 95%: -45,4 a 6,1; p=0,1).

Discusión

Destacamos la metodología empleada en el estudio por un doble motivo. Por una parte, el CMBD como fuente de información en el análisis de tendencias ha sido escasamente utilizado. El conocimiento sobre la prevalencia actual de CN de DM en la población general es limitada, ya que existen pocos estudios epidemiológicos comunitarios, y la mayoría de las observaciones se realizan sobre poblaciones seleccionadas[9]. En un entorno como el Área de Salud de Palencia, con un único complejo hospitalario público, y a falta de estudios específicos, el CMBD aporta información valiosa y extrapolable a la del conjunto de la población. Por otra, el uso de los modelos de regresión logística de joinpoint permite cuantificar tendencias y comprobar cambios en las mismas a lo largo del tiempo. De este modo podemos planificar los recursos necesarios en un futuro para atender una demanda de salud, e incluso evaluar efectos de actividades preventivas sobre un grupo poblacional[10]. Estos modelos han comenzado a utilizarse ya en el análisis de distintas patologías (neoplasias, enfermedades cerebrovasculares) con el objetivo de identificar políticas de salud locales potencialmente útiles[11,12].

En el presente estudio, más del 11% de los registros totales incluían los códigos 249.xx y 250.xx, con una tendencia al aumento de las tasas de hospitalización de pacientes con DM hasta el año 2008. A partir de entonces se comprueba un descenso en las mismas. Evidencias previas demuestran una reducción de la mortalidad por enfermedades cardiovasculares tanto en población general como en población con DM en los últimos años, relacionándose este hecho con un mejor control de los factores de riesgo cardiovascular y con la mejora de las intervenciones en las fases agudas de la enfermedad cardiovascular[3]. Dichas intervenciones, aplicadas en el ámbito de atención primaria, podrían contribuir no sólo a reducir la mortalidad, sino también las hospitalizaciones. En este caso debemos destacar la publicación entre los años 2004 y 2008 de las guías de práctica clínica de la American Diabetes Association, el National Institute for Clinical Excellence y el Ministerio de Sanidad y Consumo, y sus sucesivas actualizaciones, que si bien no fueron las primeras, sí fueron las de mayor impacto y difusión[13-18]. Coincidente en el tiempo, en el año 2008 comenzó a funcionar la Unidad de Diagnóstico Rápido del CAUPA, que pudo contribuir a la reducción de los ingresos.

Los datos difieren en lo referente a las CN. Se considera que entre el 5 y el 8% de los pacientes en el momento del diagnóstico de DM ya tienen polineuropatía, y que además es la complicación que más se incrementa a partir de ese momento, pudiendo afectar al 50% de los pacientes con DM a largo plazo[5,6]. Esto contrasta con los registros del CMBD. Una explicación es que hasta en un 50% de los casos la neuropatía es asintomática, no se detecta clínicamente y por tanto no se registra[19,20]. Otra hace referencia a un problema descrito con anterioridad: la infraestimación de la comorbilidad crónica en el CMBD. Este sesgo se produce tanto por ausencia de información suficiente en los informes de alta hospitalaria, como por una inadecuada correlación entre la DM y la CN, lo que conduce a una codificación de la complicación como entidad aislada, es decir como enfermedad neurológica y no como CN de DM[21,22]. Sin embargo, y a pesar de este sesgo, se comprueba un punto de ruptura en la tendencia en el año 2014, con

una significativa reducción en la tasa de hospitalizaciones de pacientes con CN de DM desde entonces. Este dato concuerda con la reducción de las complicaciones vasculares de DM que se observa desde hace años en determinadas poblaciones[7]. Todo apunta a un cambio de tendencia favorecido por la implementación de las Guías de Práctica Clínica en los últimos años, con un control más intenso de los pacientes con DM en todas las fases de su enfermedad.

Como limitaciones del estudio destacamos que los datos se obtuvieron retrospectivamente de un registro administrativo prolongado en el tiempo; si bien la codificación no ha sufrido cambios a lo largo de los años, las prácticas de codificación individuales sí han podido diferir ligeramente entre los médicos y codificadores. Otra limitación es la infraestimación de las CN de DM anteriormente descrita, que puede ser aún mayor con el registro según la CIE-10 que con la CIE-9.

Conflicto de intereses: ninguno.

La presente investigación no ha recibido ayudas específicas provenientes de agencias del sector público, sector comercial o entidades sin ánimo de lucro.

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ORIGINAL

Inflammatory markers in patients with asthma in a tertiary hospital in Uganda

Marcadores inflamatorios en pacientes con asma en un hospital terciario de Uganda

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Abstract

Introduction: Patients with asthma are known with increased hospital visits and sudden deaths. Aim. The study was done to evaluate the changes in hematological parameters and inflammatory markers of patients with asthma in KIU-TH, Ishaka, Uganda.
Methods: A total of 150 subjects were selected for the study comprising of 75 patients with asthma and 75 apparently healthy individuals from Ishaka, Bushenyi District attending KIU-TH.
Results: The results showed increase in total white blood cell count (P=0.000), Neutrophil (P=0.000) and no significant difference in Lymphocytes (P=0.406) of patients with asthma compared to apparently healthy individuals respectively. The results showed increase in hemoglobin (P=0.004), red blood cells (P=0.015), Packed Cell Volume (P=0.009), Mean Cell Volume (P=0.000), Red Cell Distribution Width (P=0.004) and decrease in MCHC (P=0.004) of patients with asthma compared to apparently healthy individuals respectively. The results showed increase in NLR (P=0.039), PDW (P=0.010), PCT (P=0.002), decrease in platelets (P=0.021), MPV (P=0.031) and no significant difference in PLR (P=0.066) in patients with asthma compared with the apparently healthy individuals respectively.
Conclusions: The study revealed increase in total white cell count (WBC), neutrophils and reduced levels of cell lines. It shows serious immunological alterations in the patients with asthma. The inflammatory markers as NLR and PLR were increased which showed increased inflammation in the patients with asthma. These indicators could be used to predict the severity of the disease and as well in improvement as regards prognosis of the patients.

Key words: asthma, hematological parameters, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), inflammation.

Resumen

Introducción: Los pacientes con asma son conocidos por el aumento de las visitas al hospital y las muertes súbitas. Objetivos. El estudio se realizó para evaluar los cambios en los parámetros hematológicos y los marcadores inflamatorios de los pacientes con asma en KIU-TH, Ishaka, Uganda.
Material y métodos: Se seleccionó un total de 150 sujetos para el estudio, compuesto por 75 pacientes con asma y 75 individuos aparentemente sanos de Ishaka, distrito de Bushenyi, que acudían a KIU-TH.
Resultados: Los resultados mostraron un aumento en el recuento total de glóbulos blancos (P=0,000), de neutrófilos (P=0,000) y ninguna diferencia significativa en los linfocitos (P=0,406) de los pacientes con asma en comparación con los individuos aparentemente sanos, respectivamente. Los resultados mostraron un aumento de la hemoglobina (P=0,004), de los glóbulos rojos (P=0,015), del volumen celular empaquetado (P=0,009), del volumen celular medio (P=0,000), de la anchura de distribución de los glóbulos rojos (P=0,004) y una disminución de la MCHC (P=0,004) de los pacientes con asma en comparación con los individuos aparentemente sanos, respectivamente. Los resultados mostraron un aumento de NLR (P=0,039), PDW (P=0,010), PCT (P=0,002), una disminución de las plaquetas (P=0,021), MPV (P=0,031) y ninguna diferencia significativa en PLR (P=0,066) en los pacientes con asma en comparación con los individuos aparentemente sanos respectivamente.
Conclusiones: El estudio reveló un aumento en el recuento total de glóbulos blancos (WBC), neutrófilos y niveles reducidos de líneas celulares. Esto muestra graves alteraciones inmunológicas en los pacientes con asma. Los marcadores inflamatorios como NLR y PLR estaban aumentados, lo que mostraba una mayor inflamación en los pacientes con asma. Estos indicadores podrían utilizarse para predecir la gravedad de la enfermedad y también para mejorar el pronóstico de los pacientes.

Palabras clave: asma, parámetros hematológicos, relación neutrófilos-linfocitos (NLR), relación plaquetas-linfocitos (PLR), inflamación.

Introduction

Hematological parameters are measurable blood indices that can be used as markers in the diagnosis and monitoring of certain physiological and pathological abnormalities. Hematologic parameters can be affected by medical conditions and immune responses that affect hematopoietic physiology. For example, allergic diseases can affect hematological parameters such as eosinophils and neutrophils[1-3]. Allergy is a disorder of the immune system in the form of hypersensitivity to an allergen. Asthma, allergic rhinitis, and eczema are common allergic diseases. Asthma affects the airways that carry air to and from the lungs. The lining of the airways in people with asthma may become swollen and inflamed. This swelling and inflammation makes the airways very sensitive to irritation and prone to allergic reactions. As airways narrow due to inflammation, less air can flow through them, causing tissue hypoxia and/or hypoxemia[4,5].

Asthma is a public health problem in all countries regardless of their level of development with 235 million people currently suffering from asthma[6]. Most asthma-related deaths occur in low- and middle-income countries. Asthma is underdiagnosed and undertreated. It causes significant distress to individuals and families and often limits an individual's activities throughout life[7,8]. The burden of asthma varies from region to region, depending on environmental and genetic factors. Regarding race and ethnicity, the prevalence of asthma was higher among blacks[9,10]. Asthma has reported 1.2 to 6.3 cases in most countries, with the highest prevalence (>20%) generally in Latin America and the English-speaking countries of Australia, Europe, North America, and South Africa. The lowest prevalence (<5%) was in the Indian subcontinent, Asia Pacific, Eastern Mediterranean, Northern Europe and Eastern Europe. In Africa, the prevalence is mainly observed at 10-20%, but the burden of asthma has been increasing worldwide over time[11]. Asthma is known to be an acute disease which presents with sudden onset and can alter the white cell arrangement thereby affecting the immunity of the patients. It shows that asthma affects the levels of WBC and neutrophils and suppresses lymphocytes.

Typical changes in asthma include eosinophilia and reticular thickening, which can increase the size of chronic airway smooth muscle and increase the number of mucous glands. Eosinophils, basophils, and neutrophils play important roles in the pathogenesis of allergic diseases. Therefore, this study aimed to determine hematological parameters and some inflammatory markers in patients with asthma[12].

Materials and methods

Study area

The study was done in Ishaka Uganda at Kampala International University Teaching Hospital, Ishaka, Uganda. Kampala International University Teaching Hospital, Ishaka, Uganda. Is located in the Western part of Uganda and serves both Western Uganda populace and entire Uganda.

Study Design

The study adopted cross-sectional hospital based design with purposive sampling technique where patients who attended the hospital with asthma were selected for the study on purposive sampling technique and the platelets and some inflammation markers were evaluated with the apparently healthy individuals who attended the hospital on other issues not for disease issues.

Sample Size calculation

The sample size was collected according to formulary of Araoye[13]

$N=z^2\ pq/d^2$

n=sample size, z=95%=1.96, p= prevalence, q=1-p, d=0.05

The prevalence of asthma in Uganda according to Kirenga *et al*.[14] is 11%=0.11,

q=1-0.11, q=0.89

$n=1.96^2 \times 0.11 \times 0.89/0.05^2$

=150.437

=150 of asthma patients

Therefore, a total of 150 subjects were selected for the study comprising of 75 patients with asthma and 75 apparently healthy individuals from Ishaka who have not presented with history of asthma or obstructive areaway disease who attended KIU-TH, Ishaka, Bushenyi District.

Ethical issues

Ethical approval was obtained from the institution and informed consent obtained from the subjects. The details of the study were fully explained to the subject before they gave their consent and they willing participated in the study and confidentiality assured to them.

Blood Collection and Laboratory Investigations

About 3ml of venous blood was collected from antecubital fossa following aseptic techniques into EDTA containers for FBC determinations. The laboratory investigations were carried out at Hematology Laboratory of KIU-TH, Ishaka, Uganda. The full blood counts of the subjects were determined using Mlndray BC-3000 Plus.

Data analysis

The data were analyzed using student t-test and present as mean ± standard deviation using SPSS version 20 and level of significance set at $P<0.05$

Results

Tabla I: Mean values of WBC, Neutrophils and Lymphocytes of patients with asthma and control subjects.

Parameters	Asthma	Control	P-Value
WBC (X10⁹/L)	13.37±0.72	4.83±0.35	0.000*
Neu (X10⁹/L)	9.19±0.21	5.27±0.40	0.000*
Lym (X10⁹/L)	2.37±0.60	2.90±0.79	0.406
HB (g/dl)	16.20±0.44	14.20±0.40	0.004*
RBC (X10¹²/L)	5.78±0.40	4.27±0.50	0.015*
PCV (%)	54.00±3.26	42.00±3.00	0.009*
MCV (fl)	94.50±0.62	83.33±1.53	0.000*
MCHC (g/dl)	29.47±1.10	33.67±0.58	0.004*
RDW (fl)	49.60±1.05	43.33±1.53	0.004*

The results showed that increase in WBC (13.37±0.72 X10⁹/L, 4.83±0.35 X10⁹/L, P=0.000), Neutrophil (9.19±0.21%, 5.27±0.40%, P=0.000) and no significant difference in Lymphocytes (2.37±0.60 X10⁹/L, 2.90±0.79 X109/L, P=0.406) of patients with asthma compared to apparently healthy individuals respectively. The results showed increase in hemoglobin (16.20±0.44g/dl, 14.20±0.40g/dl, P=0.004), red blood cells (5.78±0.40 X1012/L, 4.27±0.50 X1012/L, P=0.015), Packed Cell Volume (54.00±3.26%, 42.00±3.00%, P=0.009) , Mean Cell Volume (94.50±0.62fl, 83.33±1.53fl, P=0.000) , Red Cell Distribution Width (49.60±1.05fl, 43.33±1.53fl, P=0.004) and decrease in MCHC (29.47±1.10g/dl, 33.67±0.58g/dl, P=0.004) of patients with asthma compared to apparently healthy individuals respectively.

Tabla II: Mean values of inflammatory markers of patients with asthma and control subjects.

Parameters	Asthma	Control	P-Value
Platelets **(X10⁹/L)**	362.67±32.88	245.67±43.66	0.021
NLR	4.07±1.06	1.93±0.61	0.039
PLR	158.24±32.08	90.61±33.94	0.066
MPV (fl)	7.80±0.46	8.80±0.26	0.031
PDW(fl)	15.77±0.32	13.00±1.00	0.010
PCT (%)	0.25±0.02	0.14±0.02	0.002

The results showed increase in NLR (4.07±1.06, 1.93±0.61, P=0.039), PDW (15.77±0.32fl, 13.00±1.00fl, P=0.010), PCT (0.25±0.02%, 0.14±0.02%, P=0.002), decrease in platelets (362.67±32.88 X10⁹/L, 245.67±43.66 X10⁹/L, P=0.021), MPV (7.80±0.46fl, 8.80±0.26fl, P=0.031) and no significant difference in PLR (158.24±32.08, 90.61±33.94, P=0.066) in patients with asthma compared with the apparently healthy individuals respectively.

Discussion

v The results showed increase in total white blood cell count (P=0.000), Neutrophil (P=0.000) and no significant difference in Lymphocytes (P=0.406) of patients with asthma compared to apparently healthy individuals respectively. It shows that asthma may increase stress in the patients which in turn increases the level of WBC and neutrophil. These alterations in the white cell lineages will affect immunity of the patients. The oxidative stress of the patients will be elevated which may affect the red cell lineage too. These results are in agreement with the study of Hailemaryam *et al*[15]. *which* indicated absolute and relative counts of neutrophil, eosinophil and basophil white blood cell and erythrocyte sedimentation rate were significantly high in asthmatic patients compared to control group. On the other hand, absolute and relative counts of monocyte and lymphocyte were significantly low in asthmatic patients. The study also agreed with a study carried out in Southeast of Nigeria on hematological parameters of patients with asthma by Obeagu *et al*.[16] on WBC and decreased red cell line which contradicts the findings in this research here among the patients with asthma.

The study showed increase in hemoglobin, red blood cells, Packed Cell Volume, Mean Cell Volume, Red Cell Distribution Width and decrease in MCHC of patients with asthma compared to apparently healthy individuals respectively. The increase in red cell lines could be attributed to increased hematopoietic activities.

The study showed increase in NLR, PDW, PCT, and decrease in platelets, MPV and no significant difference in PLR in patients with asthma compared with the apparently healthy individuals respectively. The inflammatory markers such as NLR and PLR can be used to predict the frequency of visits to hospitals by the patients with asthma as a sign of inflammation.

Conclusion

The study revealed increase in total white cell count (WBC), neutrophils and reduced levels of cell lines. It shows serious immunological alterations in the patients with asthma. The inflammatory markers as NLR and PLR were increased which showed increased inflammation in the patients with asthma. These indicators could be used to predict the severity of the disease and as well in improvement as regards prognosis of the patients. The clinicians and health workers managing the patients should monitor the white cell levels and the inflammatory markers for prompt recovery and improvement of patients with asthma.

Conflict of Interest

The authors declare that no competing interests exist.

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ORIGINAL

Cardiovascular risk stratification in asymptomatic individuals in Bitola, North Macedonia by using High sensitive Troponin I Assay

Estratificación del riesgo cardiovascular en individuos asintomáticos de Bitola, Macedonia del Norte, mediante el uso de la prueba de troponina I de alta sensibilidad

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Abstract

Objectives: The aim of our prospective cohort study in Macedonia was to evaluate the distribution of hs-cTnI concentrations in health individuals to stratified cardiovascular risk.
Background: The latest generations of hs-cTnI could be used for the stratification of cardiovascular risk in the general population, using values within the normal range.
Methods: Study was performed from one year period in 2021 year. We measured hs-cTnI concentrations in 1201 participants 690 males and 511 females by using Abbott Architect analyzer.
Results: We found that elevated risk for cardiovascular event is higher in males compared to females, also we confirm that risk of cardiovascular events increase significantly with age in both sexes, but is predominant in males.
Conclusion: The hs-cTnI assay provides detection of troponin in a significant proportion of asymptomatic individuals. Hs-cTnI allows us to act preventively in patients at increased risk by including statin therapy, weight regulation or lifestyle changes, intensifying physical activity, while its values are parallel to the modification of cardiovascular risk. Patients should be informed that there is a possibility of cardiovascular risk assessment and more massive hs-cTnI examination.

Key words: hs-cTnI, troponin, cardiovascular disease, risk stratification.

Resumen

Objetivos: El objetivo de nuestro estudio de cohorte prospectivo en Macedonia fue evaluar la distribución de las concentraciones de hs-cTnI en individuos sanos para estratificar el riesgo cardiovascular.
Antecedentes: Las últimas generaciones de hs-cTnI podrían utilizarse para la estratificación del riesgo cardiovascular en la población general, utilizando valores dentro del rango normal.
Métodos: El estudio se realizó durante un período de un año en 2021. Se midieron las concentraciones de hs-cTnI en 1201 participantes, 690 hombres y 511 mujeres, utilizando el analizador Abbott Architect.
Resultados: Encontramos que el riesgo elevado de eventos cardiovasculares es mayor en los hombres en comparación con las mujeres, también confirmamos que el riesgo de eventos cardiovasculares aumenta significativamente con la edad en ambos sexos, pero es predominante en los hombres.
Conclusión: El ensayo hs-cTnI proporciona la detección de troponina en una proporción significativa de individuos asintomáticos. La Hs-cTnI permite actuar de forma preventiva en los pacientes con riesgo aumentado incluyendo el tratamiento con estatinas, la regulación del peso o los cambios en el estilo de vida, intensificando la actividad física, mientras que sus valores son paralelos a la modificación del riesgo cardiovascular. Se debe informar a los pacientes que existe la posibilidad de evaluar el riesgo cardiovascular y realizar un examen más masivo de hs-cTnI.

Palabras clave: hs-cTnI, troponina, enfermedad cardiovascular, estratificación del riesgo.

Introduction

Cardiovascular disease remains the leading cause of mortality worldwide, accounting for one-third of deaths[1,2]. Cardiovascular risk stratification has long been based on risk factors: atherosclerosis, demographic characteristics such as gender and age, lifestyle, smoking and physical inactivity, history of co morbidities, such as diabetes mellitus, arterial hypertension and obesity, and circulating biochemical markers, such as increased total cholesterol and low-density lipoprotein cholesterol[3]. The most important risk factor in recent times have more recently been incorporated into practical risk prediction tools developed by scientific bodies, such as the SCORE by the European Society of Cardiology or the cardiovascular risk calculator by the American Heart Association[4,5].

Troponin is a cardiac-specific structural protein and guidelines recommend its use for the diagnosis and management of acute coronary syndrome[6]. Newly established technologies allow precise measurement of low circulating troponin concentrations in the general population[7]. Troponin concentration correlates with myocyte necrosis and apoptosis. They further correlate with the prevalence of cardiovascular risk factors, metabolic disorders, and cardiac hypertrophy or dysfunction[8,9]. Assessment of circulating troponin concentrations using a robust, highly sensitive assay might therefore be suitable to predict first and subsequent adverse events[10,11]. Introduction of cardiac troponin I and troponin T, into clinical practice improved dramatically the differential diagnosis of acute chest pain, providing a reliable means for the accurate diagnosis of acute coronary syndromes[12]. The impact of troponin is indicated by the fact that the universal definition of myocardial infarction recommends a troponin rise and fall as the first requirement for the diagnosis of any form of myocardial infarction. In addition to diagnosis, troponin aid significantly in the monitoring of patients with acute coronary syndromes and in the decision-making in the case of non-ST segment elevation acute coronary syndromes[13]. Furthermore, pathological troponin elevation is observed in many disease states and hs-cTnI are independent prognostic markers in several cardiovascular and non- cardiovascular conditions, such as acute coronary syndromes, chronic coronary artery disease, acute and chronic heart failure, cancer therapy-related cardiotoxicity and chronic kidney disease[14,15].

The use of troponin in addition to diagnostic purposes can also be used for prognostic information. Patients presenting with clinical evidence of ischemia and increased troponin have worse outcomes than those without detectable troponin in the circulation[16]. Even in patients with stable coronary artery disease, high-sensitivity assays have demonstrated that detectable concentrations of troponin portend a higher incidence of heart failure and cardiovascular death[17]. Troponin has also been proven to be a potent, independent indicator of recurrent ischemic events, and an estimate for the risk of death among patients presenting with acute coronary syndromes. The risk of death from cardiovascular disease correlates with troponin levels.

Predicting cardiovascular risk is important in the prevention and treatment of cardiovascular disease. Many risk estimation systems are in existence[18,19,20]. Different guidelines recommend different risk score calculators to assess the 10-year cardiovascular risk and their management depending on their risk scores[21,22].

The latest generations of hs-cTnI have enabled us to improve the diagnostic capacity of hs-cTnI, with its help we earlier and safer control and exclusion of acute coronary syndromes and non-acute coronary syndromes pathophysiology[13,23,24,25]. One of the key analytical requirements of hs-cTnI assay in order to be characterized as 'high-sensitivity' is its detectability in >_50% of apparently healthy individuals, as set by the International Federation of Clinical Chemistry and Laboratory Medicine[26]. With the help of this feature we can accurately calculate the 99th percentile, which is considered the upper limit of normal, and imposes a very low limit of detection of single-digit pg/mL, significantly lower than the 99th percentile[7]. The commercially available hs-cTnI assays provide high-detectability rates in symptomatic individuals, reaching 96% or higher in some cases[7,27]. This considerable detectability in asymptomatic individuals gave rise to the hypothesis that hs-cTnI could be used for the stratification of cardiovascular risk in the general population, using values within the normal range, that is between the lower limit of detection and the 99th percentile of normal.

The detection of a low threshold for troponin detection in asymptomatic patients has led to the hypothesis that hs-cTnI can be used to stratify cardiovascular risk in the general population by using values in the normal range, which is between the lower limit of detection and the 99th percentile of normal. The aim of our study was to evaluate the distribution of hs-cTnI concentrations between the sexes in a prospective cohort study in Macedonia, to investigate whether the association of hs-cTnI and risk of cardiovascular death differs between women and men, and to assess whether sex-dependent differences in cardiovascular risk are modified by hs-cTnI concentrations.

Materials and methods

We made a prospective cohort study in Macedonia in Bitola city in the period of January 2021 to January 2022. Our study was approved by the ethics committee and all study participants signed a written informed consent. We measured hs-cTnI concentrations in 1201

participants 690 males and 511 females. We prepared questionnaires about the health condition of the respondents, and they were filled in by the participants, we did a physical examination, and we took blood from specially trained nurses. Future more we collected clinical data on height, weight, and waist and hip circumference. We measured systolic and diastolic blood pressure with an automated device.

For hs-cTnI the 99th percentile values in a healthy reference population have been reported to be 16 pg/ml in women and 36 pg/mL in men[7]. Before analysis, samples were centrifuged at 3000 relative centrifugal force for 15 min. We measured hs-cTnI using Abbott Architect analyzer, with STAT High Sensitive Troponin assay. The limit of detection for the assay was 1.9 pg/ml (range 0-50 000 pg/ml). We divided total patients in 8 age groups i.e. younger than 20 years, 21-30, 31-40, 41- 50, 51-60, 61-70, 71-80,81-90 years.

Exclusion Criteria:

- Patient's with increased hs-cTnI values higher than16 pg/ml in women and 36 pg/ml in men
- Patient's with type 2 diabetes mellitus
- Primary and secondary renal diseases,
- Patient's having confounding factors like fever, pregnancy, women in menstrual period, congestive cardiac failure etc.
- Hypertensive patients with BP ≥ 160/100 mmHg

Table I: Gender-specific risk stratification cut-offs of future cardiovascular event.

Troponin level		
Risk	**Male (pg/mL)**	**Female (pg/mL)**
Low risk of future cardiovascular event	<6	<4
Moderate risk of future cardiovascular event	≥6 to ≤12	≥4 to ≤10
Elevated risk of future cardiovascular event	>12	>10

Table II: Risk stratification of future cardiovascular event.

Risk stratification of future cardiovascular event		
Risk	**Males participants and %**	**Females participants and %**
Low risk	440 participants (64%)	389 participants (76%)
Moderate risk	123 participants (18%)	91 participants (18%)
Elevated risk	127 participants (18%)	31 participants (6%)

Table III: Age and sex mean hsTnI values (n=1201).

Age in years	Males		Females	
	No. of cases n=690	Mean values of hsTnI	No. of cases n=511	Mean values of hsTnI
<20	12	1.64±1.54	5	1.2±1.6
20-30	29	1.46±1.23	10	1.4±2.5
31-40	72	2.66±4.3	43	0.69±1.48
41-50	101	3.93±5.06	70	1.55±2.36
51-60	120	5.23±6.21	115	2.05±2.38
61-70	203	7.47±7.65	126	3.28 ±3.8
71-80	114	9.19±7.08	107	4.5±3.92
81-90	39	12.37±6.93	35	6.4±4.2

Results

The recommended sex-specific hs-cTnI cut-offs for cardiovascular risk stratification in asymptomatic individuals are shown in **table I**. The following cut-off points we used to aid in stratifying the risk of cardiovascular disease in asymptomatic individuals[29-31].

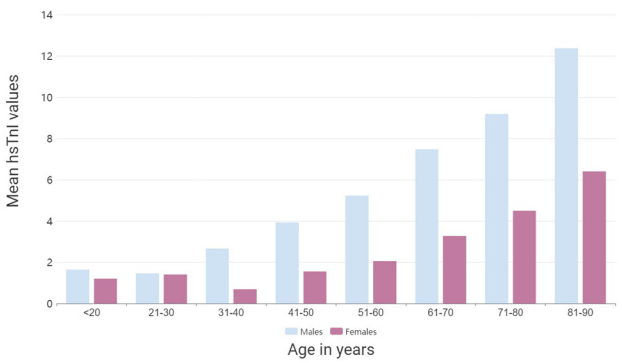
We measured circulating hs-cTnI concentrations in 690 (57%) men and 511 (43%) women. Mean age was 62±14,91 years for females, the age-range was 12-90 years, and mean age 57.93±16.07 years for males, and age-range was 7-90 years.

We evaluate the risk for cardiovascular event, and we found that elevated risk for cardiovascular event is higher in males compared to females. We found that 76% of females have low risk, 18% have moderate risk and 6% of females have elevated cardiovascular risk. Males with low risk were 64%, moderate risk have 18% and elevated risk for cardiovascular event have 18%.This dates are presented in **table II**.

Age and sex distribution of hsTnI values in all participants is mentioned in **table III**. We divided total patients in 8 age groups. Majority of patients belonged to 61-70 years in age group. We can notice that males in age group younger than 60 years have low risk for cardiovascular event; males in age groups 60 to 80 years have moderate risk for cardiovascular event and males older than 80 have elevated risk for cardiovascular event. About females, we can conclude that females younger than 70 years have low risk for cardiovascular event, and females older than 70 years have moderate risk for cardiovascular event.

In **figure 1** we present mean hsTn I value in different age groups in males and females.

Figure 1: Age and sex mean hsTnI values.



Discussion

The hs-cTnI assay provides detection of hs-cTnI in many asymptomatic individuals and can be used to overestimate the risk of cardiovascular events. Risk stratification in the asymptomatic population refers to the range of hs-cTnI values between the lower limit of detection and the 99th percentile of normal, but higher values are not included because they are indicators of disease. There are significant differences between men and women in terms of the prevalence of risk factors and the incidence of cardiovascular events. For instance, for a given age, blood pressure is higher in men than in women[32]; after puberty, left ventricular mass is greater in men than in women[33]; and women generally develop cardiovascular disease at an older age than men[34]. Age plays a vital role in the deterioration of cardiovascular functionality, resulting in an increased risk of cardiovascular disease in older adults[35,36]. The prevalence of cardiovascular disease has also been shown to increase with age, in both men and women, including the prevalence of atherosclerosis, stroke and, myocardial infarction[37].

The TIMI-IIIB study showed that in patients with acute coronary syndromes, mortality was higher in patients with elevated troponin I at the time of admission. Elevated troponin I level have an increased correlation with a relative risk of death of 7.8 among the group with the highest troponin levels, even after adjusting for age> 65, ST ECG depression, and other baseline variables. The GUSTO IIa study showed that elevated troponin T was significantly predictable for 30-day mortality in patients with acute myocardial ischemia, even after the assay was adjusted for electrocardiography category and CK-MB level[38].

The use of highly sensitive Troponin I allowed improved characterization of the cross-sectional distribution and correlations of cardiac troponin concentrations. The analysis of several studies confirmed that the circulating concentrations of cardiac troponins are significantly higher in men than in women[9,39-43]. The risk of cardiovascular events increases significantly with age in both sexes, but is predominant in males. In our study, we found that men under the age of 60 had a low risk of developing a cardiovascular; men aged 60 to 80 had a moderate risk of developing a cardiovascular, and men over the age of 80 had an increased risk of developing a cardiovascular disease. For females, we can conclude that females under 70 years of age have a low risk of cardiovascular event, and females older than 70 years have a moderate risk of cardiovascular event. According to the American Heart Association, heart disease and stroke in 2019 had an incidence of cardiovascular diseases of 77.2% in men and 78.2% in women aged 60-79 years, while the incidence of cardiovascular diseases was 89.3% in men and 91.8% in women, in adults over 80 years[44].

In the Nord-Trondelag health study of 9005 individuals without cardiovascular risk at baseline, the highest hs-cTnI tertiary (values> 10 ng/L in women and >12 ng/L in men) was associated with a 3.6-fold higher risk adjustment from cardiovascular death or hospitalization for myocardial infarct at median follow-up of 13.9 years compared with the lowest tertiary[31]. In another analysis of the same study, the predictive value of hs-cTnI for cardiovascular mortality was higher in women than in men (area below 0.84 versus 0.72)1[0]. This was confirmed by the ARIC study, which found that hs-TnI was more strongly associated with incidental coronary heart disease in women than in men[45]. These studies are very important because women are less involved in primary cardiovascular prevention and other cardiovascular examinations[46,47].

A comprehensive meta-analysis of 154,052 asymptomatic individuals showed that an increase in hs-cTnI and hs-cTnT within the reference values appropriate for both sexes, troponin levels were predictable for cardiovascular mortality and disease[48]; the highest third of hs-cTnI was associated with a 67% higher risk of fatal cardiovascular disease, a 59% higher risk of coronary artery disease, and a 35% higher risk of stroke compared to the lowest third. Some studies have shown that the prognostic value of hs-hs-cTnI is maintained in specific subgroups of the general population that are already at increased risk according to established risk factors, allowing further stratification of cardiovascular risk beyond these prognostic factors.

Conclusions and perspectives

The hs-cTnI assay provides detection of troponin in a significant proportion of asymptomatic individuals, enabling it to be considered for stratification of cardiovascular risk in the general population based on a single measurement. Hs-cTnI allows us to act preventively in patients at increased risk by including statin therapy, weight regulation or lifestyle changes, intensifying physical activity, while its values are parallel to the modification of cardiovascular risk. Patients should be informed that there is a possibility of cardiovascular risk assessment and more massive hs-cTnI examination. A guide to how to influence the lifestyle of patients at risk can be developed.

Conflict of Interest

The authors declare that no competing interests exist.

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ORIGINAL

Maternal Mortality in Jamaica: A Quantitative Analysis using time-series data, 2002-2021

Mortalidad materna en Jamaica:
Un análisis cuantitativo con datos de series temporales, 2002-2021

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Abstract

Introduction: Maternal Mortality Ratio (MMR) in Jamaica continues to be unavoidable in some cases. The pregnancy journey can be as unpredictable as the body undergoes many changes. The increase in maternal deaths can result from poor lifestyle choices and health service inequities. The Ministry of Health can implement mandatory antenatal care and encourage lifestyle programs to decrease maternal deaths in each community. This study assesses Jamaica's maternal mortality rate trend from 2000 to 2019.
Objectives: 1) To explore the trend of maternal ratio and 2) To determine the causes of maternal mortality. To establish some preventative measures for maternal mortality ratio.
Methods and material: Descriptive statistics, changes in percentages, and graphs were used to examine the incidence of maternal mortality ratio. Data collected from The World Health Organization and Statistical Institute of Jamaica was stored, retrieved, and analyzed using the Statistical Packages for the Social Sciences (SPSS) version 28.0 and Microsoft Excel.
Findings: The findings annually have been varied. However, a significant improvement since the year 2000. These findings show that the most annual change since 2000 was 53.05%, and the most minor was -25.03%.
Conclusion: The significant changes in maternal mortality since 2000 show that better health management and extra precautions can decrease maternal mortality annually.

Key words: Maternal, mortality, health, preeclampsia, preterm labor, depression, anxiety, eclampsia, hemorrhage.

Resumen

Introducción: La tasa de mortalidad materna (TMM) en Jamaica sigue siendo inevitable en algunos casos. Durante el embarazo el cuerpo experimenta muchos cambios. El aumento de las muertes maternas puede ser consecuencia de las malas elecciones de estilo de vida y de las desigualdades en los servicios sanitarios. El Ministerio de Sanidad puede implantar la atención prenatal obligatoria y fomentar programas de estilo de vida para disminuir las muertes maternas en cada comunidad. Este estudio evalúa la tendencia de la tasa de mortalidad materna en Jamaica desde 2000 hasta 2019.
Objetivos: 1) Explorar la tendencia de la tasa materna y 2) Determinar las causas de la mortalidad materna. Establecer algunas medidas preventivas para la tasa de mortalidad materna.
Material y métodos: Se utilizaron estadísticas descriptivas, cambios en los porcentajes y gráficos para examinar la incidencia de la tasa de mortalidad materna. Los datos recogidos de la Organización Mundial de la Salud y el Instituto de Estadística de Jamaica fueron almacenados, recuperados y analizados utilizando el Statistical Packages for the Social Sciences (SPSS) versión 28.0 y Microsoft Excel.
Resultados: Los hallazgos anuales han sido variados. Sin embargo, se observa una mejora significativa desde el año 2000. Estos hallazgos muestran que la mayor variación anual desde el año 2000 fue del 53,05%, y la menor del -25,03%.
Conclusión: Los cambios significativos en la mortalidad materna desde el año 2000 muestran que un mejor manejo de la salud y precauciones adicionales pueden disminuir la mortalidad materna anualmente.

Palabras clave: Maternidad, mortalidad, salud, preeclampsia, parto prematuro, depresión, ansiedad, eclampsia, hemorragia.

Introduction

The maternal mortality ratio represents the number of women who die from pregnancy-related causes per 100,000 live births. Jamaica's maternal mortality rate of 10.8 per 10 000 live births is considerably higher than the official rate of 4.8[1]. Most maternal deaths in Jamaica result from several avoidable factors: non-use of and deficiencies in antenatal care; inadequacy in ensuring the delivery in hospitals of high-risk women; and delays in taking action when signs of complications developed before, during, and after delivery. The most common causes of death in 1981-1983 were hypertensive diseases of pregnancy (26%), hemorrhages (20%), ectopic pregnancy (10%), pulmonary embolism (8%), and sepsis (8%). The largest group of avoidable factors is the non-use of any deficiencies in antenatal care; inadequacy in ensuring the delivery in hospitals of women at high risk; and delays in taking action when signs of complications initially develop, during, and after delivery[1].

Jamaica has experienced increased cases of deaths due to non-communicable diseases and non-obstetric causes[2,3], which is equally the same across the Caribbean[4]. Diabetes and Hypertension are known risk factors for maternal morbidity and mortality, and in these cases, obesity may be classified as an indirect cause posing risks to maternal health[5-8]. The leading causes of death were hypertensive disorders in pregnancy (19%) and hemorrhage (18%) in 2014[9].

Women who are obese account for 60% of death related to hypertension and all deaths from cardiac disease and diabetes[10-12]. The Maternal Health Task Force called for the following actions to be taken to address maternal mortality: i) measures to encourage women to seek antenatal care early in pregnancy; ii) improvements in antenatal monitoring; iii) the referral of high-risk women for hospital delivery; iv) the definition of standard procedures for dealing with specific complications of pregnancy (for example, eclampsia and hemorrhage; regionalization of obstetric services and criteria for referring patients to the hospital), and v) review of the provision of blood and plasma for emergency transfusions[13].

Literature review

"To improve maternal health, we have to focus on improving all women's health and access to care; not just during labor and delivery, but before and after pregnancy, and throughout their lives"[14]. Over the years, maternal death has robbed our nation of exceptional women with bright futures. The factors accounting for maternal mortality are similar across the globe[2,15]. Some of the factors accounting for maternal mortality are hemorrhages, obstructed labor, abortions, hypertensive diseases, sepsis or infections, embolism, ectopic pregnancy, and anesthesia-related deaths[15-19]. Other contributing factors are deficiency in the necessary medical care needed during childbirth and financial limitation to access medical care.

Approximately 700 women die yearly due to complications resulting from pregnancy in the United States[20]. Worldwide, 529,000 women die yearly from complications during pregnancy, childbirth, and postpartum[15]. Most of these deaths occur in developing countries, where fertility rates are very high, and a woman's risk of dying during pregnancy and childbirth is over 400 times higher compared to developed countries[21]. It is estimated that 20 million women endure lifelong disabilities such as pelvic pain, anemia, obstetric fistula, infertility and incontinence[22]. Some of the main leading causes of maternal death in developing countries are-unsafe abortion, eclampsia, obstructed labor, anemia, HIV, poor reproductive health care, such as not having access to severe bleeding, unsafe abortion, infection, eclampsia and obstructed labour; the indirect causes include anemia, malaria, heart disease, and HIV, poor reproductive health care, including not having access to proper health care during pregnancy and after childbirth, access to safe abortion where it legal, lack of education and poor nutrition.

According to a recent CDC report, the majority of maternal mortality deaths are related to cardiovascular conditions such as heart muscle disease (cardiomyopathy) (11%), blood clots (9%), high blood pressure (8%), stroke (7%), and a category combining other cardiac conditions (15%)[20]. Infection (13%) and severe postpartum bleeding (11%) are also leading causes. However, early identification and diagnosis of these conditions with the appropriate clinical interventions can save many lives[23].

What happens when a mother dies? According to the Ministry of Wellness and Health Jamaica, research reveals that approximately 1 million children are left motherless each year, making them 3 to 10 times more likely to die within two years of life than children who live with both parents. It is estimated that almost half of the 8 million infant deaths yearly result from poor maternal health and inadequate care during delivery"[11].

Based on a study done in Ethiopia, research shows that when a mother dies and the infant survives issues such as nutritional problems may occur due to lack of breastfeeding or inadequate artificial feed, which often results in the infant's death or increases the risk of infection[24]. The older children often suffer from school dropouts, disrupted education and living arrangements, and girls fall victim to early marriages, early childbearing and an increased risk of maternal death[25].

Several methods have been implemented to reduce maternal death. One of the most effective means of preventing maternal health is to improve health systems, especially primary health care that would ensure the

availability of skilled attendance at all levels and access to 24-hour emergency obstetric care. Family planning services could reduce maternal deaths and morbidities by preventing unwanted pregnancies. Access to safe abortion as allowed by law and post-abortion care services could reduce maternal deaths and injuries caused by unsafe abortions. Approximately 68,000 women die from unsafe abortions annually[22].

Methods and materials

The current study employed time series data for 20 years (2000-2019) collected from the United Nations Children's Fund (UNICEF) and the Statistical Institute of Jamaica (STATIN). The United Nations Maternal Mortality Estimation Inter-Agency Group (MMEIG) maintains an input database consisting of maternal mortality data from civil registration, population-based surveys, surveillance systems, censuses, and other specialized studies/ surveys (WHO, 2019). The maternal mortality ratio can be calculated by dividing recorded or estimated maternal deaths by total recorded or estimated live births during the same period and multiplying by 100,000. Measurement involves material on the timing of death (during pregnancy, childbirth, or within 42 days of termination of pregnancy), pregnancy status, and cause of death. Maternal mortality ratio = (Number of maternal deaths / Number of live births) X 100,000. The maternal mortality ratio can be computed directly from data gathered via household surveys such as Demographic and Health Surveys attempt to measure maternal mortality by asking respondents about the survivorship of sisters, vital registration systems, national surveys and surveillance data such as the maternal mortality surveillance database or are derived from community and hospital records.

A quantitative approach was utilized. The data was collected and analyzed using the Statistical Packages for the Social Sciences (SPSS). Descriptive statistics change in percentages, and graphs were used to examine the incidence of maternal mortality ratio.

Findings

Figure 1 displays Jamaica's Maternal Mortality rates from 2000-2019. Jamaica has been seeing an increase in Maternal Mortality Rate since 2000, with 2019 being the year with the highest maternal Mortality Rate Jamaica has seen over the two decades. **Table I** shows the percentage change in maternal mortality, with the most significant increase in 2019 of 53.05%. The year 2006 had the most significant decrease of -25.03%; however, it was not the year with the lowest maternal mortality ratio.

In **figure 2**, it can be seen that there was an increase in Maternal Mortality rates in Jamaica from 2015, a decrease in 2017 and 2018, after which a significant increase of 53.05% per cent in 2019.

Figure 3 displays the Frequency of the maternal death rates occurring in Jamaica between 2000-2019. The first Bar shows the number of deaths between 70 and 80 per 100,000 lives in the years 2001, 2003, 2006, 2007, 2008, 2009 and 2010. It further depicts that for four years, maternal mortalities occurred between 80 and 90 in 2004, 2005, 2013 and 2015. While for three years' maternal death was between 90 and 100 in the years 2011 2017 and 2018. It continues to show that for 2013, 2014, 2016, and 2019, the maternal deaths per 100 live births were over 100. The tale of the distribution indicates that the distribution is positively skewed, causing the mean to be greater than the median.

Figure 1: The Maternal Mortality Rate from 2000-2019.

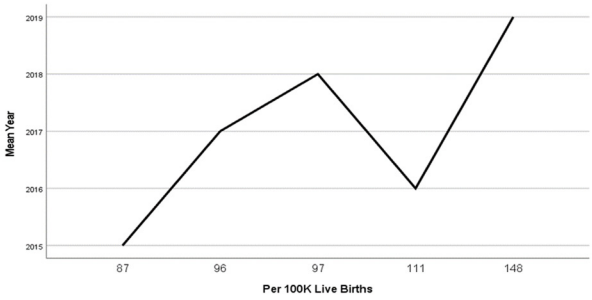


Figure 2: The Maternal Mortality Rate in Jamaica from 2015-2019.

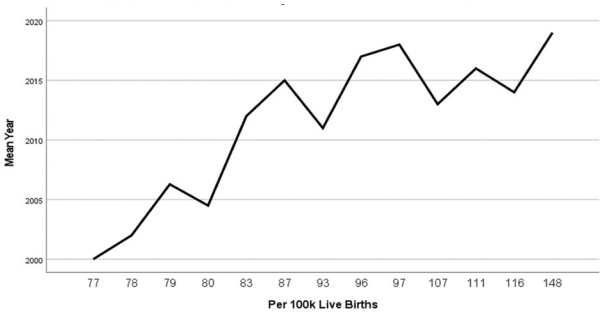


Figure 3: Frequency of Maternal Death Rates Occurring from 2000-2019.

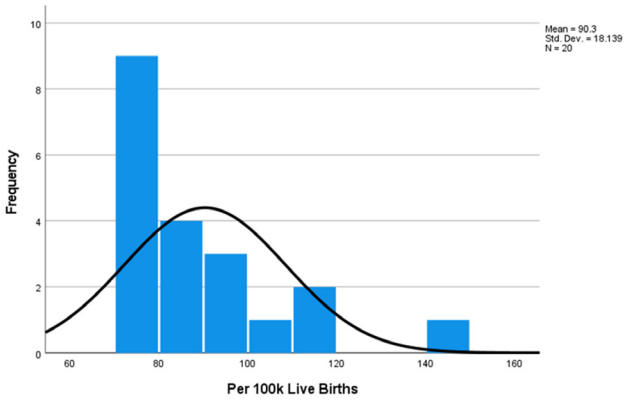


Table I below shows the maternal mortality ratio and the annual percentage change for 2000-2019. 2019 had the highest percentage change of 53.05% and the highest mortality ratio. The lowest per cent change was in 2015 at -25.03%.

Table I: Annual Per Cent Change and Maternal Mortality Ratio per 100k Live Births.

Year	Maternal Mortality Rate per 100K Births	Annual Percentage Change
2019	148	53.05%
2018	96.7	0.83%
2017	95.9	-13.29
2016	110.6	26.95
2015	87.1	-25.03%
2014	116.2	9.23%
2013	106.5	27.59%
2012	83.4	-10.51%
2011	93.2	17.97%
2010	79	0.00%
2009	79	0.00%
2008	79	0.00%
2007	79	0.00%
2006	79	-1.25%
2005	80	0.00%
2004	80	1.27%
2003	79	1.28%

Table II presents the main causes of maternal mortality. From the table, it can be deduced that over the two decades, Hypertensive disorders have been the leading cause of maternal mortality.

Table II: Causes of Maternal Deaths from 2000-2019.

Year	Maternal sepsis and other maternal infections	Maternal hypertensive disorders	Maternal hemorrhage	Ectopic pregnancy	Maternal abortion and miscarriage
2000	1	9	6	1	4
2001	1	8	5	1	4
2002	1	8	5	1	3
2003	1	7	4	1	3
2004	1	6	3	1	2
2005	1	7	3	1	3
2006	0	5	2	1	2
2007	0	5	2	1	2
2008	1	7	3	1	3
2009	0	4	2	1	1
2010	1	7	2	1	2
2011	0	6	2	1	2
2012	0	5	2	1	2
2013	0	6	2	1	2
2014	1	9	3	1	3
2015	1	7	2	1	2
2016	0	7	2	1	2
2017	0	6	2	1	2
2018	0	6	2	1	2

The maternal mortality ratio has been increasing in Jamaica (**Table III**). For the first decade (2000-2009), the average MMR was 79; for the other decade, 2010-2019, it increased to 101.6.

For the studied period (2000-2019), the average incidence of MMR for the two decades has been summarized in **figure 4**.

Table III: Average Incidence of Maternal Mortality Ratio (MMR) for the Periods 2000-2009 and 2010-2019.

Year	Maternal Mortality Rate per 100K Births	The average incidence of Maternal mortality
2019	148	101.6
2018	96.7	
2017	95.9	
2016	110.6	
2015	87.1	
2014	116.2	
2013	106.5	
2012	83.4	
2011	93.2	
2010	79	
2009	79	79
2008	79	
2007	79	
2006	79	
2005	80	
2004	80	
2003	79	
2002	78	
2001	79	
2000	77	

Figure 4: The Average Decade of Incidence of Maternal Mortality Ratio.

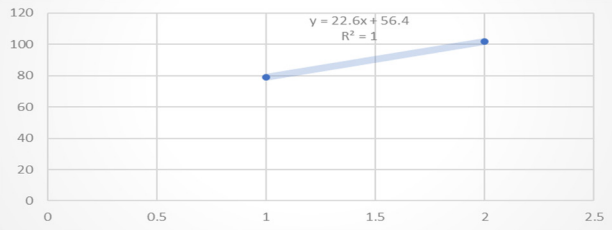
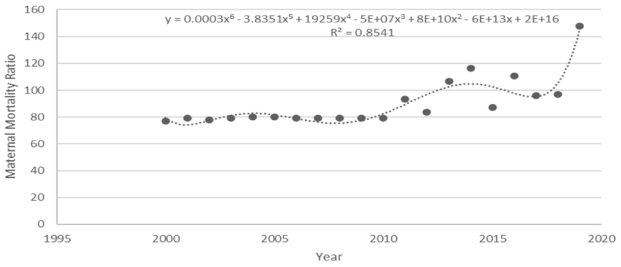


Figure 5: Annual Incidence of Maternal Mortality Ratio Per 100K Births.



Discussion

The impact of healthcare, even maternity care, takes place at a less fundamental level. At the outset of pregnancy, the health of some women and their babies is already disadvantaged through social inequalities based on class, ethnic background and residence. Such factors have been shown to influence the access to care and quality of care received by women from the lower class in society so that maternity care may compound rather than help alleviate existing social inequalities in health[26].

In Jamaica, the maternal mortality rate affects homes as the loss of this individual, who is said to be the primary caregiver at home, can undermine a family's ability to

gain necessities and vital life skills that only can be taught by a mother's perspective. Some factors that affect the mortality rate among expecting mothers in Jamaica are women of older age and lifestyle factors such as smoking and alcohol consumption. Despite these factors, Jamaica has been experiencing a slow and steady increase in maternal deaths and is slowly declining.

There have been some consequences of being overweight and obese for Jamaican women of reproductive age. This has been happening despite maternal health care services, including antenatal visits, postnatal care, and immunization coverage Kanguru et al. concluded that 63% of Jamaicans, aged 15-49 were obese; 6% were diabetic, 19% were hypertensive, and 3% were both[7]. These conditions are risk factors for morbidity and mortality; thus, obesity poses risks to maternal health in these cases. Research also showed that one in every ten women who died during or after childbirth happened to be overweight or obese.

Researchers found that in 2019, 1,125 or 3.3 per cent of the 33,462 mothers experienced pre-eclampsia in their deliveries, while the other hand, 1,219 or 3.6 per cent experienced postpartum hemorrhage. Pre-eclampsia and postpartum hemorrhage were the leading cause of illness and death among pregnant women in Jamaica in 2019[27]. The year 2019 also had the most significant percentage change of 53.05%.

From 2000-2019 the maternal mortality rate in Jamaica has stayed within the same range but slowly increased as the years went by, with 2019 reporting the highest; this research, therefore, offers some understanding and awareness of the maternal mortality rate present in Jamaica.

Conclusion

The Maternal mortality rate and its effect on our society from 2000 to 2019 has increased significantly in 2019 with a percentage of 53.05%. The leading cause of maternal mortality was hypertensive disorder in women, which increases the risk of death. However, with efficient monitoring during the antenatal visit and follow-up postpartum, the risk of pregnancy-related death may decrease. Thus, better management of health and taking the necessary precautions can help manage these rates.

Recommendations

Improving the quality of care offered to maternal mothers is founded on a holistic, human rights-based tactic for reproductive, sexual, and maternal health and is based on implementation efficiency. Firstly, the inequities in access to quality sexual, maternal and reproductive health care need to be tackled by intensifying efforts to reach vulnerable populations. Existing disparities must be identified and analyzed to tackle and reduce them[28].

They are secondly improving health systems to respond to the needs and priorities of women and girls. This strengthening will comprise hardware, for example safeguarding the availability of vital health infrastructure, commodities and amenities "software" such as the organization and management of service delivery, enhancing transparency and counteracting corruption. Priorities involve increasing health promotion and preventative services and improving the incorporation of all forms of care for women and adolescents. Governments should aid in providing resources to deploy health care providers such as midwives, doctors, and other skilled maternity care providers in ample numbers to meet population demands. Do professional associations play a crucial role in confirming norms for regulating healthcare workers and establishing professional standards for their education and core competencies?

Thirdly, ensure accountability to improve the quality of care and equity. They are planning for accountability highlights two equally significant dimensions: the enhanced capacity to measure and report progress towards ending preventable maternal mortality (EPMM) and the range of actions that citizens and civil society actors take to hold government and health system leaders accountable for their obligations in the area of maternal health care. Facility-level accountability promotes better maternal outcomes due to the creation of quality standards and performance measures that are appraised at the point of service through continuous quality enhancement activities. Lastly, monitoring and liability are fundamental human rights principles and critical aspects of the right to health that can help lower maternal mortality. Monitoring is key to assessing the scale of maternal mortality, its origins, and whether actions are being taken to deal with the difficulty. Indicators can be used to assist in monitoring progress and to emphasize where policy alterations may be necessary. The maternal mortality ratio is a standard indicator. Thus, the right to health necessitates that such indicators are disaggregated on grounds involving urban/rural, race and ethnicity[29].

Conflict of Interest

The authors declare that no competing interests exist.

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ORIGINAL

Mobile health system: A population based study

Sistema sanitario móvil: Un estudio basado en la población

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Abstract

Background: In this research, it is aimed to reveal the opinions of university students about mobile health and personal health records and to reveal whether this differs in the context of students' personal characteristics.
Methods: In the study, students' views on mobile health and personal health records were discussed in the context of effectiveness, access, benefit, protection, user-friendliness, simplicity and prevalence. In this direction, the face to face survey method, one of the data collection techniques, was used. The questionnaires were applied to Turkish and foreign students studying at Tokat Gaziosmanpaşa University.
Results: A total of 1654 individuals were included. 35.6% (n=590) of them were foreign students and 64.4% (n=1064) were Turkish students. The average age of all participants is 21.45 years. Turkish participants were a more positive attitude in this difference (Z=-20,375, p<0.05). it has been determined that there is a positive and significant relationship between age in the sub-dimensions of access and user-friendliness.
Conclusions: In the results obtained, it was determined that the students' attitudes towards mobile health and personal health records differed significantly according to their nationality.

Key words: Mobile Health, Personal Health Records, Simplicity, Prevalence.

Resumen

Antecedentes: En esta investigación, se pretende revelar las opiniones de los estudiantes universitarios sobre la salud móvil y los registros personales de salud y revelar si esto difiere en el contexto de las características personales de los estudiantes.
Métodos: En el estudio, las opiniones de los estudiantes sobre la salud móvil y los registros personales de salud se analizaron en el contexto de la eficacia, el acceso, el beneficio, la protección, la facilidad de uso, la simplicidad y la prevalencia. Para ello, se utilizó el método de encuesta cara a cara, una de las técnicas de recogida de datos. Los cuestionarios se aplicaron a estudiantes turcos y extranjeros que estudiaban en la Universidad de Tokat Gaziosmanpaşa.
Resultados: Se incluyó a un total de 1654 individuos. El 35,6% (n=590) de ellos eran estudiantes extranjeros y el 64,4% (n=1064) eran estudiantes turcos. La edad media de todos los participantes es de 21,45 años. Los participantes turcos mostraron una actitud más positiva en esta diferencia (Z=-20,375, p<0,05). Se ha determinado que existe una relación positiva y significativa entre la edad en las subdimensiones de acceso y facilidad de uso.
Conclusiones: En los resultados obtenidos se ha determinado que las actitudes de los estudiantes hacia la salud móvil y la historia clínica personal difieren significativamente según su nacionalidad.

Palabras clave: Salud móvil, Historia clínica personal, Simplicidad, Prevalencia.

Introduction

The recent changes and advancements in technology have had a tremendous impact on every industry, including the field of health services. The traditional health service delivery paradigm is altered as a result of these advancements, which also significantly alter patient expectations. Mobile technologies are one of these Technologies[1]. The rise in prices and patient volume in the sphere of health services, the inadequacy of health professionals, etc. Depending on the issues, it may be crucial to take use of the possibilities provided by mobile technology as a substitute for the long-term sustainability of the delivery of health services[2].

Around the world, governments are seeking solutions in order to reduce major concerns about the sustainability of health services[3]. While nations make enormous efforts to distribute health services that cover everyone, they also work hard to find answers to the cost increases seen in the health sector for a variety of reasons[4]. The delivery of healthcare services using mobile technology has come under scrutiny as a result of all these recent advancements in the health sector[5]. Patient records can be seen on these devices and the patient can access their medical information whenever they want using these technologies, which is one of the possible features offered by these technologies and offers enormous benefits to both the service provider and the user[6].

This study aims to establish what university students think about personal health records and mobile health system, as well as whether such perspectives vary depending on the student's individual characteristics.

Material and methods

The population of this study consists of 37950 students enrolled at Tokat Gaziosmanpaşa University for the 2021-2022 academic year, of whom 3500 are foreigners and 34450 are Turkish. The sample is made up of students who were chosen at random. The study included 1064 of 34450 Turkish and 3500 foreign students with 590 participants (a total: 1654 participants).

When gathering data for this study, the survey method was preferred. Face-to-face delivery of the questionnaires to the participants was accomplished. The survey includes an opinion scale on mobile health and personal health records in addition to questions that reveal the personal traits of university students. Koç and Bilgehan developed the scale[7]. There are a total of 31 statements in the scale, and these statements relate to the sub-dimensions of "effectiveness, access, benefit, protection, user-friendliness, simplicity, and prevalence." The statements that made up the dimensions were organized using a 5-point Likert scale, with 1 being the strongest disagreement and 5 being the strongest agreement. The scale's lowest possible score is 31, and its highest possible score is 155. The scale does not have a reverse score. The scale's internal consistency was examined using Cronbach's alpha value, which was determined to be 0.94. The said value was found to be 0.96 in this study.

Results

A total of 1654 individuals were included. 35.6% (n=590) of them were foreign students and 64.4% (n=1064) were Turkish students. The average age of all participants is 21.45 years. It is seen that Turkish participants mostly spend 4-6 hours a day on the Internet, while foreign participants spend 1-3 hours. Looking at the duration of use of smartphones by the participants, it is seen that Turkish participants use it mostly for 4-6 years, while the duration of use of foreign participants is 7 years or more. Considering the usage of mobile health applications, it is seen that there are more mobile health application users among Turkish and foreign participants. Finally, it is seen that Turkish participants using the mobile health application have been using this application for more than 2 years, while foreign participants have been using it for 1-6 months (**Table I**).

Table II shows the comparison results of the participants' views on mobile health and personal health records according to their nationality. Accordingly, in the context of the nationality variable, it was determined that the opinions of the participants about mobile health and personal health records differed significantly, and the opinions of the Turkish participants were more positive attitude in this difference ($Z=-20,375$, $p<0.05$). These results are similar in terms of sub-dimensions.

Table III shows the results of the correlation analysis between age and the participants' views on mobile health and personal health records. Accordingly, it was determined that there was no significant relationship between the views on mobile health and personal health records and age in Turkish participants ($p>0.05$, $r=0.060$). In this part, it has been determined that there is a positive and significant relationship between age in the sub-dimensions of access and user-friendliness. Similarly, it was found that there was no significant relationship between age and views on mobile health and personal health records among foreign nationals ($p<0.05$, $r=.007$). When considered in the context of all participants, it was determined that there was a significant relationship between age and views on mobile health and personal health records, and this relationship was negative ($r=-.098$, $p<.01$). This result is similar in terms of all sub-dimensions in the views on mobile health and personal health records.

Table I: Demographic data.

	Turkish Citizen		Foreign Citizen		Total	
Age	Mean 21.06	St. Deviation 1.823	Mean 22.15	St. Deviation 2.079	Mean 21.45	St. Deviation 1.988
Gender	**n**	**%**	**n**	**%**	**n**	**%**
Women	884	83.1	195	33.1	1079	65.2
Men	180	16.9	395	66.9	575	34.8
The time you spend daily on the internet	**n**	**%**	**n**	**%**	**n**	**%**
Less than 1 Hour	20	1.9	77	13.1	97	5.9
1-3 hours	193	18.1	247	41.9	440	26.6
4-6 hours	490	46.1	153	25.9	643	38.9
7 hours or more	361	33.9	113	19.2	474	28.7
How long have you been using a smartphone?	**n**	**%**	**n**	**%**	**n**	**%**
Less than 1 year	25	2.3	44	7.5	69	4.2
1-3 years	134	12.6	104	17.6	238	14.4
4-6 years	492	46.2	155	26.3	647	39.1
7 years and above	413	38.8	287	48.6	700	42.3
Have you ever used any mobile health app?	**n**	**%**	**n**	**%**	**n**	**%**
Yes	990	93.0	419	71.0	1409	85.2
No	74	7.0	171	29.0	245	14.8
If your answer is “Yes”. how long have you used this application?	**n**	**%**	**n**	**%**	**n**	**%**
1-6 months	114	10.7	207	35.1	321	19.4
7-12 months	78	7.3	80	13.6	158	9.6
1-2 years	263	24.7	75	12.7	338	20.4
More than 2 years	535	50.3	57	9.7	592	35.8

Table II: Comparison of Results of Views on Mobile Health and Personal Health Records by Nationality.

	Nationality	n	Mean Rank	Sum of Ranks	Z
The View of Mobile Health and Personal Health Records	Turkish Citizen Foreign National Total	1064 590 1654	1008.80 500.54	1073364.50 295320.50	-20.735*
Activity	Turkish Citizen Foreign National Total	1064 590 1654	985.33 542.88	1048386.00 320299.00	-18.110*
Access	Turkish Citizen Foreign National Total	1064 590 1654	994.77 525.84	1058438.00 310247.00	-19.216*
Benefit	Turkish Citizen Foreign National Total	1064 590 1654	995.48 524.56	1059195.50 309489.50	-19.271*
Protection	Turkish Citizen Foreign National Total	1064 590 1654	979.76 552.92	1042460.50 326224.50	-17.515*
User Friendly	Turkish Citizen Foreign National Total	1064 590 1654	977.15 557.63	1039683.50 329001.50	-17.224*
Simplicity	Turkish Citizen Foreign National Total	1064 590 1654	964.66 580.15	1026394.50 342290.50	-15.863*
Prevelance	Turkish Citizen Foreign National Total	1064 590 1654	958.30 591.62	1019631.50 349053.50	-15.115*

* p<0.05 (2-tailed)

Table III: Correlation Analysis Results of the Relationship Between Age and Views on Mobile Health and Personal Health Records.

Age	Turkish Citizen	Foreign Citizen	Total
The View of Mobile Health and Personal Health Records	.060	.007	-.098**
Activity	.051	.012	-.080**
Access	.090**	.002	-.074**
Benefit	.058	.020	-.081**
Protection	.021	-.012	-.105**
User Friendly	.064*	-.006	-.065**
Simplicity	.053	.010	-.073**
Prevelance	.040	-.034	-.086**

** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed).

Discussion

Health services are delivered and accessed using mobile health services and applications. Health professionals have supported the use of mobile health applications on smartphones since 2010. However, it has begun to use patient-facing mobile health applications[8]. Mobile health provides information on the closest hospital, pharmacy, step counter, heart rate monitor, meditation, and medications[9].

People who use mobile health applications benefit from having instant access to data, making appointments, and incorporating health recommendations into their daily lives around the clock. Mobile health applications have thus developed into an effective tool in the decision-making process of healthcare professionals regarding the patient, allowing for the storage of specific health data and the follow-up process to be realized when requested[10]. Mobile health applications enable remote disease management, professional collaboration, communication between patients and healthcare providers, and open access to resources regardless of location or time. With this use, patients can choose a doctor or hospital, schedule appointments online, reduce hospital wait times, and simultaneously access laboratory results from a distance. Approximately 80% of health managers think that mobile communication technologies should be used in health services[10]. According to the available statistics in 2012, 84% of smartphone users had downloaded at least one health-related app[11]. In our study, although the majority of them were Turkish citizens, it was found that 85% of the participants in total used mobile health services.

On the usability dimension, which states that the aforementioned technologies can be used by anyone easily, it has been observed that there is a generally positive opinion. Therefore, it can be concluded that personal health records and mobile health are generally well-received[12]. In this instance, it is possible to predict that these technologies will soon be embraced and proliferated. It can be said that this outcome will be a positive development in terms of more effective provision of health services in various aspects, given the potential and advantages of these technologies. In our study, it has been determined that there is a positive and significant relationship between age in the sub-dimensions of access and user-friendliness.

In the study by Arslan et al., participants between the ages of 18 and 20 were compared to participants between the ages of 21 and 23 regarding usability with regard to mobile health and personal health records; in terms of accessibility, those who use the internet primarily for shopping and reading news are those who use it for other purposes; and those who want to access their personal health records via a mobile device have a more positive opinion than those who do not[13]. Our study determined that there was no significant relationship between the views on mobile health and personal health records and age in Turkish participants (r=.060). Similarly, it was found that there was no significant relationship between age and views on mobile health and personal health records among foreign nationals (r=.007). When considered in the context of all participants, it was determined that there was a significant relationship between age and views on mobile health and personal health records, and this relationship was negative (r=-.098, p<.01).

In 2012, 84% of smartphone users had downloaded at least one health-related app, according to the data that was available. In addition, there have been some changes in the acceptance of technologies in health systems over the past few decades, and the public and policymakers have conflicting views on the application of new medical technology[14]. In our study, it is seen that there are more mobile health application users among Turkish compared to foreign participants.

Conclusions

Utilizing the mobile health system is crucial. It was determined that the student's attitudes towards mobile health and personal health records differed significantly according to their nationality. In the part of the difference, it was concluded that the attitudes of the Turkish participants were higher.

Conflict of Interest

The authors declare that no competing interests exist.

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ORIGINAL

Photorefractive keratectomy in Hyperopia: Refractive outcomes and Patients' satisfaction

Queratectomía fotorrefractiva en hipermetropía: Resultados refractivos y satisfacción de los pacientes

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Abstract

Background: This study was aimed to describe the factors that influence on refractive outcomes and patients' satisfaction after hyperopic photorefractive keratectomy (PRK).

Methods: 80 patients including 133 eyes undergoing primary PRK with a refractive target of emmetropia were assessed in this study. Patients underwent refractometry and Ophthalmologic examinations before and after operation. Refractive outcomes and patients' satisfaction, as the main studied variables, were assessed in patients. Liner and logistic regression were use the relation between satisfaction, predictability (- 0.5D POST OP SE≤ 0.5 D) as an indicator of refractive outcome, efficacy index and safety index, both as the indicators of visual outcome, with other studied variables.

Results: The mean of uncorrected visual acuity (UCVA) (log MAR before operation was 0.47 and after that was 0.07 (P-value=0.0001). The mean of postoperative best corrected visual acuity (BCVA) was not significantly different from preoperative. The mean of defocus equivalent was 1.35 ±0.94 before operation and 0.22 ±0.49 after operation. The mean of safety and efficacy were 1.01 and 0.91, respectively. Mean of patients' satisfaction score was 41.41 ±2.6 of 52 (Total Score). About predictability, 72.2% of studied eyes had post op SE within ±0.5 D of the intended refraction. Preoperative BCVA, index of success of astigmatism surgery and absolute angle of error were correlated variables to predict safety and efficacy index. Corneal haze was significantly correlated to predict patients' satisfaction score. Preoperative UCVA was significantly correlated to predictability.

Conclusion: Our findings suggest that PRK is a safe, predictable, and effective with good patients' satisfaction way of correcting of refractive error in hyperopic patients.

Key words: Photorefractive Keratectomy, Hyperopia, Refractive Outcome, Satisfaction.

Resumen

Antecedentes: El objetivo de este estudio es describir los factores que influyen en los resultados refractivos y la satisfacción de los pacientes después de la queratectomía fotorrefractiva (PRK) para hipermetropía.

Métodos: En este estudio se evaluaron 80 pacientes que incluían 133 ojos sometidos a PRK primaria con un objetivo refractivo de emetropía. Los pacientes se sometieron a una refractometría y a exámenes oftalmológicos antes y después de la operación. Se evaluaron los resultados refractivos y la satisfacción de los pacientes como principales variables de estudio. Se utilizó la regresión lineal y logística para establecer la relación entre la satisfacción y la predictibilidad (- 0,5D POST OP SE≤ 0,5 D) como indicadores del resultado refractive y el índice de eficacia y el índice de seguridad, ambos como indicadores del resultado visual.

Resultados: La media de no correcta agudeza visual corregida (UCVA) (log MAR antes de la operación fue de 0,47 y después de ella de 0,07 (valor P=0,0001). La media de mejor agudeza visual corregida (MAVC) postoperatoria no fue significativamente diferente de la preoperatoria. La media del equivalente de desenfoque fue de 1,35 ±0,94 antes de la operación y de 0,22 ±0,49 después. La media de seguridad y eficacia fue de 1,01 y 0,91, respectivamente. La media de la puntuación de satisfacción de los pacientes fue de 41,41 ±2,6 de 52 (puntuación total). En cuanto a la predictibilidad, el 72,2% de los ojos estudiados tuvieron una SE postoperatoria dentro de ±0,5 D de la refracción prevista. La AVC preoperatoria, el índice de éxito de la cirugía de astigmatismo y el ángulo de error absoluto fueron variables correlacionadas para predecir el índice de seguridad y eficacia. La turbidez corneal se correlacionó significativamente para predecir la puntuación de satisfacción de los pacientes. La UCVA preoperatoria se correlacionó significativamente con la predictibilidad.

Conclusión: Nuestros hallazgos sugieren que la PRK es una forma segura, predecible y eficaz, con buena satisfacción de los pacientes, de corregir el error refractivo en pacientes hipermétropes.

Palabras clave: Queratectomía fotorrefractiva; Hipermetropía; Resultado refractivo; Satisfacción.

Introduction

Photorefractive keratectomy (PRK) is a laser surgical correction technique of refractive error first introduced in the mid-1980s as the preferred method to correct mild to moderate myopia[3] and in the mid-1990s it was used to correct hyperopia[2]. Although PRK is considered as safe and effective method in correction of refractive errors, it soon was replaced by other methods due to pain and discomfort in the first few days after surgery corneal stromal haze, relatively long time for corneal epithelium healing and visual recovery. LASIK was introduced as the preferred laser surgical method for refractive errors correction due to less post-operative pain and discomfort, rapid healing of corneal epithelium, fairly well vision on the first day after surgery, faster stability of refractive error and removal of haze[13].

Today PRK has become prevalent internationally and also in Iran as a safe, secure and efficient method because of lower visual threatening complication (less than 1%), improved surgical techniques and laser machines. However, PRK, like any other surgical procedure, may have some complications which should be aware by the surgeon and patient, especially that candidates of refractive surgery are not required to perform refractive surgery and surgery will not remove or reduce the threat to their vision[9]. For minimizing complications, the surgeon should not be involved in PRK operation without previous experience.

Although most of these surgical operations are with low complications, post-operative complains, lack of complete refractive error correction, treatment costs and etc. are factors which cause dissatisfaction of patients. Since surgical correction of hyperopia has high prevalence, and on the other hand, a few comprehensive study has been done on details of PRK surgeries in Hyperopic patients and the factors influencing patient satisfaction, conducting current study seems necessary for determining PRK operation results on Hyperopic patients and the factors influencing patient satisfaction after Photorefractive Keratectomy.

Materials and methods

It is an analytical descriptive study conducted in 2013-14 in Isfahan Feyz Medical Educational Center. Statistical population included Hyperopic patients undergoing Photorefractive Keratectomy using Technolas 217 Z100 admitted to the center. Needed sample size in this study was estimated using sample size estimation formula for prevalence studies considering confidence level 95% (Z1-a/2 = 1.96), and prevalence of Hyperopia was estimated at about 30 percent. And error level was considered as 0.05 and sample size was estimated as 80.

Patients undergoing Hyperopic eye correction surgeries using Photorefractive Keratectomy (PRK) method were selected and following taking consent of patients for participation in the study. topographic status of patients eyes was investigated using Pentacam prior to surgery. These patients underwent Ophthalmologic examinations and refractometry before and after operation in order to detect post operative corneal haziness. Then, questionnaire form for operation was given to the patients and they were trained regarding its completion. General information and demographic information of patients was collected in attachment of questionnaire form. Finally, changes were analyzed. The safety index was calculated as the postoperative Best corrected visual acuity (BCVA) the preoperative BCVA, while the efficacy index was calculated as the postoperative uncorrected visual acuity (UCVA) the preoperative BCVA.

Data analysis

Obtained information was analyzed using SPSS 22 software. Significance level was set as less than 0.05.

Results

Table I shows the characteristics of studied patients. The mean age of respondents was 33.98 years (range: 20-59). Of the 80 studied patients, 56.25% were male and 43.75% were female. Most of subjects reported fine vision. independency for their occupation. The mean of UCVA (log MAR) before operation was 0.47 and after that was 0.07 (P-value = 0.0001) which is shown in **figure 1**.

Table I: Characteristics of studied patients.

Variables	
Age (year)	33.98 ± 10.1
Gender (Male/Female)	45(56.25)/35(43.75)
Education	
Under diploma	19(23.75)
Diploma	46 (57.5)
Academic	15 (18.75)
Occupation	
Fine Vision Independent	57 (71.25)
Fine Vision Indifferent	14 (17.5)
Fine Vision Dependent	9 (11.25)
Preoperative UCVA	0.47 ± 0.19
Postoperative UCVA	0.07 ± 0.07
Preoperative BCVA	0.02 ± 0.04
Postoperative BCVA	0.02 ± 0.03
Preoperative Defocus Equivalent	1.35 ± 0.94
Postoperative Defocus Equivalent	0.22 ± 0.49
Surgically Induced Astigmatism	2.51 ± 1.51
Index of Success of Astigmatism Surgery	0.29 ± 0.37
Magnitude of Error	- 0.35 ± 0.56
Absolute Angle of Error	5.55 ± 14.69
Arithmetic Angle of Error	- 1.43 ± 15.64
Corneal haze	47(35.3)
Data presented as mean ± SD, or number (%)	

Figure 1: Pre and post operative UCVA (P-value < 0.0001).

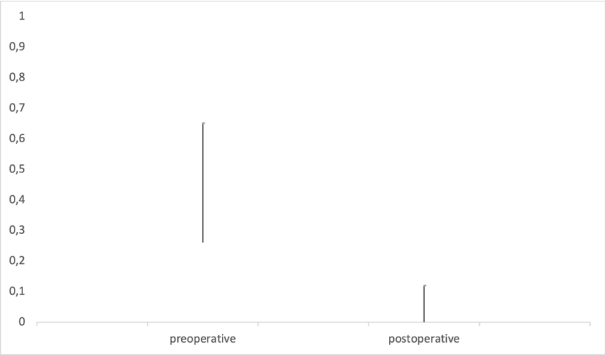

Table II shows results of safety index, efficacy index, predictability and patients' satisfaction in studied patients. As shown the mean of safety index was 1.01. The mean of efficacy index was 0.91. Also the mean of patients' satisfaction score in studied patients was 41.41 with SD, 2.6 of 52 as the total score. For predictability, SE of 96 of the 133 studied eyes (72.2%) were within ±0.5 D of the intended refraction and 37 eyes (27.8%) show SE out of ±0.5 D of the intended refraction (**Figure 1**).

Table II: Safety index, Efficacy index, Predictability, Patients Satisfaction in 133 eyes of 80 studied patients.

Variables	
Safety index	1.01 ±0.13
Efficacy Index	0.91 ±0.17
Predictability	
post op SE within ± 0.5 diopter	96(72.2)
post op SE out of ± 0.5 diopter	37(27.8)
Patients Satisfaction	4.41 ±2.6
Data presented as mean ± SD, or number (%)	

To assess the correlation between safety index and studied variables, liner regression was used. Safety index was significantly correlated with preoperative BCVA (β. -1.25; 95% CI, 1.383 to -1.117; P-value = 0.000), surgically induced astigmatism (β.- 0.017; 95% CI, -0.031 to -0.002; P-value = 0.026), index of success of astigmatism surgery (β. -0.201; 95% CI, -0.25 to -0.152; P-value = 0.000), and absolute angle of error (β, 0.004; 95% CI, 0.002 to 0.005; P- value 0.000). (See **table III**). There was no significant correlation between safety index and other studied variables.

Table III shows results of the correlation between efficacy index and studied variables.

The results of the current study showed that there was no significant correlation between studied variables with patients' satisfaction score and just the corneal haze was the only variable that was significantly correlated with patients' satisfaction score (β. 1.741; 95% CI, -0.731 to 0.749; P-value= 0.011).

Table III: Safety index, Efficacy index, Predictability, Patients Satisfaction in 133 eyes of 80 studied patients.

Variables	B	95% CI	Standardized β	P-value
Age (year)	0.000	-0.003 to 0.003	-0.007	0.939
Gender (male)	0.01	-0.034 to 0.055	0.03	0.648
Education	0.29	-0.016 to 0.073	0.108	0.201
Occupation	0.004	-0.032 to 0.039	0.015	0.836
Corneal haze	-0.057	-0.12 to 0.005	-0.159	0.071
Preoperative UCVA	0.112	-0.015 to 0.239	0.123	0.083
Preoperative BCVA	-1.089	-1.345 to -0.832	-0.554	0.000
Preoperative spherical equivalent	0.017	-0.006 to 0.039	0.152	0.14
Surgically Induced Astigmatism	-0.025	-0.053 to -0.003	-0.217	0.76
Index of Success of Astigmatism surgery	-0.272	-0.366 to -0.177	-0.587	0.000
Absolute Angle of Error	0.004	0.002 to 0.007	0.324	0.002
Arithmetic Angle of Error	-0.001	-0.003 to 0.001	-0.081	0.204

The correlation between predictability as categorical dependent variable and other studied variables, logistic regression was used and results are shown in **table IV**.

Table IV: Correlation between predictability and studied variables by logistic regression.

Variables	B (SE)	OR	95% CI OR	P-value
Age (year)	0.027 (0.34)	1. 028	0.962 to 1.098	0.416
Gender (male)	-0.152 (0.476)	0.859	0.338 to 2.182	0.749
Education	-0.198 (0.445)	0.82	0.343 to 1.964	0.656
Occupation	0.369 (0.354)	1.447	0.723 to 2.894	0.297
Corneal haze	1.2 (0.67)	3.321	0.894 to 12.341	0.073
Preoperative UCVA	-3.476	0.031	0.001 to 0.754	0.033
	(1.63)			
Preoperative BCVA	-2.682 (2.528)	0.068	0.000 to 9.7	0.289
Preoperative spherical equivalent	-2.282 (2.25)	0.754	0.462 to 1.232	0.26
Surgically Induced Astigmatism	-0.158 (0.303)	0.854	0.471 to 1.547	0.602
Index of Success of Astigmatism surgery	-3.008 (2.03)	21.933	0.41 to 1172.162	0.128
Magnitude of Error	0.186 (0.528)	1.204	0.428 to 3.389	0.725
Absolute Angle of Error	-3.079 (0.052)	0.924	0.835 to 1.024	0.131
Arithmetic Angle of Error	1.017 (0.024)	1.017	0.97 to 1.066	0.486

Discussion

The results of our study suggest that PRK is a safe, predictable, and effective with good patients' satisfaction way of correcting of hyperopia. The mean preoperative SE in the Stidham et al. study[12] was 7.36 D and postoperative was 2.10 D. in Pacella et al. study[7], the mean preoperative SE was 3.50 D and postoperative SE after one year was

- 0.01 D. In Nucci et al. study[5] postoperative SE was 3.70 D. In other study preoperative mean of SE after PRK was 2.38 D[4]. The mean of defocus equivalent was 1.35 ±0.94 before operation and 0.22 ±0.49 after operation. The differences between these findings can be explain by number of studied patients and follow-up period, sample size in our study was more than other reported studies and we measured SE 6 months after operation whereas other studies reported SE after one year follow-up. Also, predictability in our study was 72.2% of studied patients that means they had postoperative SE within ±0.50 D, and 37.8% of our patients had postoperative SE out of ±0.50 D. Similarly, in Moore et al study[4] 91% of eyes were within ±0.50 D of the intended correction and in Autrata et al. study[1] 57% of PRK eyes were within ±0.5 D of the intended refraction. Predictability in Sia et al. study[11] in PRK at 1 month was 68.5%, and at 12 months postoperatively was 92.5%.

In the present study safety was evaluated by changes in BCVA, observed after operation. The mean of safety index in our study was 1.01 with SD of 0.13, which was similar to Autrata et al. study[1] who reported 1.069 for safety index 2 years after PRK, also the safety index in Moore et al. study[4] reported 0.995 one year after PRK. The PRK safety index in children reported by Paysse et al.[8] was 1.24.The safety index Sia et al.[11] after 1 month and one year follow-up were 0.61 and 1.29, respectively. As shown, despite the differences between follow-up periods the mean of safety index in our study is similar to previous reports. Therefore, according to these findings PRK in the treatment of hyperopic seems to be safe after two years of follow-up.

Efficacy was evaluated by UCVA after operation, the mean of Efficacy index in our study postoperatively was 0.91. In agreement with our results the efficacy index in Moore et al. study[4] at 12 months follow-up was 0.92. And in Autrata et al. study[1] after 12 months follow-up was 0.953. The PRK efficacy index in Paysse et al. study[8] was 1.12. The efficacy index after 1 month and one year follow-up reported in Sia et al.[11] were 0.39 and 0.67, respectively. So, these findings showed that PRK in the treatment of hyperopic seems to be effective.

It has been asserted that higher age groups may make PRK corrections less predictable[10]. Data from our study, presented here, would seem to agree with previously two published data by Moore et al.[4] with 12-month follow-up and O'Brart et al.[6] with 7.5 years follow-up[6,8], who also found no evidence of hyperopic shift or late regression after PRK in hyperopic patients with age advancing. Though, in the present study data were collected only 6 month after PRK and patient did not followed for more time.

Conclusion

PRK has good safety and efficacy index with high rate of predictability and present it as a satisfactory way to correct of hyperopic patients' refractive error.

Conflict of Interest

The authors declare that no competing interests exist.

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ORIGINAL

Evaluation of the correlation between computed tomography and anatomopathological findings in adult renal tumors

Evaluación de la correlación entre la tomografía computarizada y los hallazgos anatomopatológicos en los tumores renales del adulto

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Abstract

Purpose: To evaluate the correlation between CT-scan findings in the diagnosis and extension workup of renal tumors to anatomical-pathology findings.
Patients and method: This is a retro-spective, analytical, comparative and single center study over a period of 10 years, including all patients who had an extended total nephrectomy or partial nephrectomy indicated for a renal tumor with preoperative CT-scan and histopathological findings of the operative specimen. The parameters studied were: age, sex and CT-scan results and the results of the anatomical-pathology examination. Data analysis was done using the software SPSS. The threshold of significance was set at a P value of 0.05. Sensitivity, specificity, PPV, NPV for the variables studied were determined from the results of the CT-scan data and histopathological examination.
Results: Forty-three patients were included with a sex-ratio of 0.8. The mean age was 43±16.9 years. In the 40 solid tumors and 3 cystic tumors suspected on CT-scan, histology had confirmed 40 malignant, 2 benign and 1 interstitial nephritis. CT-scan had a sensitivity of 100% and a PPV of 95.4%. CT-scan significantly overestimated tumor size for sizes less than 4 cm (p=0.01). For sizes between 4 and 10 cm, the size overestimation was not significant (p=0.13 and p=0.28). For sizes greater or equal than 10 cm, CT-scan underestimated size non-significantly (p=0.2). CT-scan had a high sensitivity to determine a solid or solid-cystic tumor mass but for cystic tumors it was not very sensitive but very specific. Comparing cTNM and pTNM classification, CT-scan had a specificity >90% to determine tumor size and extension except for tumors classified as T1 and T4.
Conclusion: Our results show a high sensitivity and specificity of CT-scan in the diagnosis and extension of renal tumors.

Key words: tumors, kidney, computed tomography, histology, cancer.

Resumen

Objetivo: Evaluar la correlación entre los hallazgos de la TC en el diagnóstico y la extensión de los tumores renales con los hallazgos anatomopatológicos.
Pacientes y método: Se trata de un estudio retrospectivo, analítico, comparativo y unicéntrico durante un periodo de 10 años, que incluye a todos los pacientes a los que se les realizó una nefrectomía total ampliada o una nefrectomía parcial indicada por un tumor renal con los hallazgos preoperatorios de la TC y los histopatológicos de la muestra operatoria. Los parámetros estudiados fueron: la edad, el sexo y los resultados de la TC y del examen anatomopatológico. El análisis de los datos se realizó con el programa informático SPSS. El umbral de significación se fijó en un valor P de 0,05. La sensibilidad, la especificidad, el VPP y el VPN de las variables estudiadas se determinaron a partir de los resultados de la TC y del examen histopatológico.
Resultados: Se incluyeron 43 pacientes con una proporción de sexo de 0,8. La edad media era de 43±16,9 años. En los 40 tumores sóli-dos y 3 quísticos que se sospechaban en la TC, la histología había confirmado 40 malignos, 2 benignos y 1 nefritis intersticial. La TC tuvo una sensibilidad del 100% y un VPP del 95,4%. La TC sobrestimó significativamente el tamaño del tumor para los tamaños inferiores a 4 cm (p=0,01). Para tamaños entre 4 y 10 cm, la sobreestimación del tamaño no fue significativa (p=0,13 y p=0,28). Para tamaños mayores o iguales a 10 cm, el CT-scan subestimó el tamaño de forma no significativa (p=0,2). El CT-scan tuvo una alta sensibilidad para determinar una ma-sa tumoral sólida o sólida-quística pero para los tumores quísticos fue poco sensible pero muy específico. Comparando la clasificación cTNM y pTNM, el CT-scan tuvo una especificidad >90% para determinar el tamaño y la extensión del tumor, excepto para los tumores clasificados como T1 y T4.
Conclusión: Nuestros resultados muestran una alta sensibilidad y especificidad del CT-scan en el diagnóstico y la extensión de los tumores renales.

Palabras clave: tumores, riñón, tomografía computarizada, histología, cáncer.

Introduction

A renal tumor is a benign or malignant (primary or secondary) tissue neoformation that develops at the expense of the renal parenchyma. Its incidence varies geographically. It is higher in Europe, North America and Australia and lower in China, India, Japan and Africa[1]. Tossou H et al. estimated their frequency in Dakar in 1971 at 1.1% of all urogenital cancers[2]. Currently, with the major contribution of CT-scan in the diagnosis and management of these tumors, the question that must be asked is to what extent this examination can be relied upon in the diagnosis and extension of kidney cancer, thus avoiding excessive surgical procedures such as radical nephrectomy in the case of benign tumors. The aim of this study was to evaluate the correlation between CT-scan findings in the diagnosis and extension workup of renal tumors and anatomical-pathology findings in our center.

Patients and method

This is a retrospective, analytical, comparative, single-center study from August 1, 2009 to July 31, 2019. This study focused on kidney tumor patients who had a radical nephrectomy or partial nephrectomy (PN) with complete preoperative CT-scan and anatomical-pathology findings in our center. Patients with incomplete records, non-operated patients, and patients without anatomical-pathology findings on the surgical specimen or preoperative CT-scan were not included. The parameters studied were: age, sex, CT-scan result and anatomical-pathology findings. The processing and analysis of the collected data were performed with the software SPSS. Figures were made with Microsoft Office-Excel 2007 software (Microscoft, Redmond, WA, USA). The statistical test used for the comparison of proportions was the chi-square test (Chi2). The Student's t-test was used for the comparison of means. The significance level was set at 0.05 (p=0.05). Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) for the variables studied were determined from the results of the CT-scan data and the histopathological study.

Results

Forty-three patients were included during the study period. The mean age was 43.3 ± 16.9 with extremes ranging from 18 to 81 years. The sex-ratio was 0.8. In the 43 sus-pected renal tumors on CT-scan, histology had confirmed 40 solids including 39 ma-lignant tumors and one benign tumor, 2 cystic tumors including one benign and one malignant tumor, and one interstitial nephritis. For detection of renal tumor, CT-scan had a sensitivity of 100% and a PPV of 95.4%. CT-scan significantly overestimated tumor size compared to histology for sizes less than 4 cm (p=0.01) (**Table I**). For sizes between 4 and 10cm, the size overestimation was non-significant (p=0.13 and p=0.28) and for sizes greater or equal than 10cm CT-scan underestimated size non-significantly (p=0.2) (**Table I**).

Table I: Comparison of tumor size means.

Slices of sizes	Size averages on CT-scan	Mean sizes on histology	Difference in averages	Value of P (<0,05)
Less than 4 cm	1.3	0	1.3	0.01
4 - 7 cm	5.6	5.4	0.2	0.13
7 - 10 cm	8.3	8.2	0.1	0.28
10 cm and more	15.4	15.8	-0.4	0.2

Table II: Sensitivity, specificity, PPV, NPV of CT-scan in relation to the histological nature of the mass.

	Solid	Solid-cystic	Cystic
Sensitivity	83.3%	100%	33.3%
Specificity	78.2%	78.8%	95.4%
PPV	83.3%	70.8%	33.3%
NPV	78.2%	100%	94.5%

Table III: Comparison of cTNM and pTNM classification.

T.N.M	Stage	CT- Scan	Histology	Sensitivity	Specificity	PPV	NPV
Tumor	T1	6	5	62.5%	97%	83.3%	91.9%
	T2	22	22	88%	100%	100%	86%
	T3	13	10	91%	90.6%	76.9%	97%
	T4	2	3	38%	100%	100%	87.8%
Nodes	Nx	16	34	100%	57%	47.1%	100%
	N0	14	2	56%	100%	100%	70.3%
	N1	4	2	80%	100%	100%	97.3%
	N2	6	2	67%	100%	100%	91.9%
Metastases	Mx	16	34	100%	57.1%	47.1%	100%
	M0	20	5	58.8%	100%	100%	58.8%
	M1	4	1	66.7%	100%	100%	94.7%

CT-scan is sensitive in determining the nature of the tumor mass if it was solid or solid-cystic. However, for cystic tumors it was not sensitive but was very specific (**Table II**).

On CT-scan, the Gerota fascia was invaded in 2 patients, but the histological results showed invasion in 3 patients. The CT-scan had a sensitivity of 100% to search for the involvement of the Gerota fascia with a PPV of 75%. CT-scan and histology showed that the adrenal gland was involved in one patient only. Comparing cTNM and pTNM classification, for tumor size, we noted that CT-scan had a specificity > 90%. On the other hand, for tumors classified as T1 and T4, CT-scan showed a low sensitivity with respective rates of 62.5% and 38%.

For the search for lymph node involvement and metastases, CT-scan had a specificity of 100% and a sensitivity greater than 50% (**Table III**).

Discussion

CT-scan examination remains the reference examination for the detection of a renal mass with a sensitivity greater than or equal to 94% and a specificity greater than 98%[3,4]. In our series, of the 43 cases of tumors suspected on CT-scan, 40 malignant tumors were confirmed on histology. The PPV was 95.4% and the sensitivity was 100%. It seems clear that none of the currently available imaging modalities can accurately predict the histology of a renal tumor. However, some lesions have suggestive morphological features on CT-scan that could point to a diagnosis and therefore guide the choice of therapy[5]. CT-scan is currently considered the gold-standard for accurate assessment of renal cancer, although it may appear as iso-, hyper- or hypodense on a non-contrast enhanced CT-scan, it shows significant enhancement after injection of approximately 115±48 HU in the cortico-medullary phase, and 62±25 HU in the excretory phase[6]. An enhancement level greater than or equal to 84 HU in the arterial phase characterizes clear cell carcinoma with a specificity of 100% and a sensitivity of 76%[7]. Some very characteristic but inconstant elements may also be associated: the presence of intra-tumoral calcifications and the invasion of the renal vein and the inferior vena cava. Sheir et al. had published a series where they tried to determine the histological type of renal tumors based on multi-barrier CT-scan data by comparing the data of the 3 most frequent histological types: clear cell carcinoma, papillary carcinoma, and chromophobe carcinoma[8]. He found that the degree of enhancement was significantly different between the 3 types in the cortico-medullary phase and the excretory phase (p=0.001), with higher enhancement noted in 48.6% of clear cell carcinomas, compared to 15.4% in papillary carcinoma and 4.2% in chromophobe carcinoma (p=0.001). The chromophobe subtype showed homogeneous enhancement in 75% of cases compared to 45% and 65% of clear cell and papillary subtypes (p=0.05) respectively. Calcifications were obvious in 21.6%, 23.1% and 25% of clear cells, papillary and chromophobe subtypes respectively (p=0.05). Zhang et al[9], noted that some tumor features revealed by CT-scan could point to the histological type, thus the presence of intra-tumor hemorrhage or necrosis pointed more to chromophobe carcinoma (p<0.05). The absence of cystic degeneration increased the probability of finding papillary or chromophobe carcinoma (p<0.05). In our series, clear cell carcinoma was the most frequent histological type followed by papillary carcinoma and chromophobe, which roughly agrees with the WHO results published by the EAU Guidelines in 2012[10]. Considering the great interest of tumor size measurement in the classification of kidney cancer as well as in the therapeutic choice, it is important to determine how accurate the radiological measurements were compared to the measurements found on histopathological examination. In our series, we tried to evaluate the predictive ability of CT-scan to estimate tumor size in relation to histopathologic features. The mean size of discovery of renal cancer in our series was slightly higher than the results found by Cheville et al[11]. Schlomer et al[12] published a study of 133 cases of renal cancer and found no significant difference between tumor size on CT-scan and on the resection specimen. CT-scan detects one out of two lesions among renal masses less or equal than 5mm, and 75% of masses less than 15 mm, the best results are obtained on spiral CT-scan by combining acquisitions obtained after contrast injection to the arterial and excretory phase[13]. By subdividing the tumor size into ranges, while using the TNM classification, we noticed that CT-scan tended to significantly underestimate the tumor size especially when histology did not find any tumor smaller than 4 cm. The smallest tumor found on histology was 4 cm in size, whereas on CT-scan it was 2.6 cm in size. Muscat JE et al[14] found similar results to ours where CT-scan underestimated tumor size by 1.7 to 4.4 mm for tumors smaller than 4 cm. For tumors smaller than 4 cm in our series, CT-scan significantly overestimated tumor size as well as for size between 7 cm and 10 cm. For a size of more than 10 cm, CT-scan underestimated the measurements. In addition, in their study, Muscat JE et al[14] compared the perfor-mance of the 3 most commonly used radiological modalities in kidney cancer imaging: ultrasound, CT-scan and MRI; he found that all 3 modalities were excellent in determining tumor size although CT-scan slightly and significantly underestimated tumor size for sizes smaller than 4 cm. Ultrasound and MRI also overestimated tumor size but not significantly. The correlations between tumor size on imaging and histopathological examination were similar between the three techniques with a slight advantage found for MRI[15]. In the study by Choi et al[16], the sensitivity of CT-scan for estab-lishing tumor size was 94% while the specificity was 41%. In the Hallscheidt work[17], the sensitivity of CT-scan was 88% while the specificity was 77%. Comparing these results with our own, we note that CT-scan is reliable for tumors of size 4 cm and larger. A significant dependency between tumor size and nuclear grade was demonstrated. Larger tumors often had a high nuclear grade and were potentially more aggressive[18,19]. A

renal mass is said to be cystic if it has a predominantly fluid component[20]. The diagnosis of a cystic tumor is often difficult and relies primarily on the demonstration of a solid component (wall, septum, vegetation or mural nodule) vascularized (significant enhancement after contrast) which should classify the lesion in one of the two suspicious categories (types III and IV) of the Morton Bosniak classification[20]. Category IV lesions represent the typical form of cystic CRC with a specificity of 100%[3-20]. This is in agreement with our results, which showed that for tumors of cystic nature, CT-scan was not sensitive but was very specific. The reference for the characterization of a solid renal mass is CT-scan[20], which is confirmed by our results which showed that CT-scan had a sensitivity >80% to determine the nature of the tumor mass in solid or solidcystic tumors. The renal pelvis and Gerota fascia are perfectly individualized on CT-scan. In the normal state, the perirenal fat is the site of linear elements due to the presence of vessels or fibrous elements (infectious or inflammatory history, fat necrosis phenomena). It is therefore often difficult to affirm that there is a real diffusion of tumor to the renal cavity, all the more so as the tumor may be responsible for perirenal hemorrhagic phenomena which further disturb the reading of the CT-scan. The most reliable sign is the presence of a tissue nodule of at least one centimeter in diameter, satellite of the tumor but located in the perirenal fat. This sign is valuable to differentiate a T2 or I stage from a T3a or II stage because it is very specific (98%). Unfortunately, its sensitivity is low (46%). Involvement of Gerota's fascia is strongly suspected when it presents a focal thickening opposite the tumor. This is difficult to analyze in the posteromedial regions in contact with the psoas muscles and anteriorly where the renal pelvis is very thin[10]. However, in our series, CT-scan has a sensitivity of 100% in the search for involvement of the Gerota fascia and a PPV of 75%. It is done by contiguity for tumors of the upper pole or by hematogenous route. Enlargement, displacement or even non-visualization of the adrenal gland has been associated with malignant extension in 24% of cases after histological study, conversely a normal adrenal gland on imaging is also normal on histology[21]. According to the literature, extension to the homo-lateral adrenal gland is in the range of 1.8-8.5% of patients with renal cancer[22]. Therefore, many clinical studies have been conducted to evaluate the accuracy of imaging modalities in diagnosing adrenal involvement to reduce the need for unnecessary adrenalectomy. Autorino et al[23] performed a study on 192 patients to evaluate the need for adrenalectomy in these cases. He found that CT-scan had a specificity of 92.9% and an NPV of 99.4%. These data show that a normal adrenal appearance on CT-scan correlates well with histopathologic findings. This is consistent with our results where CT-scan and histology showed that the adrenal gland was affected in just one patient. The study of tumor extension was based on tumor size, tumor boundaries, venous involvement in relation to the diaphragm, involvement of the Gerota Fascia and homo-lateral adrenal gland. The lack of visualization of the normal renal capsule on CT-scan explains the possibility of false negatives in case of early or microscopic capsular invasion. Thus, the sensitivity of CT-scan is low (44%), and not very compatible with a reliable preoperative diagnosis to differentiate a T1-T2 from a T3 [24]. Based on these data, the best classification for tumor extension is that of histopathological examination. In our series for tumor extension CT-scan had a specificity >90%. The same result was found in the study of Johnson et al[25] where the specificity was between 91% and 100%. Lymph node involvement is suspected on the basis of lymph node size criteria. However, with this criterion, there are 5-43% of false-positives[26]. The false-negative rate is low (4-5%), which tends to prove that the vast majority of invaded lymph nodes show an increase in size. Catalona et al[27] showed in their study on the place of multibarette CT-scan in the preoperative evaluation of cancer that all patients who had synchronous lymphadenopathy at the time of nephrectomy had it previously on CT-scan; the false positive rate due to reactive hyperplasia was 6.3%. In the study by Johnson et al[25], CT-scan had an ac-curacy of 83-88% for detecting lymph nodes at least 10 mm in diameter. Histo-pathological assessment of regional lymph nodes (pN) implies appropriate lymph node excision to affirm the absence of regional lymph node metastasis (pNo) and sufficient to assess the pN category[28]. In our series the specificity of CT-scan had a sen-sitivity between 56% and 100% and a specificity of 100% with a PPV of 100% and an NPV >70%. In the literature, the reliability of CT-scan in the differentiation of N0, N1 and N2 stages in kidney cancer is only 83-89%. It has recently been shown that lymph node dissection is unnecessary when there is no suspicion of lymph node involvement on CT-scan[29]. Thorco-abdomino-pelvic CT-scan is the gold standard examination for the search for metastases. It allows not only the study of the kidneys, but also a hepatic, complete abdominal and thoracic exploration. A cerebral CT-scan to search for a secondary location is performed in case of clinical signs. The analysis of all these radiological elements allows in the final phase to classify the tumor according to its distant extension. Histopathological assessment of distant metastases is only possible in case of sampling of suspicious lesions, otherwise it is limited to the perirenal fat, the fascia of Gerota and the adrenal gland if it is sampled.

Conclusion

These results show a high sensitivity and specificity of CT-scan in the diagnosis and extension assessment of renal tumors. The two complementary examinations, CT-scan and histology, should be combined for a better management of patients with renal tumors.

Conflict of Interest

The authors declare that no competing interests exist.

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ORIGINAL

Association between nonalcoholic fatty liver disease risk scales and metabolic syndrome scales in 418.343 spanish workers

Asociación entre las escalas de riesgo de enfermedad de hígado graso no alcohólico y las escalas de síndrome metabólico en 418.343 trabajadores españoles

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Abstract

Introduction: Non-alcoholic fatty liver disease (NAFLD) and metabolic syndrome (MetS) are two very frequent cardiometabolic disorders that seem to be related. The aim of this study is to search for this relationship.
Material and methods: Descriptive and cross-sectional study in 418343 Spanish workers in which the relationship between six NASH risk scales and three of MS was assessed.
Results: The mean values and the prevalence of elevated values of the NASH risk scales are higher in people with metabolic syndrome with the different criteria. In the multivariate analysis we observed that the risk of presenting metabolic syndrome with the three criteria is greater the higher the value of the different non-alcoholic fatty liver disease risk scales. The analysis of the ROC curves shows that the areas under the curve are, in general, very high, with the highest values corresponding to the metabolic syndrome when the IDF criteria are applied with all the NAFLD risk scales.
Conclusions: In our study the different NASH risk scales are quite useful in predicting the occurrence of metabolic syndrome, especially when using the IDF criteria.

Key words: non-alcoholic fatty liver disease, metabolic syndrome, fatty liver.

Resumen

Introducción: La enfermedad del hígado graso no alcohólico (EHGNA) y el síndrome metabólico (SM) son dos alteraciones cardiometabólicas muy frecuentes que parecen estar relacionadas. El objetivo de este trabajo es buscar esa relación.
Material y métodos: Estudio descriptivo y transversal en 418343 trabajadores españoles en los que se valora la relación entre seis escalas de riesgo de EHGNA y tres de SM.
Resultados: Los valores medios y la prevalencia de valores elevados de las escalas de riesgo de EHGNA son mayores en las personas que presentan síndrome metabólico con los diferentes criterios. En el análisis multivariante observamos que el riesgo de presentar síndrome metabólico con los tres criterios es mayor cuanto mayor es el valor de las diferentes escalas de riesgo de hígado graso no alcohólico. El análisis de las curvas ROC muestra que las áreas debajo de la curva son, en general, muy elevadas correspondiendo los valores más altos al síndrome metabólico cuando se aplican los criterios IDF con todas las escalas de riesgo de EHGNA.
Conclusiones: En nuestro estudio las diferentes escalas de riesgo de EHGNA son bastante útiles para predecir la aparición de síndrome metabólico, especialmente cuando empleamos los criterios IDF.

Palabras clave: enfermedad del hígado graso no alcohólico, síndrome metabólico, hígado graso.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is currently the most prevalent liver disorder in the world, affecting one in four people[1] and continues to increase at a worrying rate[2] and is the main cause of liver-related morbidity and mortality[3]. NASH has been related to different pathological entities such as obesity[4], type 25 diabetes, dyslipidemia[6], arterial hypertension[7] and insulin resistance[8]. In the initial stages, triglyceride accumulation is observed in hepatocytes, which increases as new elements of the metabolic syndrome appear[9]. This initial phase, called isolated hepatic steatosis, is a benign process, although a percentage of them will develop significant inflammatory activity that will progress to nonalcoholic steatohepatitis, with or without fibrosis[10].

Metabolic syndrome is a pathological entity that groups together physiological, analytical and clinical alterations that will increase the risk of presenting cardiometabolic alterations that could lead to death. In summary, insulin resistance, excess abdominal fat, atherogenic dyslipidemia, endothelial dysfunction and elevated blood pressure, among others, usually coexist in this clinical picture[11].

The aim of this study is to assess the relationship between NAFLD and metabolic syndrome as determined with different scales.

Material and methods

Descriptive and cross-sectional study carried out in 418.343 workers from different Spanish regions and belonging to different labor sectors, mainly public administration, health, construction and commerce. The workers included in this research were selected from the health examinations performed between the months of January 2017 and December 2019 in the different companies participating in the study. The inclusion criteria were as follows: age between 18 and 69 years, working in one of the companies included in the study, not being on temporary disability, signing the informed consent to participate in the study and to use their data for epidemiological purposes.

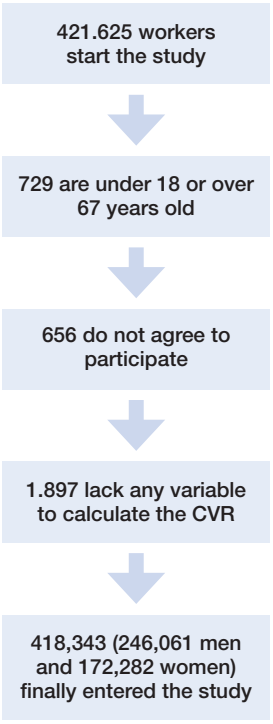
Figure 1 shows the flow diagram of the study participants.

Measurements and data collection

Different anthropometric and analytical parameters were determined in all the participants in the study.

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

Figure 1: Flow chart.



To determine weight (in kg) and height (in cm), a SECA 700 scale with an attached SECA 220 telescopic measuring rod was used. Waist circumference (WC) was measured with a SECA measuring tape while the person was standing upright, with feet together, trunk straight and abdomen relaxed. The tape was placed parallel to the floor at the level of the last floating rib.

Blood pressure was obtained with a calibrated OMRON M3 automatic sphygmomanometer and with the person seated and after a 10-minute rest. Three measurements were taken at one-minute intervals and the mean of the three was obtained. The determinations of the different parameters in blood were obtained after 12 h of fasting. The samples were sent to reference laboratories and processed within 2-3 days. Automated enzymatic methods were used to determine glucose, total cholesterol and triglycerides. HDL-c was determined by a precipitation process with dextran sulfate-MgCl2. LDL-c was calculated using the Friedewald formula (valid for triglyceride values below 400 mg/dL). The values of all these parameters are expressed in mg/dL.

Friedewald formula:
LDL = colesterol – HDL – tryglicerides/5

To assess the metabolic syndrome (MS) we used 3 different criteria, the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP-III), the Joint Interim Statement (JIS) and the update of the International Diabetes Federation (IDF)[12].

The risk of NAFLD is determined by applying different scales:

- Fatty liver index[13]

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

FLI values are considered to be high risk if they are above 60.

- Hepatic steatosis index (HSI)[14]

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

- Zhejian University index (ZJU index)[15]

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

- Fatty liver disease index (FLD)[16]

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

- Framingham steatosis index (FSI)[17]

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

- Lipid accumulation product (LAP)[18]

Men (waist (cm) – 65) × (tryglicerides (mMol))
Women (waist (cm) – 58) × (tryglicerides (mMol))

Values are considered to be high risk if they are above 42,7.

Smoker is any person who has smoked at least one cigarette/day (or its equivalent in other types of consumption) in the last month, or who has stopped smoking less than a year ago.

Social class was determined by applying the proposal of the social determinants group of the Spanish Society of Epidemiology[19]. Three categories were considered:

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

Statistical analysis

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

Bivariate association analysis was performed using the chi2 test (with correction for Fisher's exact statistic when conditions required it) and Student's t test for independent samples (for comparison of means). Multivariate techniques were used to establish the variables associated with the most significant risk factors. For multivariate analysis, logistic regression was used, with calculation of the odds ratio and the Hosmer-Lemeshow goodness-of-fit test. ROC curves were performed, and the area under the curve

(The statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) version 28.0 (IBM Company, New York, NY, USA) for Windows, with an accepted statistical significance level of 0.05.

Ethical considerations and/or aspects

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

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

Results

Table I shows the anthropometric and clinical characteristics of the individuals included in the study. A total of 418343 (246061 men and 172282 women) were included in the analyses. The mean age of the sample was 40.2 ± 11.0 years with the largest group being between 30 and 49 years. Anthropometric, clinical and analytical values were higher in men. Most of the

workers, 75.9% were of social class III. One out of three workers were smokers.

Mean values of the different nonalcoholic fatty liver disease risk scales according to the presence or absence of metabolic syndrome with the three criteria by sex.

Table II shows the mean values of the different nonalcoholic fatty liver disease risk scales according to the presence or absence of metabolic syndrome with the three criteria in men and women. The mean values of all the aforementioned risk scales show much higher values, in both sexes, in persons with metabolic syndrome with the three criteria.

Table III shows the results of the multivariate analysis using multinomial logistic regression. The risk of presenting metabolic syndrome with the three criteria is greater the higher the value of the different non-alcoholic fatty liver disease risk scales.

Figure 2 and **table IV** show the ROC curves of the different NASH risk scales for predicting the presence of metabolic syndrome applying the three criteria in both sexes. It can be seen that the areas under the curve are, in general, very high, with the highest values corresponding to the metabolic syndrome when the IDF criteria are applied with all the NASH risk scales.

Table V shows the cut-off points, sensitivity, specificity and Youden index of the different NASH risk scales for predicting the presence of metabolic syndrome with the three criteria. We observe that the highest levels of sensitivity, specificity and Youden index also correspond to the different EHGNA scales for predicting metabolic syndrome with the IDF criteria.

Table I: Characteristics of the population.

	Women n=172.282 Mean (SD)	Men n=246.061 Mean (SD)	Total n=418.343 Mean (SD)	p-value
Age	39.6 (10.8)	40.6 (11.1)	40.2 (11.0)	<0.0001
Height	161.8 (6.5)	174.6 (7.0)	169.4 (9.3)	<0.0001
Weight	66.2 (14.0)	81.4 (14.7)	75.1 (16.2)	<0.0001
BMI	25.3 (5.2)	26.7 (4.5)	26.1 (4.8)	<0.0001
Waist	74.8 (10.6)	86.2 (11.1)	81.5 (12.2)	<0.0001
SBP	117.4 (15.7)	128.2 (15.5)	123.7 (16.5)	<0.0001
DBP	72.6 (10.4)	77.8 (11.0)	75.6 (11.0)	<0.0001
Cholesterol	190.6 (35.8)	192.6 (38.9)	191.8 (37.7)	<0.0001
HDL-c	56.8 (8.7)	50.3 (8.5)	53.0 (9.1)	<0.0001
LDL-c	116.1 (34.8)	118.0 (36.7)	117.2 (35.9)	<0.0001
Triglycerides	89.1 (46.2)	123.7 (86.4)	109.5 (74.6)	<0.0001
Glycaemia	87.8 (15.1)	93.3 (21.3)	91.0 (19.2)	<0.0001
	%	%	%	p-value
18-29 years	20.7	18.8	19.6	<0.0001
30-39 years	29.7	27.6	28.4	
40-49 years	29.6	30.0	29.9	
50-59 years	16.8	19.7	18.5	
≥60 years	3.2	3.9	3.6	
Social class I	6.9	4.9	5.7	<0.0001
Social class II	23.4	14.9	18.4	
Social class III	69.7	80.3	75.9	
Non smokers	67.2	66.6	66.9	<0.0001
Smokers	32.8	33.4	33.2	

BMI Body mass index. SBP Systolic blood pressure. DBP Diastolic blood pressure. HDL-c High density lipoprotein-cholesterol. LDL-c Low density lipoprotein-cholesterol

Table II:

Men	Non MS ATPIII Mean (SD) n=204597	Yes MS ATPIII Mean (SD) n=41464	p-value	Non MS IDF Mean (SD) n=213558	Yes MS IDF Mean (SD) n=32503	p-value	Non MS JIS Mean (SD) n=178147	Yes MS JIS Mean (SD) n=67914	p-value
FLI	30.9 (23.1)	70.8 (22.5)	<0.0001	31.5 (23.1)	79.2 (15.6)	<0.0001	27.0 (20.5)	65.1 (23.9)	<0.0001
HSI	35.7 (6.1)	42.4 (7.1)	<0.0001	35.6 (6.0)	44.2 (6.7)	<0.0001	35.1 (5.8)	41.6 (7.0)	<0.0001
ZJU	35.9 (4.7)	43.4 (6.0)	<0.0001	35.9 (4,7)	44.8 (5.5)	<0.0001	35.3 (4.4)	42.4 (5.7)	<0.0001
FLD	31.0 (4.6)	37.6 (5.7)	<0.0001	30.9 (4.5)	39.1 (5.1)	<0.0001	30.4 (4.3)	36.7 (5.4)	<0.0001
FSI	0.2 (0.1)	0.4 (0.2)	<0.0001	0.2 (0.1)	0.5 (0.2)	<0.0001	0.1 (0.1)	0.4 (0.2)	<0.0001
LAP	24.2 (20.8)	69.2 (52.2)	<0.0001	24.7 (21.3)	78.4 (53.3)	<0.0001	21.3 (17.1)	59.2 (46.6)	<0.0001
Women	**n=155772**	**n=16510**	**p-value**	**n=156169**	**n=16113**	**p-value**	**n=153102**	**n=19180**	**p-value**
FLI	14.0 (16.5)	56.3 (26.6)	<0.0001	13.8 (16.2)	60.0 (23.2)	<0.0001	13.6 (16.3)	53.5 (25.9)	<0.0001
HSI	35.4 (6.2)	44.9 (7.1)	<0.0001	35.3 (6.1)	45.7 (6.7)	<0.0001	35.3 (6.2)	44.2 (7.0)	<0.0001
ZJU	35.9 (5.3)	46.0 (6.4)	<0.0001	35.9 (5.2)	46.5 (5.8)	<0.0001	35.8 (5.3)	45.2 (6.2)	<0.0001
FLD	29.2 (5.1)	38.4 (6.2)	<0.0001	29.1 (5.1)	39.0 (5.5)	<0.0001	29.1 (5.1)	37.7 (5.9)	<0.0001
FSI	0.1 (0.1)	0.4 (0.2)	<0.0001	0.1 (0.1)	0.4 (0.2)	<0.0001	0.1 (0.1)	0.4 (0.2)	<0.0001
LAP	14.9 (12.4)	48.0 (32.4)	<0.0001	14.7 (12.2)	50.6 (31.0)	<0.0001	14.6 (12.1)	45.9 (31.0)	<0.0001

FLI Fatty liver index. HSI Hepatic steatosis index. ZJU Zhejiang University index. FLD Fatty liver disease. FSI Framingham Steatosis index. LAP Lipid accumulation product. MS ATPIII. Metabolic syndrome Adult Treatment Panel III. MS IDF Metabolic syndrome International Diabetes Federation. Metabolic syndrome Joint Interim Statement.

Table III: Multinomial logistic regression.

	MS NCEP ATP III OR (CI 95%)	p-value	MS IDF OR (CI 95%)	p-value	MS JIS OR (CI 95%)	p-value
FLI low	1	<0.0001	1	<0.0001	1	<0.0001
FLI moderate	2.29 (2.15-2.45)		2.79 (2.60-2.99)		2.93 (2.76-3.11)	
FLI high	6.18 (5.56-6.86)		7.44 (6.53-8.49)		9.55 (8.76-10.41)	
HSI low	1	<0.0001	1	<0.0001	1	<0.0001
HSI moderate	1.19 (1.11-1.27)		1.72 (1.51-1.96)		1.12 (1.05-1.19)	
HSI high	1.63 (1.34-1.98)		21.24 (10.47-43.07)		1.64 (1.40-1.92)	
ZJU normal	1	<0.0001	1	<0.0001	1	<0.0001
ZJU high	2.99 (2.70-3.31)		3.28 (2.88-3.72)		2.45 (2.26-2.66)	
FLD normal	1	<0.0001	1	<0.0001	1	<0.001
FLD high	1.32 (1.28-1.36)		1.45 (1.41-1.48)		1.11 (1.05-1.16)	
LAP normal	1	<0.0001	1	<0.0001	1	<0.0001
LAP high	2.82 (2.60-3.06)		4.30 (3.88-4.77)		2.54 (2.39-2.71)	

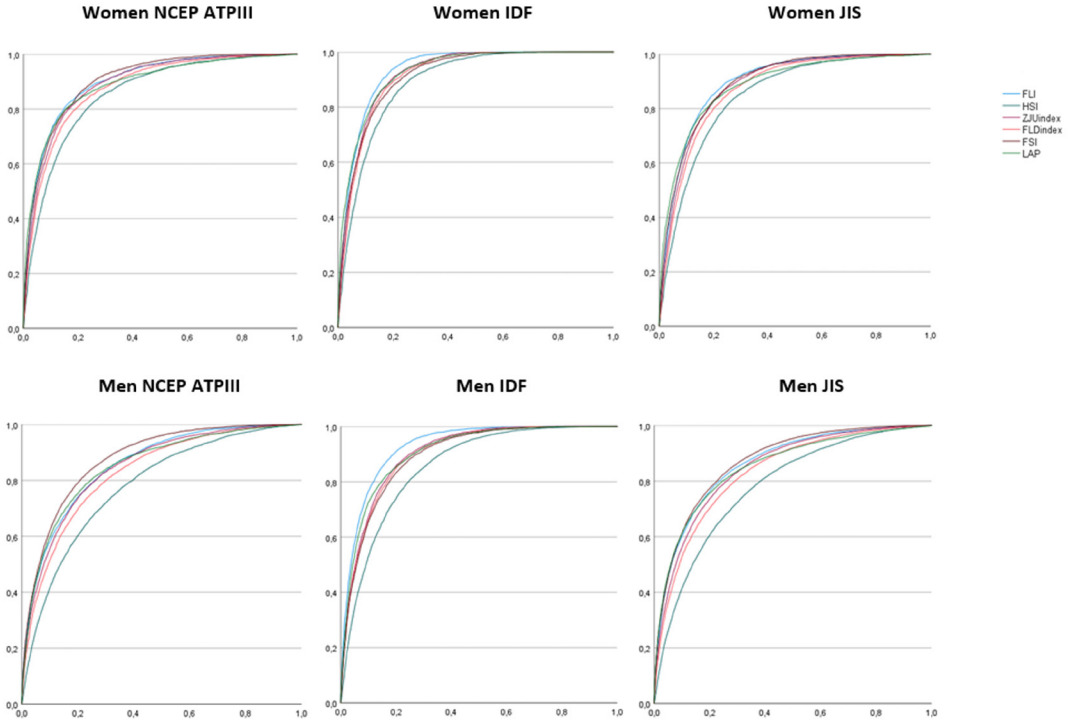
FLI Fatty liver index. HSI Hepatic steatosis index. ZJU Zhejiang University index. FLD Fatty liver disease. LAP Lipid accumulation product.
MS ATPIII. Metabolic syndrome Adult Treatment Panel III. MS IDF Metabolic syndrome International Diabetes Federation. Metabolic syndrome Joint Interim Statement

Table IV: Areas under the curve of the different nonalcoholic fatty liver disease risk scales for predicting the presence of metabolic syndrome with the three criteria by sex.

	Women n=172.282		
	MS NCEP ATPIII AUC (95% CI)	**MS IDF AUC (95% CI)**	**MS JIS AUC (95% CI)**
Fatty liver index	0.900 (0.895-0.906)	0.935 (0.931-0.938)	0.897 (0.892-0.902)
Hepatic steatosis index	0.855 (0.848-0.862)	0.891 (0.886-0.896)	0.849 (0.843-0.855)
Zhejian University index	0.892 (0.887-0.898)	0.921 (0.918-0.925)	0.887 (0.882-0.892)
Fatty liver disease index	0.879 (0.873-0.885)	0.916 (0.912-0.920)	0.874 (0.869-0.880)
Framingham steatosis index	0.904 (0.899-0.909)	0.916 (0.911-0.920)	0.895 (0.890-0.900)
Lipid accumulation product	0.890 (0.884-0.897)	0.928 (0.925-0.932)	0.888 (0.883-0.894)
	Men n=246.061		
Fatty liver index	0.856 (0.851-0.860)	0.928 (0.926-0.931)	0.863 (0.859-0.866)
Hepatic steatosis index	0.779 (0.774-0.785)	0.855 (0.851-0.860)	0.781 (0.776-0.786)
Zhejian University index	0.848 (0.843-0.853)	0.905 (0.901-0.908)	0.850 (0.845-0.854)
Fatty liver disease index	0.829 (0.823-0.834)	0.900 (0.896-0.904)	0.832 (0.828-0.837)
Framingham steatosis index	0.877 (0.873-0.881)	0.895 (0.891-0.899)	0.871 (0.868-0.875)
Lipid accumulation product	0.851 (0.846-0.856)	0.908 (0.904-0.912)	0.852 (0.847-0.856)

MS ATPIII. Metabolic syndrome Adult Treatment Panel III. MS IDF Metabolic syndrome International Diabetes Federation. Metabolic syndrome Joint Interim Statement

Figure 2: ROC curves with the three criteria by sex.



MS ATPIII. Metabolic syndrome Adult Treatment Panel III. MS IDF Metabolic syndrome International Diabetes Federation. Metabolic syndrome Joint Interim Statement

Table V: Cut-off points, sensitivity, specificity and Youden index of the different nonalcoholic fatty liver disease risk scales for predicting the presence of metabolic syndrome with the three criteria by sex.

	Women n=172.282		
	MS NCEP ATPIII Cutoff-Sens-Specif-Youden	MS IDF Cutoff-Sens-Specif-Youden	MS JIS Cutoff-Sens-Specif-Youden
Fatty liver index	27.08-82.7-82.7-0.654	31.10-86.3-86.2-0.725	25.20-82.5-82.4-0.649
Hepatic steatosis index	39.40-78.3-78.2-0.565	40.00-81.5-81.4-0.629	39.09-77.8-77.8-0.556
Zhejian University index	40.30-81.7-81.7-0.634	41.00-85.0-85.0-0.700	39.90-81.2-81.1-0.623
Fatty liver disease index	33.06-80.4-80.4-0.608	33.82-84.3-84.1-0.684	32.74-80.0-80.0-0.600
Framingham steatosis index	0.18-82.0-82.0-0.640	0.19-83.5-83.5-0.670	0.18-80.2-80.0-0.602
Lipid accumulation product	25.60-82.0-82-0.640	27.30-85.0-85.0-0.700	24.44-81.3-81.3-0.626
	Men n=246.062		
Fatty liver index	52.21-77.3-77.0-0.543	61.14-85.2-85.2-0.704	47.11-78.4-78.3-0.567
Hepatic steatosis index	38.22-71.0-71.0-0.420	39.25-77.6-77.4-0.550	37.54-71.2-71.2-0.424
Zhejian University index	39.00-77.0-76.9-0.539	39.94-82.5-82.5-0.650	38.22-77.1-77.1-0.542
Fatty liver disease index	33.65-75.2-75.2-0.505	34.64-82.0-81.9-0.639	32.96-75.6-75.5-0.511
Framingham steatosis index	0.23-79.6-79.5-0.591	0.25-81.5-81.5-0.630	0.20-78.7-78.7-0.574
Lipid accumulation product	37.54-77.8-77.8-0.556	41.86-83.2-82.9-0.661	33.55-77.8-77.7-0.555

MS ATPIII. Metabolic syndrome Adult Treatment Panel III. MS IDF Metabolic syndrome International Diabetes Federation. Metabolic syndrome Joint Interim Statement

Discussion

In our group, the values of the different NASH scales show higher mean values in persons with metabolic syndrome with the three criteria used. The analysis of the ROC curves allows us to affirm that all the NASH risk scales are quite useful for predicting the appearance of metabolic syndrome, although the greatest areas under the curve, sensitivity, specificity and Youden index are found when applying the IDF criteria.

We have not found articles that assess the relationship between NASH and MS risk scales, so we will focus our discussion on assessing whether or not there is a relationship between the two entities.

An article in Lancet20 in 2014 entitled "Non-alcoholic fatty liver disease as a cause and a consequence of metabolic syndrome" already showed a relationship between both clinical entities by observing that two key elements of metabolic syndrome such as glycemia and tryglicerides were underproduced by the liver, so that it can be considered a key element in these metabolic alterations. Another link between the two entities is that both obesity and excessive consumption of sugars or a sedentary lifestyle increase the prevalence of both. Another 2015 study21 that also assessed the relationship between the two pathological conditions concluded that NASH is not simply the hepatic manifestation of metabolic syndrome, but is a pathogenic determinant of the syndrome. Subsequent research22 has emphasized the relationship between NAFLD and MS, indicating that since NAFLD is generally associated with insulin resistance, abdominal obesity, dyslipidemia, hypertension, and hyperglycemia, NAFLD is often considered the hepatic manifestation of the metabolic syndrome. There is evidence that this relationship between NAFLD and metabolic syndrome is bidirectional, as NAFLD may predispose to metabolic syndrome, which in turn may increase NAFLD or increase the risk of its development in those without a prior diagnosis.

Strengths and limitations

As strengths of the study, we can highlight the large sample size (more than 400,000 workers) and the large number of NASH and metabolic syndrome risk scales used. The main limitation is that no diagnostic techniques for NASH or other than risk scales were used.

Conclusions

According to the results obtained in our study, we can conclude that in this group of workers the different NASH risk scales are quite useful for predicting the appearance of metabolic syndrome, especially when we use the IDF criteria.

Conflict of Interest

The authors declare that no competing interests exist.

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ORIGINAL

Isolation and identification of microorganisms in individuals associated with refuse disposal sites and collection centres in Awka metropolis, Nigeria

Aislamiento e identificación de microorganismos en individuos asociados a los vertederos y centros de recogida de basuras en la metrópoli de Awka, Nigeria

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Abstract

Introduction: Despite the attendant health risks inherent in waste dump sites, certain individuals make their living by foraging and packing the waste for survival. To isolate, characterize and identify pathogens associated with waste dump sites that may be of public health importance.

Methods: A total of 280 samples were collected from the waste collectors, scavengers, and people living and trading around refuse dump sites, collection centers, and refuse dump sites in Awka Metropolis. The bacterial and fungal isolates were further subjected to pathogenicity testing using Wistar rats.

Results: A total of 6 bacterial genera which included *Staphylococcus aureus, Streptococcus pneumonia, Escherichia coli, Pseudomonas aeriginosa, Klebsiella pneumonia, Bacillus subtilus, Staphylococcus epidermidis* and 4 fungal genera namely Aspergillus niger, *Aspergillus fumigatus, Mucor spps* and *Candida albicans*. The incidence of microbial isolates from different sampled groups prior to their work differed significantly ($P < 0.05$) when compared with the isolates during their work. It was also observed that the prevalence of different microorganisms isolated after daily activities was higher than that of those isolated before daily activities.

Key words: Refuse dump sites, waste collectors, scavengers, microorganisms, public health.

Resumen

Introducción: A pesar de los riesgos sanitarios inherentes a los vertederos, algunos individuos se ganan la vida rebuscando en los residuos y empaquetándolos para sobrevivir. Aislar, caracterizar e identificar los agentes patógenos asociados a los vertederos que puedan tener importancia para la salud pública.

Material y métodos: Se recogieron un total de 280 muestras de recolectores de residuos, carroñeros y personas que viven y comercian en los alrededores de los vertederos de residuos, centros de recogida y vertederos de residuos en la metrópolis de Awka. Los aislados bacterianos y fúngicos fueron sometidos a pruebas de patogenicidad con ratas Wistar.

Resultados: Un total de 6 géneros bacterianos que incluían *Staphylococcus aureus, Streptococcus pneumonia, Escherichia coli, Pseudomonas aeriginosa, Klebsiella pneumonia, Bacillus subtilus, Staphylococcus epidermidis* y 4 géneros fúngicos, a saber, *Aspergillus niger, Aspergillus fumigatus, Mucor spps* y *Candida albicans*. La incidencia de los aislados microbianos de los distintos grupos muestreados antes de su trabajo difería significativamente ($P < 0,05$) cuando se comparaba con los aislados durante su trabajo. También se observó que la prevalencia de los diferentes microorganismos aislados después de las actividades diarias era mayor que la de los aislados antes de las actividades diarias.

Palabras clave: Vertederos, recolectores de residuos, carroñeros, microorganismos, salud pública.

Introduction

Domestic solid waste is any unwanted or discarded solid materials from residential activities that cause environmental, social and health problems. The World Health Organization refers to waste as something which the owner no longer wants at a given time and space which has no current or perceived market value. In the words of Ikhuoria[1], waste is refuse, garbage, ashes and rubbish that are derived from places of human and animal habitation. He further grouped solid waste elements into two – decomposable refuse and non-decomposable refuse. Nwobu[2] in his study of solid waste disposal and management in Awka, Anambra state, defined solid waste as anything discarded or unwanted whose physical state is solid or semisolid.

Kimberly[3] carried out a study on composition of solid waste in Florida State, United States of America. In his study, he made a classification of solid wastes based on the material composition. The daily activities of humans give rise to a large variety of wastes and when these waste materials are disposed off, microorganisms of different types such as bacteria, fungi and worms colonize the waste and begin to degrade them[4].

The improper disposal of these waste constitute serious health problems, such as transmission of infectious diseases to humans and animals living within the vicinity[5], as they pollute the air, soil and freshwater bodies.

During the activities of scavengers and waste collectors they are exposed to various infectious agents[6] as well as to various toxic substances which may cause illness/sickness. They are also exposed to potentially pathogenic bio-aerosols that may lead to the spread of various diseases. Research conducted by Douwes *et al*.[7] revealed that exposures to bioaerosols in both the occupational and residential indoor environment could have adverse effects with major public health impact, including contagious infectious diseases, acute toxic effects, allergies and cancer. Ajadike[8], states that urban waste crisis arises in Nigeria because of three fundamental factors namely, rapid increase in urban population, heavy consumption pattern of urban dwellers and the inefficiency of the authorities whose statutory responsibilities includes efficient waste disposal in cities. Adesoji[9] took a study of solid waste disposal in Ibadan, he discovered that various landfill sites and open dump sites in the town are mismanaged and these sites harbor disease carrying pathogens such as rat, cockroaches, mosquitoes, houseflies, fleas etc.

Though there are available methods of waste disposal, such as composting, landfill and incineration, open dumping continues to be the only method available in Nigeria particularly in major cities like Port Harcourt, Awka, Nnewi and Onitsha even though these are strongly discouraged in the National Sanitation Policy[10]. The non-chalant attitude of the people on issues concerning waste management and environmental best practices has become a major source of worry. Wastes are left on the streets for days or weeks, without proper sorting before they are disposed to the final dumpsites or relocated to open lands[11].

Materials and methods

Study design

This prospective study was performed to determine some microorganisms in individuals associated with refuse dumpsites and collection centers in Awka metropolis.The sampling method used was a Convenience Sampling Technique, a non-probability sampling technique where the subjects were selected based on convenience, accessibility, proximity to the researcher and not necessarily a representative of the entire population.

Study area

Ethical consideration

Ethical clearance was obtained from the Faculty of Health Sciences and Technology and Authorization from the Anambra State Waste Management Authority. Informed Consent was also sought from various waste scavengers and waste collectors who willingly volunteered to be part of this study. It entailed the purpose of the study, benefits, privacy/confidentiality and conflict of interest. Participation was absolutely voluntary and each subject had the opportunity to participate or opt out at any point in the course of the survey.

Sampling period and sample population

The study was carried out between June 2016 and August 2016, using scavengers and waste collectors within the age bracket of 18-45 years and Control subjects of same age bracket. A total of 350 samples were collected, 30 samples from individuals living and trading around refuse dump sites, 60 samples from waste collectors, 60 samples from waste scavengers, 10 samples from waste vehicles, 40 samples from waste collection centers and 10 samples from main refuse dump sites, and 140 samples from the Control group.

Microbial analysis

Waste Sample

Waste Samples [20g] were collected from different portion of the main dump sites and collection centers for even distribution, to ensure that no organisms were missed. The samples were collected in sterile containers, using a special spatula. Thereafter, 1g of each prepared waste sample was added into 9ml of 0.1% bacteriological peptone [10^{-1}dilution] shaken vigorously for at least 1 minute. The diluents were left to sediment for a short period. Further ten-fold serial dilutions were made up to 10^{-4}, using sterile pipettes. Cultures from the last 2

dilutions [10^{-3} and 10^{-4}] were made by transferring an aliquot [0.1ml] into surface dried Nutrient agar, and MacConkey Agar plates and spread evenly with a spreader. The culture plates were incubated aerobically at 370C for 24hrs.

Collection, culture and identification of fungal isolates in waste dump site, scavenger, waste collectors

Waste samples

One milliliter [10ml of sterilised distilled water was added to 1g of waste] of each prepared waste sample was added into 9 ml of 0.1% bacteriological peptone [10^{-1} dilution]. An aliquot [1.0ml] was transferred into the next test tubes and diluted serially in one-tenth stepwise to 10^{-3} dilution using sterile pipettes. From the dilution of 10^{-1}, 10^{-2} and 10^{-3} of each waste sample, 0.1 ml aliquot was transferred aseptically onto freshly prepared Potato Dextrose Agar [PDA] plates of which 0.2 ml of 0.5% Ampicillin was added to inhibit the growth of bacteria and allowing the growth of fungi[12]. The inoculums were spread with a sterile bent glass rod. The inoculated plates were inverted and incubated at room temperature for 5 to 7 days.

Antibiotic susceptibility testing

The antibiotic susceptibility of the isolates was determined by the disc diffusion method on nutrient agar. Bacterial isolates were tested against Ciprofloxacin [CFX 5 µg], Streptomycin [S-10 µg], 30µg], Gentamycin [GEN 10µG], Augmentin [AUG 30µg], Chloramphenicol [C 30 µg], Erythromycin [E 15 µg], Ceftazidme [CTX 30µg], Tetracycline [T 30 µg], Ofloxacin [OFL 5µg], Vancomycin [V 30 µg], Rifampicin [R 5µg] and Amoxicillin [AMX 30µg].Colonies from the slants were picked and inoculated onnutrient broth and incubated for 18hr. Fresh media were prepared. Picking of colonies from the broth cultures was done using sterile applicator stick and proper swabbing unto the surface of the prepared plates was done, after which antimicrobial discs were applied using a sterile forceps.The discs were firmlypressed down to prevent falling off of the discs from the plates during incubation. The plates were incubated at 37ºC for 4hours.After incubation, the zones of inhibition formed were measured in two perpendicular planes with the averages determined. After this, the results were interpreted using standard tables to determine if the bacteria are Sensitive [S], Intermediate [I] or Resistant [R] to the antimicrobial drugs. The diameter of the zone of clearance [including the diameter of the disk] was measured to the nearest whole millimeter and interpreted on the basis of CLSI guideline[13].

Statistical analysis

Data collected were subjected to statistical analysis using percentages, Student's t-test and analysis of variance (ANOVA).Values will be deemed significant at $P<0.05$.

Results

The results obtained from the waste collectors, scavengers and people living and trading around the waste bin, after daily activities were compared with the results obtained from them prior to work.

Frequency of bacterial and fungal isolates from waste collectors

From the waste collectors 2(11.8%) *Staphylococcus aureus* were isolated prior to waste collection while 15(88.2%) were isolated after waste collection, 2(13.3%) *Klebsiella pneumonia* were isolated prior to waste collection, while 13(86.7%) were isolated after waste collection from Nasal swab and Hand swab. The remaining isolates were only isolated after work, they are *Streptococcus pneumonia* 4(5.26%), *Escherichia coli* 6(7.9%), *Pseudomonas aeruginosa* 8(10.5), *Bacillus subtilus* 4(5.26%), *Staphylococcus epidermidis* 2(2.63%), *Aspergillus niger* 7(9.21%), *Aspergillus fumigatus* 2(2.63%), *Mucorspp* 4(5.26%), and *Candida albicans* 7(9.21%) (**Table I**)

Frequency of bacterial and fungal isolates from scavengers

From the Scavengers, 2(12.5%) *Staphylococcus aurues* were isolated before Scavenging while 14(87.5%) were isolated after Scavenging. The remaining isolates were only isolated after scavenging, they are *Streptococcus pnuemoniae* 1(1.92%), *Escherichia coli* 4(7.69%), *Pseudomonas aeruginosa* 6 (11.5), *Klebsiella pneumonia* 8(15.4%), *Bacillus subtilis* 2(3.84%), Staphylococcus epidermidis1(1.92%), *Aspergillus niger* 4(7.69%), *Aspergillus fumigatus* 3(5.8%), *Mucorspp* 1(1.92%) and *Candida albicans* 6(11.53%) (**Table II**).

Frequency of bacterial and fungal isolates from people living /trading around refuse dump sites

From people trading around the bins as nobody resides around the main dump sites, no microorganism was isolated before business, but after business, *Staphylococcus aureus* 9(81.8%), *Klebsiella pneumoniae* 1(9.09%) and *Candida albicans* 1(9.09%) were isolated. Few microorganisms were isolated probably because they don't associate directly with the refuse unlike the scavengers and waste collectors (**Table III**).

Frequency of bacterial and fungal isolates from different inanimate sources.

The most frequently encountered microbial isolates from the waste bins were *Pseudomonas aeruginosa* 21(30%), *Staphylococcus aureus* 14(20%), *Klebsiella pneumoniae* 13(18.57%) and *Bacillus subtilis* 10(14.29%) while the least encountered were *Aspergillus niger* 3(4.29%), *Candida albicans* 3(4.29%), *Aspergillus fumigatus* 2(2.86%) and *Mucormucedo*.1(1.43%).

The most frequently encountered microbial isolates from the waste vehicle were Klebsiella pneumoniae 8(30.77%), *Staphylococcus aureus* and *Pseudomonas aeruginosa* 4(15.39%), *Aspergillus niger* and *Mucormucedo* 3(11.54%) while the least encountered were *Escherichia coli*, *Aspergillus fumigatus* and *Bacillus subtilis* 1(3.85%).

The most frequently encountered microbial isolates from the Refuse dump were *Klebsiella pneumoniea* 5(21.74%), *Escherichia coli* 4(17.39), *Aspergillus niger* 3(13.04), while the least encountered were Mucorspp. and *Pseudomonas aeruginosa* 2(8.7), *Candida albicans*, *Aspergillus fumigatus*, *Streptococcus pnuemoniae* and *Staphylococcus aureus* 1(4.35%).

The most frequently encountered microbial isolates from air around the main refuse dump were *Klebsiella pneumoniae* 7(33.33), *Staphylococcus aureus*, *Pseudomonas aeruginosa, Aspergillus fumigatus* 3(14.29), while the least encountered were *Aspergillus niger* 2(9.52) (**Table IV**).

Table I: Frequency of bacterial and fungal isolates from waste collectors.

WASTE COLLECTORS

Bacterial and fungal isolates	Urine N=20 [%]	Nasal swab N=20[%]	Hand swab N=20 [%]	Control N=10 [%]	Total N [%]
Staphylococcus aureus	6 (22.2)	5 (22.72)	4 (17.39)	2 (50.00)	17 (22.4)
Streptococcus pneumoniae	3 (11.11)	1 (4.54)	0 (0.00)	0 (0.00)	4 (5.26)
Escherichia coli	3 (11.1)	1 (4.54)	2 (8.70)	0 (0.00)	6 (3.95)
Pseudomonas aeruginosa	3 (11.1)	3 (13.60)	2 (8.70)	0 (0.00)	8 (10.52)
Klebsiella pneumoniae	5 (18.5)	5 (22.72)	3 (13.00)	2 (50.00)	15 (19.73)
Bacillus subtilis	1 (3.70)	2 (9.09)	1 (4.35)	0 (0.00)	4 (5.26)
Staphylococcus epidermidis	1 (3.70)	0 (0.00)	1 (4.35)	0 (0.00)	2 (2.63)
Aspergillus niger	0 (0.00)	2 (9.09)	5 (21.74)	0 (0.00)	7 (9.21)
Aspergillus fumigatus	0 (0.00)	1 (4.54)	1 (4.54)	0 (0.00)	2 (2.63)
Mucor Mucedo	0 (0.00)	2 (9.09)	2 (8.70)	0 (0.00)	4 (5.26)
Candida albicans	5 (18.52)	0 (0.00)	2 (8.70)	0 (0.00)	7 (9.21)
TOTAL	27 (100)	22 (100)	23 (100)	4(100)	76 (100)

Table II: Frequency of bacterial and fungal isolates from the scavengers.

SCAVENGERS

Bacterial and fungal isolates	Urine N=20 [%]	Nasal swab N=20 [%]	Hand swab N=20 [%]	Control N=10 [%]	Total N [%]
Staphylococcus aureus	5 (21.7)	6 (42.9)	3 (23.1)	2 (100)	16 (30.8)
Streptococcus pneumoniae	1 (4.35)	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.92)
Escherichia coli	4 (17.39)	0 (0.00)	0 (0.00)	0 (0.00)	4 (7.69)
Pseudomonas aeruginosa	3 (13.00)	2 (14.2)	1 (7.69)	0 (0.00)	6 (11.5)
Klebsiella pneumoniae	6 (26.1)	0 (0.00)	2 (15.39)	0 (0.00)	8 (15.4)
Bacillus subtilis	0 (0.00)	2 (14.28)	0 (0.00)	0 (0.00)	2 (3.84)
Staphylococcus epidermidis	0 (0.00)	0 (0.00)	1 (7.69)	0 (0.00)	1 (1.92)
Aspergillus niger	0 (0.00)	2 (14.28)	2(15.39)	0 (0.00)	4 (7.69)
Aspergillus fumigatus	0 (0.00)	2 (14.28)	1 (7.69)	0 (0.00)	3 (5.76)
Mucor Mucedo	0 (0.00)	0 (0.00)	1 (7.69)	0 (0.00)	1 (1.92)
Candida albicans	4 (17.39)	0 (0.00)	2 (15.39)	0 (0.00)	6 (11.53)
TOTAL	23 (100)	14 (100)	13 (100)	2 (100)	52 (100)

Table III: Frequency of bacterial and fungal isolates from People living/trading around the waste bin.

People living/trading around the bin

Bacterial and fungal isolates	Urine N=10 [%]	Nasal swab N=10 [%]	Hand swab N=10 [%]	Control N=10 [%]	Total N [%]
Staphylococcus aureus	2 (66.67)	3 (75.00)	4 (100.00)	0 (0.00)	9 (81.81)
Klebsiella pneumoniae	0 (0.00)	1 (25.00)	0 (0.00)	0 (0.00)	1 (9.09)
Candida albicans	1 (33.33)	0 (0.00)	0 (0.00)	0 (0.00)	1 (9.09)
TOTAL	3 (100)	4 (100)	4 (100)	0 (0.00)	11 (100)

Table IV: Frequency of bacterial and fungal isolates from different inanimate sources.

Bacterial /Fungalisolates	Waste receptacles N=40[%]	Refuse Vehicles N=10[%]	Refuse [%]	Air around the Dumpsites	Control (N=10)	TOTAL
Staphylococcus aureus	14 (20)	4 (15.39)	1 (4.35)	3 (14.29)	2 (50.00)	24 (16.6)
Streptococcus pneumoniae	0 (0.00)	0 (0.00)	1 (4.35)	1 (4.76)	0 (0.00)	2 (1.38)
Escherichia Coli	3 (4.29)	1 (3.85)	4 (17.39)	0 (0.00)	0 (0.00)	8 (5.55)
Pseudomonas aeruginosa	21 (30.00)	4 (15.39)	2 (8.70)	3 (14.29)	1 (25.00)	31 (21.52)
Klebsiella pneumoniae	13 (18.57)	8 (30.77)	5 (21.74)	7 (33.33)	1 (25.00)	34 (23.61)
Bacillus subtilis	10 (14.29)	1 (3.85)	2 (8.70)	1 (4.76)	0 (0.00)	14 (9.72)
Staphylococcus epidermidis	0 (0.00)	0 (0.00)	1 (4.35)	0 (0.00)	0 (0.00)	1 (0.69)
Aspergillus niger	3 (4.29)	3 (11.54)	3 (13.04)	2 (9.52)	0 (0.00)	11 (7.63)
Aspergillus fumigatus	2 (2.86)	1 (3.85)	1 (4.35)	3 (14.29)	0 (0.00)	7 (4.86)
Mucor mucedo	1 (1.43)	3 (11.54)	2 (8.70)	1 (4.76)	0 (0.00)	7 (4.86)
Candida albicans	3 (4.29)	1 (3.85)	1 (4.35)	0 (0.00)	0 (0.00)	5 (3.47)
Total	70 (100)	26 (100)	23 (100)	21 (100)	4 (100)	144 (100)

Table V: Incidence of different microbial isolates from various sampled groups.

	COLLECTORS			SCAVENGERS			PLAWB			CONTROL			P-value
	PreA	PosA	Mean	PreA	PosA	Mean	PreA	PosA	Mean	PreA	PosA	Mean	
Urine		27	1.35		23	1.15		6	0.30		3	0.15	0.001
Nasal swab	4	23	1.15	2	15	0.75	1	8	0.40	1	2	0.1	0.008
Hand swab	0	23	1.15	0	13	0.65	0	8	0.40	0	1	0.05	0.002

KEY: PreA= Pre Activity, PosA= Post Activity, PLAWB= People living/trading around refuse bins. P is significant at P<0.05.

Table VI: Susceptibility profile of commonly used antibiotics against Gram positive bacterial isolates.

Isolates	Susceptibility	CPX	S	GN	AUG	C	E	CT	V	R
Staphylococcus aureus N=42	NS (%)	17 (40.5)	22 (52.4)	19 (45.2)	25 (59.5)	14 (33.3)	16 (38)	23 (54.8)	20 (47.6)	26 (62)
	NR (%)	25 (59.5)	20 (47.6)	23 (54.8)	17 (40.5)	28 (66.7)	26 (62)	19 (45.2)	22 (52.4)	16 (38)
Streptococcus Pneumoniae N=5	NS (%)	4 (80)	4 (80)	5 (100)	4 (80)	3 (60)	4 (80)	4 (80)	2 (40)	3 (60)
	NR (%)	1 (20	1 (20)	0 (00)	1 (20)	2 (40)	1 (20)	1 (20)	3 (60)	2 (40)
Bacillus subtilus N=6	NS (%)	2 (33.3)	2 (33.3)	1 (16.7)	1 (16.7)	4 (66.7)	2 (33.3)	3 (50)	3 (50)	2 (33.3)
	NR (%)	4 (66.7)	4 (66.7)	5 (83.3)	5 (83.3)	2 (33.3)	4 (66.7)	3 (50)	3 (50)	4 (66.7)

KEY: CPX–Ciprofloxacin,S-Streptomycin,GN-Gentamycin,AUG-Augumentin,C- Chloramphenicol, E-Erythromycin, CT- Ceftriaxone, V- Vancomycin, R-Rifampicin. NS- Number sensitive, Number resistant.

Table VII: Susceptibility profile of commonly used antibiotics against Gram negative bacterial isolates.

Isolates	Susceptibility	CPX	S	GN	AUG	C	CT	AMX	OFX
Escherichia coli N=10	NS(%)	4(40)	3(30)	4(40)	8(80)	2(20)	7(70)	7(70)	4(40)
	NR(%)	6(60)	7(70)	6(60)	2(20)	8(80)	3(30)	3(30)	6(60)
Klebsiella pneumoniae N=24	NS(%)	9(37.5)	4(16.7)	8(33.3)	2(8.3)	12(50)	10(41.7)	10(41.7)	6(25)
	NR(%)	15(62.5)	20(83.3)	16(66.7)	22(91.7)	12(50)	14(58.3)	14(58.3)	18(75)
Pseudomonas aeruginosa N=14	NS(%)	4(28.6)	6(42.9)	6(42.9)	3(21.4)	8(57.1)	3(21.4)	12(50)	3(21.4)
	NR(%)	10(71.4)	8(57.1)	8(57.1)	11(78.6)	6(78.6)	11(78.6)	12(50)	11(78.6)

KEY: CPX–Ciprofloxacin,S-Streptomycin,GN-Gentamycin,AUG-Augumentin,C-Chloramphenicol, CT- Ceftriaxone, AMX-Amoxicillin, OFX- Ofloxacin.
NS- Number sensitive, NR-Number resistant.

Discussion

This study revealed that the predominant bacteria in waste dump sites were *Staphylococcus aureus*, *Klebsiella pneumoniae, Pseudomonas aeruginosa, Streptococcus pneumoniae, Escherichia coli, Bacillus subtilis, Staphylococcus epidermidis, Aspergillus niger, Aspergillus fumigatus*, and *Candida albicans*. The bacterial species identified in this study are similar to those reported by Aboagye-Larbi *et al*.[14]. Most of the bacteria, which commonly occur in the air and soil, are opportunistic pathogens which may cause infection. For instance, Staphylococcus aureus can cause food poisoning, wound infection and acute osteomyelitis in children and young adults. Pseudomonas aeruginosa can also cause wound and burn infections and are difficult to treat with some antibiotics. The microorganisms present in the air may cause infectious diseases in susceptible individuals.

Most of the microbial isolates that were not isolated from the subjects before their daily activities were isolated after their daily activities and the number of microbial isolates from the test subjects were higher than the ones from control subjects.This agrees with the work done by Aboagye-Larbi *et al*.[14]. Most of these microorganisms had earlier been reported by Wachukwu *et al*.[10] as being associated with waste decay. The isolates obtained from the dump sites and workers in this study were essentially similar. As earlier reported by Markanday *et al*.[15], most of these isolates are known to be involved in the biodegradation of organic matters. The most frequently isolated fungi in the present study belonged to the genus *Aspegillus*. This conforms with Wienrich *et al*.[16] which suggested that Aspergillusniger and *Aspergillus fumigatus* as the leading species of fungi in the biowaste due to their frequency of detection. These two species were also encountered in this study Aspergillus is known to produce aflatoxin, a mycotoxin that is toxic and carcinogenic. High amount of aflatoxins present in contaminated food exerts their toxicological effect in animals and man. *Aspergillus fumigatus* is known to be associated with dust and its endotoxins are found in landfills and compost plants. *Mucormucedo* were identified in and around the environment of the main dump sites and in the collection centers.

Another group of microbial isolates from the waste dump and human are the endospores forming bacteria such as *Bacillus subtilis* and *Escherichia coli*, which are important organisms that cause urinary tract infection and gastroenteritis in children. *Bacillus subtilis* produce spores and are commonly found in the soil, therefore they can easily get through to the scavengers. If waste collectors are not protected, there is tendency of these pathogens gaining entry into the body.The resultant effect will be infection, general body malaise and in some cases death. Wachukwu *et al*.[10] and Aboagye-Larbi *et al*.[14] shared similar views. *Staphylococcus aureus* showed significant increase in the case of scavengers and waste collectors. *Staphylococcus* observed in this group of people may indicate the presence of bacterial infections especially with the *Staphylococcus aureus* which may result in skin injuries or disorders[17]. Staphylococcal disease of the skin if left untreated usually results in a localized collection of pus known as an abscess, boil or furuncle. When Staphylococccus is in the blood, it can cause high fever, chills and low blood pressure. The direct health risk of concern is mainly for the worker on the field who handles refuse or who live near the disposal sites, if not properly protected.

Of the 4 groups sampled, the number of bacterial and fungal isolates significantly differed between the 4 groups at 5% significance level (*P=0.008*).Further post ANOVA analysis showed that this difference was only between collectors and control and not between any other groups. This may be due to collectors and scavengers handle the wastes with their bare hands while the PLAWB and control did not. Comparison between the number of organisms isolated from nasal and hand swabs before and after were statistically significant at the 5% significance level (*P=0.001*) and (*P=0.001*) respectively. This meant that the carriage of these microorganisms by waste collectors, scavengers at the waste dump sites might be as a result of their activities, while the carriage by the PLAWB were because of their presence around the bin, as these organisms are airborne and people around the waste bin inhaled them. In addition, carriage of these microbes by some of the control subjects may depend on where they reside as most of the microorganisms were isolated before the day activities. These might explain why most of the Scavengers and workers experienced recurrent respiratory and urinary tract infections, with some presenting with skin rashes.

From the resulst obtained in this study, antibiotic resistant bacteria were widespread as most of the isolated organisms were resistant to most of the antibiotics for which they were tested. This might be due to either the intrinsic resistance of many microorganisms to antibiotics or acquired resistance of the organisms enabled by the transfer of drug resistance plasmids among members of the isolates. A high level of resistance has been found with members of the family Enterobacteriaceae which were believed to have incidence of pathogenic strains of bacteria with acquired antibiotics resistance. The origin of this resistance can be traced to the faecal constituent of the waste produced by people or animals that have been treated indiscrimately with various types of antibiotics and to natural antibioticproduction by soil microorganisms[18].

Conclusion

The study showed that microbial loads at waste dump sites and collection centres pose a great threat not only to scavengers, waste collectors, and people living or trading around collection centers, but to the entire society. The study showed that microorganisms isolated from scavengers and waste collectors in Awka, Nigeria, induced lung and kidney dysfunctions in

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Conflict of Interest

The authors declare that no competing interests exist.

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ARTÍCULO ESPECIAL

Novedades de la insuficiencia cardíaca y los inhibidores del cotransportador de sodio-glucosa 2

New developments in heart failure and sodium-glucose cotransporter 2 inhibitors

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Resumen

Introducción: La insuficiencia cardíaca es un tema de actualidad debido a su crecimiento entre la población, sobre todo de edad avanzada, gracias a los avances en la efectividad de su tratamiento. La insuficiencia cardíaca, según su etiología, puede ser sistólica o diastólica y según la rapidez de instauración de los síntomas, aguda o crónica. Además de las alteraciones anatómicas cardíacas, la activación neurohumoral juega un papel muy importante en el cuadro clínico. Es por ello, que las dianas terapéuticas de los tratamientos más novedosos tienen en cuenta ambos factores.

Objetivos: Revisión de la inclusión y últimas novedades de los iSLGT2 en el tratamiento médico de la insuficiencia cardíaca según su FEVI y rapidez de la instauración de sus síntomas.

Resultados y discusión: El grupo donde mejor establecidos están los iSGLT2 es el de FEVI reducida. Tanto el estudio DAPA-HF (2019) como el EMPEROR-Reduced (2020) establecen el beneficio de la dapagliflozina y de la empagliflozina en la reducción de hospitalizaciones y mortalidad y por ellos la guía ESC 2021 ya los incluye entre sus recomendaciones para FEVI reducida. Los estudios más novedosos son los que dan un paso más y apuestan por los iSGLT2 en FEVI preservada. El EMPEROR-Preserved (2021) y el DELIVER (fase III) gracias a sus resultados apoyan su uso en este grupo y se espera su incorporación en las próximas guías de la ESC. El EMPA-RESPONE-AHF (2019) y el EMPULSE TRIAL (2022) estudian su uso en IC aguda con aparentes buenos resultados.

Palabras clave: Insuficiencia cardiaca; FEVI; Dapagliflozina; empagliflozina.

Abstract

Introduction: Heart failure is a current issue due to its growth among the population, especially the elderly, thanks to advances in the effectiveness of its treatment. Heart failure, depending on its etiology, can be systolic or diastolic and depending on the speed of onset of symptoms, acute or chronic. In addition to cardiac anatomical alterations, neurohumoral activation plays a very important role in the clinical picture. For this reason, the therapeutic targets of the most innovative treatments take both factors into account.

Objectives: Review of the inclusion and latest developments of iSLGT2 in the medical treatment of heart failure according to LVEF and speed of onset of symptoms.

Results and discussion: The group where iSGLT2 are best established is that of reduced LVEF. Both the DAPA-HF (2019) and the EMPEROR-Reduced (2020) studies establish the benefit of dapagliflozin and empagliflozin in reducing hospitalizations and mortality, and therefore the 2021 ESC guide already includes them among its recommendations for reduced LVEF. The most innovative studies are those that go one step further and bet on iSGLT2 in preserved LVEF. Thanks to their results, EMPEROR-Preserved (2021) and DELIVER (phase III) support their use in this group and their incorporation in the next ESC guidelines is expected. The EMPA-RESPONE-AHF (2019) and the EMPULSE TRIAL (2022) study its use in acute HF with apparent good results.

Key words: Heart failure; LVEF; Dapagliflozin; empagliflozin.

Introducción

La insuficiencia cardiaca (IC) es uno de los problemas sociosanitarios más importantes en la actualidad, cuya incidencia sigue en continuo crecimiento, relacionado con el envejecimiento de la población, una prevalencia creciente de factores de riesgo mal controlados (HTA, DM y obesidad) y un aumento de la supervivencia en pacientes con IC debido a la mejora de los tratamientos. Es la razón cardiovascular más común de ingreso hospitalario entre las personas mayores de 60 años[1,2].

Definición y tipos de insuficiencia cardíaca

En términos generales la insuficiencia cardiaca es el estado fisiopatológico en el que algún tipo de disfunción del corazón provoca su incapacidad para bombear sangre en la cantidad necesaria para suplir los requerimientos metabólicos del organismo. A lo largo del siglo XX se ha producido un enorme avance en la comprensión y el conocimiento de la fisiopatología y los mecanismos compensadores que se ponen en marcha cuando un paciente desarrolla insuficiencia cardíaca. Hasta los años 50, la IC era entendida como un cuadro en el que el riñón era incapaz de eliminar la congestión hídrica causada por la disfunción cardíaca (modelo cardiorrenal). En los 70, la monitorización de estos pacientes y el desarrollo del cateterismo cardíaco llevó a explicar la IC por alteraciones en las presiones, los flujos y los gradientes en las distintas cámaras cardíacas y vasculares (modelo hemodinámico) que supuso también cambios en los fundamentos y aplicaciones terapéuticas. A principios de los años noventa, el descubrimiento de la participación del sistema nervioso autónomo y la activación secundaria de varios sistemas endocrinos como fenómenos compensatorios en la IC llevó a idear un modelo neurohormonal. Este modelo se ha mantenido en los últimos 10 años y ha permitido avanzar de manera sustancial en el tratamiento. La época actual está determinada por la investigación de mecanismos moleculares con dianas en muy diferentes localizaciones que contribuirá a una nueva forma de entender la enfermedad y conllevará avances en el tratamiento. Cada uno de estos modelos no sustituye al anterior, sino que lo asume y lo perfecciona[3,4].

A continuación, más que una clasificación, vamos a desarrollar los diversos términos que definen este síndrome, que ayuda a acotar el concepto y dan forma a la insuficiencia con la que podemos encontrarnos.

Insufiencia cardíaca sistólica y diastólica

La insuficiencia cardiaca diastólica consiste en que el músculo liso no se relaja lo suficiente o con la suficiente rapidez porque el miocardio esta engrosado, hay hipertrofia ventricular que impide el llenado ventricular y limita que se admita la sangre oxigenada proveniente de los pulmones. La consecuencia es que los volúmenes, y por tanto las presiones retrógradas se elevan ocasionando principalmente síntomas congestivos o retrógrados (edema de miembros y ascitis en lado derecho y edema agudo de pulmón en el izquierdo) y síntomas de bajo gasto o anterógrados (fatigabilidad, intolerancia al ejercicio, debilidad, etc.). Se trata de una insuficiencia cardiaca con fracción de eyección del ventrículo izquierdo preservada o FEVI ≥50%. Suele predominar en mujeres de edad avanzada y con antecedentes de hipertensión arterial. Por otro lado, tenemos la insuficiencia cardiaca sistólica, que se caracteriza por dilatación de la cavidad y por ende una contracción deficiente que se traduce en una FEVI reducida cuando esta es ≤40 o una función del ventrículo izquierdo levemente reducida si la FEVI se encuentra entre el 41% y el 49%. Es la más habitual y predomina en varones de edad media con antecedentes de cardiopatía isquémica. La sintomatología es fundamentalmente de bajo gasto o anterógrada, por hipoperfusión tisular sobre todo del riñón, lo que lleva a la retención de agua y sodio, del músculo esquelético, que causa fatigabilidad, y el cerebro, en el que provoca disminución del nivel de conciencia, aunque con la evolución aparecen también síntomas retrógrados. Hay que tener en cuenta que teóricamente se habla de dos tipos de IC pero que en la mayoría de los pacientes coexisten anomalías de la función sistólica y diastólica independientemente de la fracción de eyección del ventrículo izquierdo y que la justificación de esta clasificación radica en la mejora de los resultados en pacientes con FEVI ≤40 con el tratamiento y por ello es el clasificador más utilizado en los ensayos clínicos. Igual pasa con la clínica, ambos aspectos de la IC se dan simultáneamente, pero los mecanismos compensadores están más dirigidos a corregir la hipoperfusión tisular por lo que la sintomatología retrógrada o congestiva es más evidente en los pacientes[3,4,5].

Insuficiencia cardíaca aguda o crónica

En función de la rapidez de instauración de la insuficiencia cardíaca y de la capacidad de los mecanismos compensadores de ponerse en marcha se distinguen la IC aguda y la crónica.

La insuficiencia cardíaca crónica (ICC) es la forma más habitual de presentación, en esta el inicio de los síntomas es gradual porque los mecanismos compensadores se han puesto en marcha y el paciente puede estar sintomático pero estable. Decimos que la IC crónica esta compensada cuando los mecanismos de compensación permiten que a pesar de la IC el individuo siga vivo.

La insuficiencia cardiaca aguda (ICA) se produce cuando el corazón sufre de forma brusca una lesión ya sea anatómica o funcional (como una rotura de una válvula cardíaca o un infarto agudo de miocardio o infartos masivos que afecten a la pared libre del ventrículo) sin dar tiempo a la aparición de mecanismos compensadores, generando síntomas

severos de congestión (sobre todo el edema pulmonar agudo) o de hipoperfusión (shock cardiogénico), sin que se produzca la acumulación global de fluidos, el aumento de peso y la cardiomegalia característicos de las formas crónicas de IC. La insuficiencia cardiaca aguda deriva en altas tasas de hospitalización y mortalidad hospitalaria siendo una de las principales causas de hospitalizaciones en sujetos mayores de 65 años. La ICA puede ser la primera manifestación de una IC (nueva aparición) o, más frecuentemente, deberse a una descompensación aguda de una IC crónica. En comparación con los pacientes con insuficiencia cardíaca aguda descompensada, aquellos con insuficiencia cardíaca de nueva aparición pueden tener una mortalidad hospitalaria más alta pero tienen tasas más bajas de mortalidad posterior al alta y de rehospitalización[3,4,5].

Insuficiencia cardíaca izquierda y derecha

La insuficiencia cardíaca también puede ser el resultado de una disfunción del ventrículo derecho (VD) que se altera en el contexto de una sobrecarga de presión o de volumen y que puede ser secundario a hipertensión pulmonar ocasionada en la mayoría de los casos por un aumento de presiones izquierdas por fallo del ventrículo izquierdo, es decir una insuficiencia cardiaca sistólica que trasmite retrógradamente las presiones hacia la circulación pulmonar y que llegados a este punto de la evolución de la IC además de los síntomas anterógrados de hipoperfusión, los síntomas retrógrados se realzan y producen disnea, ortopnea y edema agudo de pulmón. En resumen, la clínica congestiva en el territorio venoso pulmonar se origina en una disfunción izquierda. En cambio, si el origen de la insuficiencia del ventrículo derecho es primario ya sea una hipertensión primaria, un infarto de miocardio derecho, una miocardiopatía arritmogénica del ventrículo derecho (ARVC) o una valvulopatía los síntomas anterógrados son idénticos a los del lado izquierdo (datos de bajo gasto), pero los retrógrados cambian y se produce la famosa tríada de edema periférico, ingurgitación yugular y hepatomegalia. Es decir, la congestión sistémica se origina en una disfunción derecha. Recalcar que el origen de fallo derecho en la mayoría de ocasiones se debe a fallo izquierdo[3,4,5].

Fisiopatología de la insuficiencia cardíaca

El calcio y los miocitos cardíacos

En situación de normalidad, durante la sístole, en la segunda fase de salida de calcio, el calcio que entró procedente del LEC induce la salida de las reservas de calcio del retículo sarcoplásmico (RS) por medio de los receptores de rianodina (RyR2) que se encuentran en la membrana. Durante la diástole estos receptores deben estar cerrados gracias a la calstabina2 o FKBP12.6. Merecen especial interés pues en la insuficiencia cardíaca los RyR2 son fosforilados por la proteína quinasa A (PKA) como resultado de la sobreestimulación adrenérgica, la calstabina se separa de los RyR2 y el Ca2+ sale del RS. Esta salida aumentada tiene dos consecuencias: la generación de post despolarizaciones tardías que pueden disparar una taquicardia ventricular y provocar la muerte súbita, de aquí la importancia de las arritmias en IC y la disminución de las reservas de calcio el cual también es importante como segundo mensajero en vías de señalización, dentro de las cuales están aquellas que, en la IC, se relacionan con la remodelación cardiaca[5,6].

Remodelación cardíaca

Los miocitos cardiacos son células que no tienen capacidad de división por lo que el crecimiento cardiaco se basa en el crecimiento del tamaño celular. A la vez que ocurre este crecimiento también se produce un cambio en la expresión génica de proteínas como el péptido natriurético y proteínas cardiacas fetales y otras no adaptativas que generan fibrosis.

Cuando la hipertrofia es secundaria a una sobrecarga de volumen, el crecimiento de los miocitos ocurre por adición de nuevos sarcómeros en serie, es decir, los miocitos se alargan y el corazón presenta una hipertrofia excéntrica, dilatada, con aumento del radio (IC sistólica). En cambio, cuando la hipertrofia ocurre secundaria a una sobrecarga de presión, los sarcómeros se agregan en paralelo (uno a la par del otro), lo que provoca un engrosamiento de la pared ventricular, una hipertrofia concéntrica que disminuye el radio (IC diastólica). La reserva coronaria está disminuida en la hipertrofia, por lo que aumenta el riesgo de infarto de miocardio.

Generalmente, el inicio de la remodelación cardiaca se produce antes de la sintomatología pues es compensatorio, pero continúa después de la aparición de estos y contribuye sustancialmente en el deterioro del cuadro clínico apareciendo la IC congestiva y las arritmias. La angiotensina II (ANGII), la aldosterona, la endotelina, la vasopresina (ADH) y las citoquinas, son los responsables de esta remodelación[5,6].

Activación neurohumoral

En la insuficiencia cardíaca se produce un desbalance entre el gasto cardíaco y las resistencias vasculares periféricas que conduce a la activación de alteración neuroendocrina en la que, el sistema simpático, el sistema renina-angiotensina-aldosterona (SRAA), la vasopresina (ADH) y los péptidos natriuréticos[5,6].

Sistema adrenérgico

En el comienzo de la disfunción miocárdica se produce la activación del sistema simpático, con el fin de compensar la reducción del gasto cardíaco con un aumento de la frecuencia y la contractibilidad. Conforme la IC avanza, el tono simpático aumenta, lo que deteriora el miocardio tanto a nivel estructural como funcional. El origen del deterioro se sitúa en la activación de los receptores ß1 adrenérgicos,

que activan a la PKA la cual como se comentaba anteriormente se encarga de fosforilar ciertas proteínas y modificar su funcionamiento; entre ellas a los receptores RyR2 aumentando la probabilidad de apertura y la salida de Ca del retículo sarcoplásmico, y a los miofilamentos como la troponina I y la proteína C que al ser fosforiladas reducen su sensibilidad al calcio. En cambio, el fosfolamban se encuentra menos fosforilado, lo que significa que la recaptura del Ca2+ hacia el RS está disminuida traduciéndose en una depleción del mismo. Todos estos puntos conducen finalmente a un efecto inotrópico negativo

También se ha demostrado que la exposición prolongada de los miocitos a altas concentraciones de catecolaminas, tiene un efecto tóxico que degrada las miofibrillas y aumenta el colágeno[5,6].

El sistema renina-angiotensina-aldosterona

En la IC, tanto la caída de la perfusión renal como la activación del sistema adrenérgico, estimulan la liberación de renina y con ello también la de la angiotensina II (ANGII) y la de la aldosterona. La ANGII produce vasoconstricción periférica y aumenta la liberación de aldosterona y catecolaminas. Todo ello se traduce en daño del endotelio vascular, incremento de los radicales oxidativos intracelulares y en efecto mitógeno sobre los miocitos cardíacos.

La aldosterona genera retención continua de sodio y agua y como resultado de esto, empeoramiento de la congestión. La aldosterona también influye en el estrés oxidativo, en la disminución en la producción de óxido nítrico y en el aumento de la inflamación con fibrosis cardiaca que se traduce en arritmias El nivel de renina y aldosterona en el plasma de los pacientes con IC, guarda relación con la severidad y el pronóstico de esta patología.

En la insuficiencia cardíaca también se produce una liberación no osmótica de la hormona antidiurética o ADH, aun cuando la natremia es baja, produciendo hiponatremias y favoreciendo la congestión[5,6].

Péptido natriurético

En la IC aumentan los niveles sanguíneos tanto del péptido atrial natriurético (PAN) secretado por los miocitos de las aurículas como del péptido cerebral natriurético (PCN) o BNP secretado por los miocitos ventriculares. El primero estaría relacionado con cambios agudos de la IC y el segundo con cambios crónicos y se liberan como consecuencia del aumento y distensión de las cavidades cardíacas. A diferencia de los efectos destructivos de la activación del sistema simpático y del SRAA, las acciones de los péptidos natriuréticos son fisiológicamente beneficiosas pues facilitan la natriuresis, relajan el músculo liso y por ende disminuyen las resistencias vasculares periféricas reduciendo la poscarga y la precarga y contrarrestan la remodelación cardíaca. Estos efectos beneficiosos se ven reducidos conforme avanza la IC porque su liberación se atenúa con el tiempo y se reducen los receptores, así como también se ven reducidos en pacientes obesos.

La elevación de los péptidos natriuréticos se utiliza para pronóstico y como pruebas diagnósticas iniciales en pacientes con síntomas sugestivos de IC, sobre todo para descartar el diagnóstico, porque una concentración plasmática de BNP <35 pg/mL, o de proANP <40 pmol/L hacen poco probable el diagnóstico de IC. Aunque son bastante útiles hay que tener en cuenta que los péptidos natriuréticos también se pueden ver elevados en la fibrilación auricular, la edad avanzada y la enfermedad renal aguda o crónica[5,6].

Alteraciones electrofisiológicas

Debido a los mecanismos comentados anteriormente (la activación de los RyR2, el hiperaldosteronismo) la probabilidad de que se generen arritmias es mucho más alta. La taquicardia ventricular es la causa del 50% de las muertes en la ICC y cerca del 80% de los pacientes con IC sistólica presentan esta arritmia[5,6].

Estadiaje de la insuficiencia cardíaca

La clasificación funcional de la New York Heart Association (NYHA) de 1994[7] (estadios I a IV) es la herramienta más utilizada para la estratificación del riesgo de IC y determina la elegibilidad para ensayos clínicos y la candidatura para medicamentos y dispositivos. Sin embargo, aunque su uso esté muy extendido debido a la sencillez de su uso y terminología, hay que tener presente que la NYHA es subjetiva, ya que se basa solamente en síntomas y que la clase funcional puede fluctuar rápidamente en descompensaciones, por lo que no se puede utilizar en periodos inestables y que existen otros indicadores de pronóstico para la IC que deben ser tenidos en cuenta sobre todo en IC avanzada a la hora de guiar la selección de trasplantes cardíacos y terapias con dispositivos. Hay estudios que concluyen que la NYHA discrimina mal a los pacientes[8].

Debidas a estas razones y con el objetivo de poder comprender mejor el proceso evolutivo de la insuficiencia cardíaca las Guías de Práctica Clínica del American College of Cardiology/American Heart Association (ACCF/AHA)[9] establecieron en 2001 una clasificación en función de los estadios de progresión de la enfermedad más acorde con los conceptos actuales que incluya estadios preclínicos pudiendo identificar a pacientes en etapas precoces con actitud preventiva. En 2020 un comité de redacción compuesto por miembros de la Heart Failure Society of America (HFSA), la Heart Failure Association of the European Society of Cardiology (HFA/ESC) y la japonesa la Heart Failure Society (JHFS) elaboró un documento en el que se revisaron dichos estadios[10].

Tabla I: Clasificación sintomática de la insuficiencia cardíaca según la New York Heart Association.

CLASE I	No limitación de la actividad física. La actividad ordinaria no ocasiona excesiva fatiga, palpitaciones, disnea o dolor anginoso.
CLASE II	Ligera limitación de la actividad física. Confortables en reposo. La actividad ordinaria ocasiona fatiga, palpitaciones, disnea o dolor anginoso.
CLASE III	Marcada limitación de la actividad física. Confortables en reposo. Actividad física menor que la ordinaria ocasiona fatiga, palpitaciones, disnea o dolor anginoso.
CLASE IV	Incapacidad para llevar a cabo cualquier actividad física sin disconfort. Los síntomas de insuficiencia cardíaca o de síndrome anginoso pueden estar presentes incluso en reposo. Si se realiza cualquier actividad física, el disconfort aumenta.

Tabla II: Estadios evolutivos de la insuficiencia cardíaca, según la ACCF/AHA revisados.

EN RIESGO (ESTADIO A)	Paciente en riesgo para IC, pero sin síntomas ni signos de IC. No hay cambios estructurales cardíacos o elevación de los biomarcadores de daño cardíaco
PRE-IC (ESTADIO B)	Pacientes que nunca han mostrado signos o síntomas de IC, pero hay evidencia de uno de los siguientes: 1. Cardiopatía estructural; 2. Función cardiaca anormal; 3. Elevación de péptido natriurético o troponinas cardiacas.
IC SINTOMÁTICA (ESTADIO C)	Pacientes con síntomas y signo de IC causados por cardiopatía estructural o funcional.
IC AVANZADA (ESTADIO D)	Pacientes con cardiopatía estructural avanzada y síntomas acusados de IC, a pesar de tratamiento médico máximo, y que requieren intervenciones especializadas como trasplante, soporte circulatorio externo o cuidados paliativos

Aunque estas etapas de la insuficiencia cardíaca son bien reconocidas entre los profesionales de la salud, no son una nomenclatura muy utilizada. Es menos probable que los pacientes que viven con insuficiencia cardíaca se identifiquen con esta clasificación en comparación con la familiaridad con la FEVI y la carga de síntomas subjetivos (NYHA). En los ensayos clínicos tampoco se han utilizado mucho los estadios evolutivos de la IC, y la mayoría de las estrategias de tratamiento no se guían por ellos[11]. Una subcategorización muy utilizada en los estudios a la hora de definir los tratamientos recomendados es de acuerdo con la FEVI. Según la actualización citada anteriormente, dicha clasificación sería:

- IC con fracción de eyección reducida (HFrEF) – IC sintomática con FEVI ≤40%
- IC con fracción de eyección levemente reducida (HFmrEF): IC sintomática con FEVI 41-49% (anteriormente etiquetada como IC con fracción de eyección de rango medio)
- IC con fracción de eyección preservada (HFpEF) – IC sintomática con FEVI ≥50%
- IC con fracción de eyección mejorada (HFimpEF): una nueva clasificación que se define claramente como IC sintomática con una FEVI inicial ≤40 %, un aumento de ≥10 puntos desde la FEVI inicial y una segunda medición de FEVI >40 %

No obstante, los objetivos de las diversas clasificaciones no son reemplazarse entre ellas, sino complementarse con la información aportada por cada una.

Diagnóstico de insuficiencia cardíaca

La definición de IC enfatiza que es un síndrome clínico con síntomas y/o signos causados por una anomalía cardiaca estructural y/o funcional y corroborada por niveles elevados de péptidos natriuréticos y/o evidencia objetiva de congestión pulmonar o sistémica. Por ello, según la última revisión de la ESC (Sociedad Europea de Cardiología)[5] para el diagnóstico de insuficiencia cardiaca son necesarios la presencia del síndrome clínico, pero siempre acompañado de evidencia objetiva de disfunción cardíaca, ya que los síntomas individualmente carecen de la precisión necesaria para el diagnóstico. Los síntomas cardinales que nos harían sospechar de IC serían el edema de miembros inferiores con fóvea o signos como la ascitis, la hepatomegalia o el aumento de la presión venosa yugular, la ortopnea, la disnea paroxística nocturna o la disnea de esfuerzo. Las pruebas que confirmarían la IC son:

- La medición positiva de péptido natriurético NP; siendo esta la concentración plasmática de péptido natriurético tipo B (BNP) >35 pg/mL o péptido natriurético tipo B N-terminal (NT-proBNP) >125 pg/mL. Si el PN es positivo el diagnóstico de IC es directo. En caso de no obtenerlo;
- El ecocardiograma puede confirmar el diagnóstico y proporcionar la FEVI, necesaria para la clasificación de la IC, así como tamaño de la cámara, HVI o anomalías en el movimiento del miocardio.
- El electrocardiograma también nos puede guiar, pues un ECG normal hace poco probable la IC.
- Se recomienda una radiografía de tórax para investigar otras posibles causas de disnea (p. ej., enfermedad pulmonar). También puede proporcionar evidencia de apoyo de IC si aparece congestión pulmonar o cardiomegalia.
- Se recomiendan investigaciones básicas como urea y electrolitos séricos, creatinina, hemograma completo, pruebas de función hepática y tiroidea para diferenciar la insuficiencia cardíaca de otras afecciones, proporcionar información pronostica y guiar la terapia potencial.

Tratamiento base de la insuficiencia cardíaca

Los pacientes con IC y FEVI reducida son los que tienen el tratamiento mejor estudiado y definido debido a que son en los que se evidencian mayores cambios.

Como se hablaba en el apartado de fisiopatología, la enfermedad se ve como un síndrome con múltiples mecanismos sistémicos que involucran a la inflamación, al SRAA, el sistema simpático y el endotelio que derivan en síndrome cardio-renal. Es por ello que los principios generales de farmacología en IC FEVIr y con una fuerte recomendación en las guías internacionales (IA), y siguiendo la última actualización de la guía ESC 2021[5] se basan en la modulación del SRAA con inhibidores de la enzima convertidora de angiotensina (IECA) o un inhibidor del receptor de angiotensina-neprilisina, sacubitrilo/valsartán (ARNI), beta bloqueantes y antagonistas de los receptores de mineralocorticoides (MRA) como terapia base fundamental a menos que esté contraindicado. Todos los pacientes sintomáticos con IC FEVIr deben recibir estos medicamentos en combinación, preferiblemente en las dosis máximas toleradas debido a la mejora en la supervivencia, la disminución de la mortalidad y de las hospitalizaciones. Además, a menos que este contraindicado, las últimas guías recomiendan el uso de los inhibidores del cotransportador de sodio-glucosa 2 (SGLT2), dapagliflozina y empagliflozina, agregados a la triada anterior, en todos los pacientes con FEVIr independientemente de que sean diabéticos o no.

Tabla III: Triada de fármacos recomendados como terapias fundamentales en IC FEVIr.

IECA/ARNI	+	Beta bloqueante	+	MRA
		+		
		ISGLT2		

IECA y los betabloqueantes:

Se recomiendan en todos los pacientes y deben iniciarse lo antes posible porque reducen la mortalidad y la morbilidad. Se comienza con dosis bajas y se elevan hasta las máximas toleradas, hay que tener cuidado con la infradosificación debida a una preocupación excesiva con los efectos adversos como son la hipotensión, la hiperpotasemia o el deterioro de la función renal porque la ocurrencia de estos no disminuye los beneficios en la supervivencia y privan a los pacientes de tratamientos que salvan vidas.

Antagonistas de los mineralcorticoides:

Los MRA, espironolactona o eplerenona, reducen la mortalidad, las hospitalizaciones y la sintomatología, por ello forman parte de la triada básica de tratamiento de la IC FEVIr. La eplerenona es más selectiva y produce menos ginecomastia. Hay que controlar la función renal y el nivel sérico de potasio.

Inhibidor del receptor de angiotensina-neprilisina:

El sacubitrilo/valsartán, es un ARNI que según el ensayo PARADIGM-HF (12) , demostró ser superior a enalapril (IECA) en la reducción de las hospitalizaciones y de la mortalidad. Por lo que se recomienda reemplazar el IECA por un ARNI en pacientes con FEVIr y sintomáticos

Inhibidores del cotransportador de sodio-glucosa 2:

El filtrado de glucosa diario en el glomérulo es de aproximadamente 180 g, la cual es reabsorbida en su mayoría por el cotransportador de sodio-glucosa (SGLT). Hay dos isoformas de este cotransportador, SGLT1 Y SGLT2. Los inhibidores de SGLT2 (iSGLT2) son fármacos que reducen la glucosa plasmática al inducir glucosuria. Este mecanismo de acción, además de reducir la glucemia en plasma, corrige una serie de problemas metabólicos y anomalías hemodinámicas que constituyen factores de riesgo de ECV. Diversos estudios que analizaremos a fondo en la discusión han investigado los beneficios de estos fármacos en pacientes con IC FEVIr y finalmente la guía ESC 2021 (5) recomienda dapagliflozina o empagliflozina asociado a la triada de IECA/ARNI + Betabloqueante + MRA en pacientes con IC FEVIr independientemente de la diabetes.

Otros fármacos a considerar en pacientes con IC FEVIr

Diuréticos: Se recomiendan los diuréticos de asa para reducir los signos y síntomas de la congestión, aunque no haya evidencias sobre su efecto en la morbi-mortalidad.

Ivadrabina, Inhibidor del canal I f: Reduce la frecuencia cardíaca en el nódulo sinusal, por lo que es necesaria una FC reposo ≥75 lpm.

Digoxina: Puede ser útil en el tratamiento de la IC con FA sintomática cuando no haya otras opciones terapéuticas[1,5].

Por ello, iniciamos esta revisión proponiéndonos los siguientes objetivos:

- Realizar una revisión de las últimas novedades de sobre los tipos, la fisiopatología, el estadiaje, el diagnóstico y el tratamiento general de la insuficiencia cardíaca.
- Analizar los últimos avances respecto al uso de iSGLT2 en IC y FEVI reducida y preservada
- Analizar los últimos avances respecto al uso de iSGLT2 en IC aguda descompensada

Material y método

Se ha realizado una revisión sistemática utilizando la base de datos científica PubMed. Se escogieron como palabras clave "FEVI", "heart failure", "cardiovascular risk" y "SGLT2 inhibitors".

La fecha de publicación de los artículos utilizados va desde 2004 a 2022, aunque la mayoría de ellos están acotados entre 2018 y 2022, con el fin de proporcionar una información reciente y actualizada.

Los criterios de inclusión de estudios para esta revisión fueron los siguientes: los artículos debían ser metaanálisis, ensayos clínicos controlados aleatorizados o revisiones sistemáticas. Se escogieron estudios cuyo idioma de publicación fuera inglés o español.

Se desestimaron estudios publicados en revistas de bajo impacto, estudios que se desviaban de los objetivos principales, se centraban en otras patologías o que duplicaban información.

La media de la Escala JADAD fue 3,5/4.

Discusión y resultados

Evidencia en el uso de ISGLT2 en insuficiencia cardíaca y fevi reducida

El Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF)[13] es un ensayo aleatorizado controlado con placebo y publicado en noviembre de 2019 que mostró una reducción en el riesgo de muerte cardiovascular u hospitalización por insuficiencia cardíaca con el uso de dapagliflozina en pacientes con FEVI menor del 40% independientemente de la presencia o ausencia de diabetes. Para ello se seleccionaron 4.744 pacientes y fueron asignados al azar para recibir dapagliflozina 10 mg o un placebo equivalente una vez al día. Los requisitos de elegibilidad de los pacientes incluían:

- Fracción de eyección del 40% o menos + síntomas de clase II, III o IV de la NYHA.
- Nivel plasmático de péptido natriurético tipo B Nterminal pro (NT-proBNP) de al menos 600 pg por mililitro (o ≥400 pg por mililitro si habían sido hospitalizados por insuficiencia cardíaca en los 12 meses anteriores).
- Los pacientes debían recibir terapia estándar con dispositivo para insuficiencia cardíaca (un desfibrilador cardioversor implantable, terapia de resincronización cardíaca o ambas) y terapia farmacológica estándar (IECA+ Beta-bloqueante+ MRA). Si el paciente era diabético continuaban con su tratamiento habitual.

Se excluyeron aquellos pacientes que habían sido tratados recientemente con un inhibidor SGLT2, DM1, síntomas de hipotensión o presión arterial sistólica de menos de 95 mm Hg y una tasa de filtración glomerular estimada (eGFR) por debajo de 30 ml por minuto.

Como comentaba en el párrafo anterior, el estudio concluyó que la dapagliflozina redujo tanto las hospitalizaciones que hubieran necesitado terapia intravenosa para el control de las descompensaciones cardíacas como las muertes por causas cardiovasculares, es decir redujo el evento primario del estudio, siendo estas de 386 pacientes (16,3 %) en el grupo de dapagliflozina y en 502 pacientes (21,2 %) en el grupo placebo. El número de pacientes que deberían haber sido tratados con dapagliflozina para prevenir un evento primario fue de 21. Su uso también resultó en menos síntomas de insuficiencia cardíaca.

Estos resultados se dieron de manera homogénea, incluso en los pacientes sin diabetes, aunque se podría destacar que los pacientes con clase de NYHA II tuvieron mejores resultados que los de clase III o IV de la NHYA.

Otro estudio muy esperado que reafirma y completa al anterior es el EMPEROR-Reduced (14), un ensayo doble ciego que se publicó en agosto del 2020 y que analizó el efecto de empagliflozina en pacientes con insuficiencia cardiaca y fracción de eyección del ventrículo izquierdo reducida sobre la mortalidad cardiovascular y hospitalizaciones por insuficiencia cardiaca, en un total de 3.730 pacientes, seguidos durante un tiempo medio de 16 meses. Los pacientes fueron asignados al azar para recibir empagliflozina 10mg o un placebo equivalente una vez al día.

De la población seleccionada, hay que destacar que la mitad de los pacientes eran diabéticos, el 73% presentaban una FEVI < 30% y el 79% tenían un NT-proBNP > 1.000 pg/ml, con un 18,3% de pacientes en tratamiento con sacubitrilo/valsartán. El 31% tenían implantado un desfibrilador automático implantable (DAI) y un 11,8% terapia de resincronización cardiaca. Además, el 48% tenían un eGFR < 60 ml/min/1,73 m^2.

En el grupo de empagliflozina, el evento primario (muerte cardiovascular u hospitalización por IC ocurrió en un total de 361 pacientes (19,4%) frente a 462 (24,7%) en el grupo. El efecto de empagliflozina sobre el objetivo primario era independiente de la presencia de diabetes mellitus (DM), del filtrado renal mayor o menor de 60 ml/min/1,73 m^2, o del tratamiento concomitante con sacubitrilo/valsartán, El número de pacientes que deberían haber sido tratados con empaglifozina para prevenir un evento primario fue de 19.

Además de los beneficios cardiovasculares observados, la empagliflozina desaceleró la tasa anual de reducción

del filtrado renal (eGFR) que fue de -0,55 ml/min/1,73 m^2 en el grupo de empagliflozina, frente a 2,28 ml/min/1,73 m^2 en el brazo placebo. En consecuencia, la capacidad de la empagliflozina para influir favorablemente en la función renal es evidente en pacientes con diabetes, en aquellos con insuficiencia cardíaca y en aquellos con ambas afecciones. Solo las infecciones genitales no complicadas fueron más frecuentes con empagliflozina.

Los hallazgos con empagliflozina se pueden comparar con los efectos de dapagliflozina en el ensayo DAPA-HF con la diferencia de que el ensayo EMPEROR-Reduced cuenta con una población con una fracción de eyección marcadamente más reducida, niveles más elevados de péptidos natriuréticos, más uso de dispositivos y de sacubitrilo/valsartán, obteniendo beneficios muy claros y precoces en relación con la reducción del total de hospitalzaciones por IC a lo largo del seguimiento, y enlenteciendo la progresión de la enfermedad renal.

En conclusión, tanto el estudio EMPEROR-Reduced como el estudio DAPA-HF proporcionan dos opciones válidas que ofrecer a los pacientes con IC FEVIr y completar así su tratamiento. Estos fármacos deben implementarse en el tiempo más corto posible que el paciente tolere, para mejorar su esperanza y calidad de vida. Gracias al peso de los resultados de estos estudios, la guía ESC 2021[5] ya incluye entre sus recomendaciones de tratamiento para pacientes con FEVI reducida a los iSGLT2.

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Últimas evidencias en el tratamiento de la insuficiencia cardíaca y FEVI conservada

El grupo de insuficiencia cardíaca y FEVI conservada se envuelve de falta de consenso, empezando por cuál es el punto de corte óptimo de la FEVI para definir el grupo de pacientes con IC sin fracción de eyección manifiestamente reducida. La guía ESC 2021[5] mantiene el punto de corte de la IC con FEVI preservada en el 50%. Hay que tener en cuenta que este grupo difiere de la IC con FEVI reducida o levemente reducida en que los pacientes son mayores, sobre todo mujeres y que la fibrilación auricular, la enfermedad renal crónica y las comorbilidades no cardiovasculares son más comunes con FEVI preservada que reducida.

Según la guía ESC 2021 ninguno de los grandes ensayos clínicos aleatorizados que se habían realizado hasta el momento había demostrado que algún tratamiento redujese la mortalidad y la morbilidad de manera efectiva en pacientes con IC y FEVIc. A día de hoy sí que hay publicado un estudio que demuestra la reducción de estas dos variables con el uso de inhibidores de SGLT2 (EMPEROR-Preserved), del que hablaremos más adelante, pero cuyas recomendaciones no están incluidas aún en la ESC 2021. Es cierto que se nombra en esta guía la existencia de dichos estudios, por lo que es probable que en próximas actualizaciones aparezcan entre sus recomendaciones.

A pesar de la falta de evidencia sobre tratamientos específicos que modifiquen el curso de la enfermedad en el grupo de FEVIc, dado que la gran mayoría de los pacientes tienen hipertensión o patología coronaria de base, muchos ya están tratados con IECA/ARAII, betabloqueantes o MRA.

La guía señala que las opciones de tratamiento para este grupo están siendo revisadas a medida que se publica la guía y se apoyan en que la Administración de Alimentos y Medicamentos (FDA) ha respaldado el uso de sacubitrilo/valsartán y espironolactona en aquellos con una FEVI ligeramente reducida. Para sacubitrilo/valsartán, esta decisión se basó en el análisis del estudio PARAGON-HF[15], que mostró una reducción de las hospitalizaciones por insuficiencia cardíaca en aquellos con una FEVI <57%.

Con respecto a la espironolactona, se tomó el estudio TOPCAT[16] que mostró una reducción significativa en el criterio principal de valoración de muerte CV y hospitalización por IC, y posteriormente una reducción significativa en los resultados para aquellos con una FEVI <55%.

Es por todo esto que se ha incorporado en la guía un apartado específico para los pacientes con IC con FEVI ligeramente reducida en el que los que se incluyen los IECA, ARA-II, betabloqueantes, ARM y ARNI como tratamiento con recomendación clase IIb y nivel C.

Finalmente, la ESC 2021 aconseja que el tratamiento de elección en todos los casos debe estar dirigido a reducir los síntomas de congestión con diuréticos. Reducir el peso corporal en pacientes obesos y aumentar el ejercicio debe considerarse en los pacientes apropiados pues mejora la sintomatología.

El campo del tratamiento de la insuficiencia cardiaca con FEVI preservada ha visto una importante incorporación gracias a los buenos resultados del estudio EMPEROR-Preserved[17], es un ensayo doble ciego publicado en agosto de 2021 compuesto por 5.988 pacientes y que analizó el efecto de la empagliflozina en pacientes con insuficiencia cardíaca de clase NYHA II-IV y una fracción de eyección de más del 40%. El estudio concluyó que el uso de la empagliflozina disminuía la muerte cardiovascular y hospitalización por insuficiencia cardíaca. El seguimiento de los pacientes se extendió por 26 meses y fueron asignados al azar para recibir empaglifozina 10mg una vez al día o placebo añadido a su terapia habitual.

Para la selección de la población, los pacientes debían estar diagnosticados de insuficiencia cardíaca crónica de clase funcional II-IV NYHA con FEVI superior al 40% y elevación demostrada de péptidos natriuréticos medidos con el NT-proBNP mayor a 300 pg/ml en ritmo sinusal o mayor a 900 pg/ml en fibrilación auricular. De la población seleccionada casi la mitad de los pacientes tenían diabetes y la mitad tenía una eGFR de menos de 60 ml por minuto por 1,73 m^2. Dos tercios de los pacientes tenían una fracción de eyección del ventrículo izquierdo del 50% o más.

El objetivo primario fue una combinación de muerte cardiovascular u hospitalización por insuficiencia cardiaca. Durante el tiempo de seguimiento se produjo el evento primario en 415 de 2.997 pacientes (13,8%) en el grupo de empagliflozina y en 511 de 2.991 pacientes (17,1%) en el grupo de placebo. Este efecto se relacionó principalmente con un menor riesgo de hospitalización por insuficiencia cardiaca en el grupo de empagliflozina, en concreto con un 29% menos de riesgo. El número necesario a tratar para evitar un evento primario fue de 31 pacientes, generando una reducción del riesgo relativo del 21%. Los efectos de la empagliflozina parecieron consistentes en pacientes con o sin diabetes.

Al igual que en el estudio EMPEROR-Reduced[11], la velocidad de disminución de la tasa de filtrado glomerular fue más lenta en el grupo de empagliflozina que en el grupo de placebo (1,25 frente a -2,62 ml por minuto

por 1,73 m^2) pero, las infecciones genitales y del tracto urinario no complicadas y la hipotensión se informaron con mayor frecuencia con empagliflozina.

Como hemos comentado, el campo de la IC con FEVIc está en continuo estudio pues ningún fármaco había resultado favorable en los ensayos clínicos para el objetivo primario, en los que el ingreso por insuficiencia cardiaca suponía el principal problema. La empagliflozina ha supuesto un gran paso, al comprobar que añadiéndola al tratamiento habitual se reduce el riesgo de hospitalización y muerte por IC. Hay que tener en cuenta que EMPEROR-Preserved no muestra tanto beneficio en pacientes con FEVI superior a 60%. Influye que se trate de un grupo de pacientes más añosos, con más sobrepeso, más mujeres y péptidos más bajos que el resto. Por lo que, a día de hoy, se recomienda combinar los buenos resultados de EMPEROR-Preserved con el control de las comorbilidades, el estilo de vida saludable, la rehabilitación cardiaca y la prevención. Se espera que ensayos que se encuentran en curso en la actualidad, como el ensayo DELIVER aclaren las partes más dudosas de los beneficios de estos fármacos en este grupo de pacientes.

El DELIVER[18] es un ensayo en fase III, el cual evalúa los efectos de la administración de 10mg de dapagliflozina en comparación con el placebo sobre la mejora en la hospitalización, la muerte o visitas a urgencias por IC con FEVI ligeramente reducida y conservada.

La población está formada por un total de 6.263 pacientes con una distribución de edad, sexo y clase funcional de la NYHA similar a EMPEROR-Preserved. La presencia de comorbilidades como la hipertensión arterial y la diabetes mellitus tipo 2, así como el rango de FEVI (media inicial 54,2%) también son similares a EMPEROR-Preserved. Como rasgo diferencial de la población del DELIVER destaca que es el único que ha incluido pacientes con FEVI mejorada (pacientes que en el momento tienen criterios de inclusión, pero que tenían antecedentes de FEVI <40%) y pacientes hospitalizados (1000 participantes estaban hospitalizados o se encontraban dentro de los 90 días posteriores a la hospitalización) en comparación con otros ensayos recientes.

Un rasgo importante del estudio es que se han dividido los pacientes en tres grupos según la FEVI (entre 41 y 49%, entre 50% y 59% y 60% o más) pudiendo estudiar más a fondo las características de cada subrgrupo. De esta manera y gracias tanto a la publicación del estudio EMPEROR-Preserved junto con el ensayo DELIVER, probablemente se permita incorporar los inhibidores de la SGLT2 dentro de las recomendaciones de los pacientes con FEVI levemente reducida (entre 41 y 49%).

El DELIVER, al incluir pacientes con FEVI mejorada que no estaban representados en otros estudios, ha abierto las puertas a un escenario en el que haya un aumento del número de pacientes que mejoren su FEVI gracias a nuevas terapias, en las que se evaluaran los efectos de la dapagliflozina.

En conclusión, el ensayo DELIVER proporciona un importante avance en el ámbito de la evidencia científica para el uso de iSGLT2 en pacientes que no habían estado representados en estudios anteriores.

Insuficiencia cardíaca aguda e ISGLT2

En el campo de la insuficiencia cardíaca aguda los dos estudios más recientes que existen sobre la eficacia del uso de iSGLT2 son el EMPA-RESPONSE-AHF del 2019 y el EMPULSE-TRIAL de 2022.

El EMPA-RESPONSE-AHF[19] es un estudio piloto, multicéntrico, doble ciego y controlado con placebo publicado en noviembre de 2019. En él, 80 pacientes con IC aguda fueron aleatorizados en las primeras 24 horas de la hospitalización a recibir empagliflozina 10mg o placebo durante 30 días. El objetivo primario era evaluar los cambios desde la inclusión hasta el cuarto día utilizando la escala de disnea VAS, la respuesta diurética a la furosemida, la duración de la estancia hospitalaria; y el cambio porcentual de NT-proBNP.y de forma secundaria evaluando los cambios en los eventos clínicos mediante el empeoramiento de la IC que precisara diurético intravenoso o ventilación mecánica, hospitalización por IC o muerte por todas las causas.

La edad media de los pacientes fue de 76 años, 47% tenían IC de nueva aparición y la media de la FEVI fue del 36%. Únicamente, un tercio de los pacientes tenían DM2.

A los 4 días de tratamiento no hubo diferencias significativas entre los pacientes tratados con empagliflozina y placebo en la escala de disnea, en la respuesta diurética a furosemida, en el porcentaje de NT-proBNP o en la duración de la hospitalización, pero su administración fue segura (se registraron 8 eventos adversos serios en el grupo de empagliflozina por 11 en el grupo de placebo) y redujo la incidencia de empeoramiento/hospitalización por IC (4 frente a 13 eventos) o muerte a los 60 días. No se registraron diferencias significativas en la incidencia de eventos renales o genitourinarios entre ambos grupos.

En conclusión, el uso de empagliflozina no tuvo efectos beneficiosos a corto plazo, pero sí hubo mejoría significativa de los eventos clínicos a 60 días, añadido a que se demostró que su uso es seguro, pues no hubo mayor hipotensión ni incidencia de empeoramiento de la función o fallo renales agudo pese a su uso concomitante con dosis elevadas de diuréticos apoya el potencial beneficio de los iSGLT2 en la fase vulnerable de la enfermedad tras una descompensación aguda de IC.

El estudio más novedoso actualmente es el EMPULSE-TRIAL[20] publicado en marzo de 2022 en el cual se evalúa la empagliflozina 10 mg en 530 pacientes hospitalizados por insuficiencia cardiaca aguda independientemente de la fracción de eyección, con o sin diabetes mellitus. Las características de estos pacientes (70 años, predominantemente varones, NYHA II-III, ProBNP 3200 pg/ml, filtrado glomerular 50 ml/min/m^2 o 45% diabéticos) son muy parecidas a la población, lo que avala su validez externa y la aplicabilidad a la práctica clínica. Se aleatorizó la toma de empagliflozina 10mg o placebo entre el día 1 y el 5 y se realizó el seguimiento durante 90.

EMPULSE-TRIAL demostró que la empagliflozina es más eficaz que placebo en la reducción de un 36% del objetivo primario, el cual está compuesto por mortalidad cardiovascular, hospitalizaciones por IC o mejoría de la calidad de vida (según el cuestionario de Kansas City). Cuando se desglosan de forma individualizad cada uno de los puntos del objetivo primario, se observa una reducción del 4,2% en la mortalidad por todas las causas en el grupo de empagliflozina en comparación con el 8,3% en el grupo de placebo, mientras que los eventos de insuficiencia cardíaca ocurrieron en el 10,6% de los del grupo de empagliflozina en comparación con el 14,7% en el grupo de placebo.

Al igual que en el estudio EMPA-REPONSE-AHF no se observaron diferencias en cuanto a hipotensión, cetoacidosis, hipoglucemias o infecciones genitales. Pero sí se observó un beneficio en cuanto a protección renal del fármaco (empeoramiento renal en el 7,7% de los tratados con empagliflozina frente al 12,1% de los tratados con placebo) y una pérdida de peso superior a los 2 kg, lo que constituye un dato muy relevante en el perfil de pacientes analizados, en los que la congestión es un claro marcador pronóstico adverso.

EMPULSE-TRIAL, al igual que EMPA-REPONSE-AHF, respalda la utilización precoz de los fármacos iSGLT2, tanto porque ambos han demostrado que su uso es seguro, como por los beneficios que supone su implementación en el tratamiento de la IC aguda, señalando nuevos beneficios que no se habían visto antes como es la mejora en la congestión.

Conclusiones

iSGLT2 y FEVI reducida

Tabla IV: Estudio DAPA-HF.

Año publicación	2019
Número de pacientes	4744
Fármaco	Dapagliflozina 10mg
Características Población	FEVI <40 NTporBNP mínimo 600 pg/ml Terapia con dispositivo para IC eGFR> 30ml/min
Objetivo Primario	Hospitalización con tto IV o muerte CV
Resultados	16,3% (dapagliflozina) Vs 21,2% (placebo) 21 es el número de pacientes que necesitan ser tratados para evitar 1 evento primario. Independiente de la DM

Tabla V: Estudio EMPEROR-Reduced.

Año publicación	2020	
Número de pacientes	3730	
Fármaco	Empagliflozina 10mg	
Características Población	**73% FEVI < 30%** **79% NTproBNP > 1000 pg/ml** Terapia con dispositivo eGFR > 30ml/min	**IC más avanzada**
Objetivo Primario	Hospitalización con tto IV o muerte CV	
Resultados	**19,4%** (empagliflozina) Vs **24,7%** (placebo) **19** es el número de pacientes que necesitan ser tratados para evitar 1 evento primario. Independiente de la DM Protección de la función renal	**Mejores resultados**

iSGLT2 y FEVI preservada

Tabla VI: Estudio EMPEROR-Preserved.

Año publicación	2021
Número de pacientes	5988
Fármaco	Empagliflozina 10mg
Características Población	FEVI >40% (2/3 FEVI >50%) NTporBNP >300 pg/ml Clase funcional NYHA II-IV
Objetivo Primario	Hospitalización por IC o muerte CV
Resultados	13,8% (dapagliflozina) Vs 17,11% (placebo) 31 es el número de pacientes que necesitan ser tratados para evitar 1 evento primario. **Reducción del 29% en el riesgo de hospitalización**. Independiente de la DM **Protección renal** **Más infecciones del tracto urinario no complicadas e hipotensión arterial**.

Tabla VII: Estudio DELIVER.

Año publicación	Ensayo en Fase III
Número de pacientes	6263
Fármaco	Dapagliflozina 10mg
Características Población	FEVI >40% (2/3 FEVI >50%) NTporBNP >300 pg/ml Clase funcional NYHA II-IV Pacientes con FEVI mejorada Pacientes hospitalizados **Nuevas inclusiones** **Mismas características poblacionales que EMPEROR-Preserved**
Objetivo Primario	Hospitalización por IC o muerte CV
Resultados	División de la población en 3 grupo según FEVI➔ Posible nueva incorporación de iSGLT2 en FEVI (41%-49%) Posible aumento del porcentaje de pacientes que mejoren su FEVI **Resultados relacionados sobre todo con pacientes no antes representados**

iSGLT2 e IC aguda

Tabla VIII: Estudio EMPA-RESPONSE-AHF.

Año publicación	2019
Número de pacientes	80
Fármaco	Empagliflozina 10mg en las primeras 24h tras hospitalización y manteniendo el tratamiento 30 días
Características Población	Hospitalizados por IC Edad media 76 años 47% IC de nueva aparición FEVI media del 36%
Objetivo Primario	Evaluar cambios del 1º día al 4º día mediante: • Escala VAS • Respuesta diurética a furosemida • Duración estancia hospitalaria • Variaciones en el NT-proBNP **Eventos a corto plazo**
Resultados	No se observan beneficios a corto plazo, pero SÍ mejoras en los eventos clínicos a los 60 días. Demostró que su uso es seguro (no hubo empeoramiento de la función renal)

Tabla IX: Estudio EMPULSE-TRIAL.

Año publicación	2022 (marzo)
Número de pacientes	530
Fármaco	Empagliflozina 10mg comenzando entre el 1º y el 5º día de hospitalización con seguimiento durante 90 días
Características Población	Hospitalizados por IC Edad media 70 años NHYA II-III ProBNP 3200 pg/ml FG 50 ml/min 45% DM **Características muy similares a la población normal, lo que permite aplicabilidad clínica**
Objetivo Primario	Mortalidad cardiovascular. Hospitalización por insuficiencia cardíaca. Mejoría en la calidad de vida (Kansas City) **Eventos a largo plazo**
Resultados	Empagliflozina demostró una reducción del 36% en el objetivo primario (eventos a largo plazo) **Cierto beneficio de protección renal** **Pérdida de 2 kg de peso➔ relacionado con la mejoría en la congestión**. **Nuevos beneficios, mejoría en congestión y protección renal**

Conflicto de intereses

Los autores declaran no tener ningún conflicto de ineteres.

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ARTÍCULO ESPECIAL

¿Deberían modificarse los criterios de financiación de medicamentos para el tratamiento del tabaquismo en España?

Should the financing criteria for medicines for the treatment of smoking in Spain be modified?

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Resumen

El tabaquismo se considera una enfermedad adictiva crónica, es la primera causa de muerte evitable, y mata hasta a la mitad de quienes lo consumen.
El mejor tratamiento es el que combina el tratamiento farmacológico con el cognitivo-conductual.
Se exponen los buenos resultados en cesación obtenidos mediante la financiación de estos tratamientos en diversos países.
Desde enero de 2020, vareniclina y bupropión fueron financiados por el Sistema Nacional de Salud para todo el estado Español, bajo unas condiciones concretas, que excluían gran número de fumadores.
Se discuten los criterios de financiación, que deberían ser ampliados a todos los fumadores y a todos los medicamentos autorizados para su tratamiento, según el criterio de sociedades científicas, ciudadanas y profesionales sanitarios.
La Terapia Sustitutiva con Nicotina (TSN), salvo excepciones, y la citisina son medicamentos no financiados, por el momento, en España, pese a que presentan un demostrado perfil de eficacia y seguridad en numerosos estudios.

Palabras clave: Cesación tabáquica, tratamiento, financiación pública, terapia sustitutiva con nicotina, citisina.

Abstract

Smoking is considered a chronic addictive disease, it is the leading cause of preventable death, and it kills up to half of those who consume it.
The best treatment is the one that combines the pharmacological with the cognitive-behavioral treatments.
The good results in cessation obtained by financing these treatments in various countries are exposed.
Since January 2020, varenicline and bupropion have been financed by the National Health System for the entire Spanish state, under specific conditions, which excluded a large number of smokers.
The financing criteria are discussed, which should be extended to all smokers and to all medications authorized for their treatment, according to the criteria of scientific, citizen and health professional societies.
Nicotine Replacement Therapy (NRT), with exceptions, and cytisine are currently not coverage by financing drugs in Spain, although they present a proven profile of efficacy and safety in numerous studies.

Key words: Smoking cessation, treatment, public financing, nicotine replacement therapy, cytisine.

Introducción

El tabaquismo es la primera causa de muerte evitable, la primera prevenible de morbi-mortalidad en los países desarrollados, y mata hasta a la mitad de quienes lo consumen.

Fallecen siete millones de personas al año, en el mundo, por consumo directo, y 1,2 millones como fumadores pasivos[1].

En España, el 32,3% de la población entre 15 y 64 años se declara fumador diario[2].

El tabaquismo es una enfermedad adictiva y crónica, reconocida como tal por la Organización Mundial de la Salud desde 1975[3]

El 18 de junio de 2018, la OMS publica su nueva clasificación de enfermedades CIE-11 (ICD-11 en inglés), que está oficialmente en vigor desde el 11 de febrero de 2022. Aparecen los apartados 6C4A (trastornos debidos al consumo de nicotina), el 6C4A.2Z (dependencia de la nicotina), el 6C41 (trastornos por consumo de cannabis), y el QE 12 (consumo de nicotina en formas sin tabaco)[4].

El mejor tratamiento del tabaquismo es aquel que combina el tratamiento farmacológico con el tratamiento psicológico (cognitivo-conductual). Dicha combinación dispone de una evidencia científica grado A[5].

La Terapia Sustitutiva con Nicotina (TSN), en varias presentaciones y de diferentes fabricantes, Zyntabac® (bupropión), Champix® (vareniclina) y, más recientemente, Todacitan®(citisina) son los medicamentos aprobados, hasta el momento, para su utilización con esta indicación, y con suficiente evidencia científica[6].

Financiación del tratamiento farmacológico del tabaquismo

A pesar de que diferentes guías en varios países valoraran con el mayor nivel de evidencia (A) la existencia de tratamientos farmacológicos eficaces para dejar de fumar, de que la eficiencia (coste/efectividad) era mayor para estos tratamientos que para los de otras enfermedades crónicas, como la hipercolesterolemia o la hipertensión arterial, con el mismo nivel de evidencia, y de que el tratamiento para la cesación tabáquica era la mejor intervención de todas las preventivas, también con evidencia A, existían numerosos obstáculos para su financiación, lo que resultaba sorprendente para la comunidad científica, máxime considerando que enfermedades crónicas como las citadas disponían de un importante arsenal terapéutico financiado por sistemas de salud públicos y privados[7].

Ya en 2008, Jiménez-Ruiz y cols. realizaron propuestas de financiación que contemplaban diferentes condiciones, algunas de ellas recogidas en el modelo actual[7].

Pero no fue hasta enero de 2020 en que se comenzaron a financiar estos tratamientos por el Sistema Nacional de Salud español, concretamente Champix® y Zyntabac® para todo el Estado y posteriormente, se añadieron los parches de nicotina para la Comunidad Foral de Navarra y la Comunidad Autónoma de Canarias[8].

Resultados de la financiación

Minué-Lorenzo y cols revisan algunos estudios realizados en diferentes países en relación con la financiación de los tratamientos para dejar de fumar, la mayoría realizados en el ámbito de la sanidad privada, en los que se demuestra que dicha financiación aumenta las tasas de abstinencia tabáquica[9]. Se resumen, a continuación, algunos de ellos.

En los Países Bajos, durante 2011, se financiaron totalmente la TSN, vareniclina y bupropión. Durante ese año, los médicos de atención primaria quintuplicaron las prescripciones de estos fármacos, principalmente los dos primeros, y disminuyó un 4% la prevalencia del tabaquismo. Sin embargo, una vez que cesó la cobertura farmacológica, disminuyó la prescripción de medicamentos y repuntó la prevalencia del tabaquismo, en ambos casos hasta los niveles previos a la financiación[10].

Similar conclusión obtuvo un estudio clínico aleatorizado pragmático sobre 1380 participantes realizado en Canadá entre marzo de 2009 y septiembre de 2010. La adopción de una política de cobertura de medicamentos para dejar de fumar (vareniclina, bupropión o parches/chicle de nicotina), permitió mejorar las tasas de cesación a las 26 semanas, pero revertieron una vez que se suspendió la cobertura[11].

En una revisión Cochrane de 2017, realizada sobre diez estudios en el ámbito de la sanidad privada en USA, tres en Canadá, uno en el Reino Unido y dos en Países Bajos, se concluye que mediante las intervenciones financieras dirigidas a los fumadores, y en mayor caso si son completas, en tratamientos farmacológicos y conductuales, se conseguía un aumento de intentos de cesación, de tratamientos prescritos y tratamientos utilizados (duplicando la tasa de uso de la TSN y triplicando la de bupropión), y también de resultado final de abandono del tabaco. Cuando los incentivos se dirigían hacia los profesionales sanitarios solamente aumentaba el uso de la terapia conductual, aunque sólo se encontraron tres estudios con este tipo de incentivos. Admitiendo las limitaciones de la revisión, se concluye que considerando la gran cantidad de fumadores en el mundo, incluso un resultado modesto de la financiación del tratamiento para dejar de fumar ya tendría un enorme efecto en la Salud Pública global[12].

A partir de estos datos, y para evaluar el efecto del tratamiento farmacológico subvencionado en las tasas de cesación tabáquica en el ámbito de la Atención Primaria de un sistema sanitario público, como el español, y antes de que se autorizara la financiación en nuestro país, Minué-Lorenzo y cols llevaron a cabo un ensayo clínico pragmático, aleatorizado, por conglomerados.

Los del grupo de intervención recibieron tratamiento farmacológico de primera línea de forma gratuita. El principio activo (nicotina, vareniclina o bupropión) fue escogido por el profesional de la salud de acuerdo con las preferencias del paciente. Las dosis de tratamiento fueron estándar: TSN en relación al número de cigarrillos fumados, bupropión 150-300 mg/día y vareniclina 1-2 mg/día. Se permitieron combinaciones de tratamiento a criterio del médico, como TSN parches con forma oral, o bupropión con chicles de nicotina. La duración media propuesta fue de 8 semanas para TSN y bupropión, y de 12 semanas para vareniclina. Los medicamentos se distribuyeron a los participantes desde los Servicios de Farmacia hospitalarios. A los pacientes del grupo control

se les prescribió el tratamiento en la consulta y tuvieron que adquirirlo en farmacias.

Se llevó a cabo con 1154 pacientes de 23 centros de salud de Madrid, constatando un aumento de las tasas de abstinencia, autoinformadas o confirmadas por carboximetría, a 12 meses en tratamientos financiados, que pasó del 9,6% al 15,4%[9].

Los autores constatan que sus resultados fueron similares a los de otros estudios, como el ya citado de Selby *et al.*, y el riesgo relativo de la Revisión Cochrane de 2017 estuvo dentro del mismo rango.

También citan el de Twardella *et al.*, que con un diseño similar por conglomerados encontraron una tasa de abstinencia continua del 9% para un grupo al que se proporcionó formación y financiación frente al 1% en un grupo tratado según la práctica clínica habitual[13]. Y el de Kaper *et al.*, que presentaron una tasa de abstinencia validada bioquímicamente del 5,5 % en el grupo intervención y del 2,8% en el grupo control, y una abstinencia autoinformada del 7,8% y del 5,5%, respectivamente. El uso de farmacoterapia fue del 10,8% en el grupo financiado y del 4,1% en el control[14].

En un informe técnico de enero de 2021, la OMS relaciona la efectividad de las intervenciones en cesación tabáquica basándose en las revisiones Cochrane más recientes, y concluye que los sistemas de financiación en Salud son las intervenciones más efectivas, más que cualquier otra intervención o tratamiento, alcanzando hasta un 338% de incremento en la tasa de cesación si la financiación se dirige a los fumadores frente a la no financiación, y un 33% si se dirige a los proveedores de salud[15].

Criterios de financiación

El Sistema Nacional de Salud español, para permitir la financiación de medicamentos para el tratamiento del tabaquismo, estableció unos criterios de inclusión que deberían cumplir, en su totalidad, los pacientes fumadores susceptibles de recibir su prescripción y que, en el momento de escribir este artículo, son los siguientes:

1. Edad mayor de 18 años.
2. Motivación expresa de dejar de fumar, que se pueda constatar con un intento de dejar de fumar en el último año.
3. Que fume 10 o más cigarrillos al día.
4. Que tenga, además, un alto nivel de dependencia, definido por un Test de Fagerstrom ≥ 7[8].

Discusión

El primer criterio conduce a la pregunta: ¿qué hacemos con los adolescentes?. A pesar de la tendencia decreciente del consumo de tabaco en este grupo poblacional en los últimos años (acompañado del incremento exponencial del uso de las nuevas formas de fumar) según los datos de la última Encuesta sobre uso de drogas en Enseñanzas Secundarias en España (ESTUDES), realizada en 2021 sobre estudiantes entre 14 y 18 años, todavía se confiesan como fumadores diarios un 8,8% de los chicos, con una media de 6,8 cigarrillos/día y un 9,2% de las chicas, con una media de 5,4[16].

Por otra parte, aunque es cierto que bupropión y vareniclina indican en su ficha técnica que no deben prescribirse a menores de 18 años, la TSN se ha demostrado segura y efectiva en adolescentes, y aparece la indicación de uso para mayores de 12 años en algunas de las fichas técnicas autorizadas en España de sus medicamentos[17].

En cuanto al segundo criterio, ¿se puede afirmar con rotundidad que una persona que lleva años fumando, y que probablemente habrá realizado varios intentos de cesación en ese tiempo, no muestra motivación si uno de esos intentos no se ha llevado a cabo durante el último año?.

El tercer criterio es fácilmente rebatible por la abundante bibliografía aportada durante los últimos años, pudiéndose afirmar que no hay nivel seguro de fumar[17]. A continuación se exponen las conclusiones de diferentes estudios al respecto.

- Fumar solamente de uno a cuatro cigarrillos al día ya se asocia con un riesgo significativamente mayor, frente a no fumadores, de fallecer por cardiopatía isquémica o por otros eventos cardiovasculares, y el riesgo de morir por cáncer de pulmón se multiplica por tres en hombres y por cinco en mujeres[18].

- El riesgo de muerte temprana es un 64% mayor, y nueve veces más probable padecer un cáncer de pulmón, entre quienes han fumado un solo cigarrillo al día durante toda su vida, frente a los no fumadores, disminuyendo el riesgo en proporción a cuanto menor es la edad en la que se abandona el tabaco[19].

- Fumar un solo cigarrillo al día ya supone la mitad del riesgo de enfermedad o accidente cardiovascular del que comporta fumar veinte[20].

-Un fumador de menos de cinco cigarrillos al día durante un año puede perder la misma funcionalidad pulmonar que un fumador de más de treinta al día durante nueve meses[21].

El cuarto criterio, relativo al Test de Fagerström (TF), el tan reconocido test de dependencia física de la nicotina, requiere alguna reflexión. ¿Deben descartarse fumadores con TF inferior a 7, valores que sugerirán una dependencia física moderada o leve?.

Parece necesario flexibilizar también este criterio, ya que existen guías clínicas e incluso fichas técnicas de medicamentos de TSN que indican pautas de tratamiento farmacológico desde TF 5 e incluso para menores de 5[22,23], y algunos autores indican que la puntuación de 6 a 7 ya indica adicción moderada y debe tratarse farmacológicamente con TSN[24].

Sociedades científicas, organizaciones no estatales y ciudadanas, profesionales sanitarios y políticos se han expresado en numerosas ocasiones solicitando la ampliación de la financiación de los tratamientos farmacológicos del tabaquismo a todos los fumadores e incluyendo todos los fármacos disponibles que han demostrado su efectividad. Se citan algunos ejemplos a continuación.

En el decálogo redactado en 2019 por expertos sanitarios de distintos ámbitos de la Atención Primaria como consenso para el abordaje multidisciplinar del tabaquismo se indica, en el punto 9: "los tratamientos farmacológicos para la cesación tabáquica que dispongan de eficacia demostrada deben ser financiados por el Sistema Nacional de Salud"[25].

El senador Sánchez López, el 23 de enero de 2020, en pregunta escrita al Gobierno de la nación, indicando que "numerosos médicos de familia y expertos en adicciones han alertado sobre las limitaciones de diseño y de puesta en práctica de las medidas", demanda por qué motivos el Gobierno ha dejado fuera de la cobertura financiera pública la TSN, pese a su extendida utilización y recomendaciones de los especialistas en tabaquismo[26].

De Granda-Orive et al. exponen que la terapia farmacológica de primera línea combinada con el soporte psicológico se ha demostrado que es coste-efectiva y debe ofrecerse a todos los fumadores que deseen llevar a cabo un intento serio de cesación, y que financiar los tratamientos farmacológicos para ayudar a dejar de fumar implica un beneficio económico significativo a los sistemas nacionales de salud. Por otra parte, se preguntan los autores el motivo por el que no se incluyó la TSN, conociéndose que su uso es coste-efectivo, que existe una evidencia amplia de efectividad y que la TSN combinada (parches junto con una forma oral) consigue los mismos ratios de abstinencia que vareniclina[27].

Arroyo et al, tras valorar el alto impacto económico del tabaquismo en costes relativos a servicios de salud, exponen que debería incluirse la financiación de todos los tratamientos farmacológicos de la dependencia nicotínica en el SNS, demostrada su eficacia, para aquellos pacientes que no pueden afrontar el coste del tratamiento de esta enfermedad crónica[28].

Finalmente, la declaración de instancia al Gobierno de España firmada por 70 sociedades científicas y asociaciones ciudadanas, de consumidores y organizaciones no estatales, en línea con el objetivo conocido internacionalmente como el "tobacco endgame" para el año 2030, en el apartado 9 de "acceso a tratamientos para dejar de fumar", expone lo siguiente: "ampliar la financiación y el acceso a los tratamientos para dejar de fumar: que las personas fumadoras puedan acceder a todas las terapias farmacológicas y conductuales cuya eficacia y seguridad para dejar de fumar se haya demostrado científicamente"[29].

Tratamientos farmacológicos no financiados

Los medicamentos de la TSN y la citisina, no financiados (a excepción de los parches de TSN en dos CCAA, como se ha indicado) disponen de una amplia evidencia científica de efectividad y seguridad en el tratamiento del tabaquismo.

Terapia Sustitutiva con Nicotina (TSN)

Es muy destacable la revisión Cochrane de 2018 de Hartmann-Boyce *et al*.[30], citada por Aguiló[17], de TSN frente a placebo o a no tratamiento, incluyendo 136 ensayos clínicos y 64.640 participantes, con una calidad de evidencia alta, concluyendo que todas las formas autorizadas de TSN pueden ayudar a quien intenta dejar de fumar, incrementando sus posibilidades de éxito en un 50-60%, con independencia del entorno, y sugiriendo que es poco probable que posteriores investigaciones modifiquen esta conclusión[17].

Asimismo, Aguiló y Serantes[31] citan otra revisión Cochrane, de Lindson et al en 2019[32] en la que, a partir de 63 estudios con 41509 participantes, se concluye que la TSN combinada es igual de efectiva que vareniclina, entre un 15 y un 36% más efectiva que la TSN como monofármaco, y que la evidencia es alta en cuanto a que la TSN es segura y efectiva para dejar de fumar, y justifica la utilización de dosis elevadas, como la de 25 mg con parches de 16 horas, en fumadores con alta dependencia[31].

Jiménez-Ruiz *et al*, revisando los principales estudios de eficacia y seguridad de los medicamentos disponibles en España para el tratamiento del tabaquismo, concluyen que la TSN ha demostrado su eficacia en una gran cantidad de ensayos clínicos y metaanálisis. Junto con los dos estudios ya citados, mencionan las sugerencias de la American Thoracic Society en cuanto a prolongar la pauta habitual de tratamiento con TSN de 12 semanas

hasta las 24 semanas, tanto como monofármaco como en TSN combinada, en pacientes con elevada dependencia física por la nicotina y en los que en ese tiempo no se obtuvieron resultados[33,34].

Por otra parte, la TSN ha demostrado la seguridad en fumadores tanto sin comorbilidades como en los casos que presentan patologías asociadas, tanto psiquiátricas, como cardiovasculares o la enfermedad pulmonar obstructiva crónica (EPOC)[33].

Citisina

La eficacia clínica se demostró frente a placebo por West y cols. en 2011[17], en estudio doble ciego de grupos paralelos con 740 participantes asignados aleatoriamente al fármaco activo o al placebo, la mitad a cada uno de ellos, a los que se les suministró de forma gratuita, con la pauta habitual de 25 días. Se comprobó la abstinencia a 12 meses, siendo de 8,4% en el grupo que tomó citisina, frente al 2,4% en el grupo control[35,33].

Posteriormente, se confirmó dicha eficacia mediante diferentes revisiones y metaanálisis[17], como el de Hajek y cols en 2013[36], Cahill y cols en 2016[37], y el de Tutka y cols en 2019[38].

En cuanto a la seguridad de citisina, hay que considerar que millones de fumadores la han utilizado, ya que se comercializa desde hace casi 60 años en países de Europa Central y del Este, y en algunos de Asia Central, donde se puede adquirir libremente sin receta, no habiéndose reportado efectos secundarios graves[17].

Su seguridad se ha podido comprobar en distintos ensayos clínicos y metaanálisis, presentando efectos adversos leves, principalmente gastrointestinales[33], y se ha asociado con menores tasas de cefalea y náuseas que la vareniclina[37].

Conflicto de intereses

El autor declara no tener ningún conflicto de interés.

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ARTÍCULO ESPECIAL

Revisión ginecológica: el cambio de una estrategia

Gynecologic screening: the change of a strategy

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Resumen

Partiendo de una revisión histórica del origen del procedimiento preventivo del cáncer de cuello uterino, se actualiza su recomendación preventiva así como la de la revisión ginecológica.

Palabras clave: Revisión ginecológica, cáncer cervical, prevención.

Abstract

Based on a historical review of the origin of the cervical cancer preventive procedure, its preventive recommendation as well as that of gynecologic screening is updated.

Key words: Gynecologic screening, Cervical cancer, Prevention.

Introducción

¿Qué es la serendipia? El hallazgo casual no planificado de algo cuando se están buscando otras cosas. Un neologismo –*serendipity* en inglés– acuñado por Horace Walpole en 1754 a partir de un cuento tradicional persa llamado «Los tres príncipes de Serendip», en el que los protagonistas, unos príncipes de la isla de Serendip —antiguo nombre persa de la isla de Ceilán, la actual Sri Lanka— solucionaban sus problemas a través de increíbles casualidades. Se ha escrito que el descubrimiento de América –Colón– y de la penicilina –Fleming– son dos claros ejemplos de serendipia. George Nicholas Papanicolaou descubrió en 1953 en una acción llena de serendipia[1] la capacidad que la citología exfoliativa de cuello de útero podía tener para la prevención y/o el diagnóstico precoz del cáncer de cuello de útero (CCU) y lo comunicó en la *Third Race Betterment Conference*[2]. Posteriormente, años más tarde, publicó un trabajo al respecto que tuvo gran repercusión[3]. Hubo dos ensayos prospectivos de alta calidad que a partir de la información inicial de Papanicolaou demostraron con alto nivel de evidencia que la aplicación sistemática de la citología exfoliativa de cuello de útero en una población femenina provocaba en el medio / largo plazo una muy importante disminución de la incidencia del CCU, una demostración indiscutible e indiscutida de la efectividad del procedimiento: las publicaciones de Christopherson[4] y de Walton, especialmente esta última, un ensayo decisivo por su impecable diseño y análisis de resultados, conocido desde entonces como *The Walton Report*, piedra angular de la aplicación universal del Pap-test[5], de la citología cérvico-vaginal, en los protocolos de prevención secundaria del CCU.

El impacto de esta aplicación está referenciado en muy numerosos trabajos y su uso está recomendado en los protocolos de todos los organismos internacionales y nacionales que se preocupan de esta actividad preventiva[6,7]. Repetir la citología con la frecuencia adecuada y con la calidad necesaria en toma, lectura e informe está firmemente comprobado que impacta de forma muy significativa sobre la incidencia del CCU en la comunidad revisada[8].

A raíz de la publicación por Zur Hausen de su trabajo realizado en su laboratorio de Friburgo, Alemania, que identificó al virus del papiloma humano (VPH)[9], y de la comprobación posterior inequívoca en un trabajo cooperativo de un grupo internacional –con el español Xavier Bosch en él– liderado por Walboomers desde la *Vrije Universiteit*, en Amsterdam[10] del papel necesario

de este virus en la génesis del CCU, se iniciaron trabajos prospectivos y controlados para estudiar si la determinación sistemática del VPH en el cérvix de la mujer podría tener un papel en la prevención secundaria del cáncer de esta localización. Una referencia clave en la comprobación de la excelencia efectiva y eficiente del uso del test de VPH en el cribado del CCU es la publicación de los resultados de un estudio europeo –con las españolas Silvia de Sanjosé y Belén Lloveras participando en él– liderado por Joakim Dillner[11], en el que se demuestra fehacientemente que el valor predictivo negativo de un test de VPH –realizado siempre mediante un test validado[12]– es notablemente superior al de la citología, lo que permite alargar con seguridad el intervalo de control, llevándolo con seguridad desde el trienal citológico a los cinco años.

En consecuencia, ahora mismo las normas internacionales[6] y la última Orden al respecto del Ministerio de Sanidad Español[13] confirman la recomendación del uso del test de VPH para cribado del CCU en mujeres a partir de los 35 años, con control a los 5 años de los negativos, pero no a las de menos edad, que deberán seguir siendo controladas con citología. El por qué es la alta capacidad inmunitaria natural de aclarar la presencia viral en mujeres más jóvenes[14], lo que hace decrecer en ellas el valor predictivo positivo para CCU de una determinación positiva.

Surge la pregunta: ¿el control ginecológico de salud pasa a ser trienal o quinquenal? En absoluto debe caerse en este error asistencial, no confundamos, no asociemos el control preventivo del CCU con el control de otras patologías o circunstancias que puedan confluir en una mujer. El cáncer de mama y los de vulva, endometrio y ovario –y también el colorectal– tienen su propia agenda preventiva y, además lo tienen otras patologías o circunstancias asistenciales, como problemas menstruales, anticoncepción, deseo y/o control de gestación, entre otros. Hay que ajustar el calendario de control de salud ginecológica –y seguro también de la general– según el perfil de la mujer que nos consulta, no asociando tempos preventivos exclusivamente al CCU. Esta Medicina Personalizada constituye sin duda el área de trabajo en el que debemos desenvolvernos. Evaluar bien a la persona que nos consulta, establecer bien sus perfiles de riesgo y actuar en consecuencia, estableciendo, de acuerdo con ella, su agenda de control de salud, siempre atendiendo las recomendaciones vigentes de Sociedades y Agencias Sanitarias Nacionales e Internacionales. Este es nuestro deber.

Conflicto de intereses

Los autores declaran no tener ningún conflicto de interés.

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CASE REPORT

Rheumatoid Arthritis: A Case Study

Artritis reumatoide: Un estudio de caso

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Abstract

Introduction: Rheumatoid Arthritis, is an autoimmune and inflammatory disease. NSAIDs are the most commonly used drugs in reducing pain while Glucocorticoids used especially in acute cases. Over the last 3 decades, five different TNF-α inhibitors have been administered: infliximab, etanercept, adalimumab, golimumab, and certolizumab-pegol for RA treatment. This case study provides further evidence that changes in treatment modalities for RA management leads to a significant improvement in disease activity in patients with severe disease.

Case Report: We present a 44 years old female, diagnosed for the first time with RA in 2008. In consultation with the staff, the doctors decided to start treatment with Golimumab and MTX in 2021. The assessment of the ACR coefficient is with improvement in ACR20.

Conclusion: The use of Golimumab with MTX reduces clinical signs and symptoms in patients with AR, thereby improving both qualities of life and pain relief.

Key words: Rheumatoid Arthritis, golimumab, treatment.

Resumen

Introducción: La Artritis Reumatoide, es una enfermedad autoinmune e inflamatoria. Los AINE son los fármacos más utilizados para reducir el dolor, mientras que los glucocorticoides se emplean sobre todo en los casos agudos. En las últimas 3 décadas, se han administrado cinco inhibidores del TNF-α diferentes: infliximab, etanercept, adalimumab, golimumab y certolizumab-pegol para el tratamiento de la AR. Este estudio de caso proporciona una prueba más de que los cambios en las modalidades de tratamiento para el manejo de la AR conducen a una mejora significativa de la actividad de la enfermedad en pacientes con enfermedad grave.

Informe de un caso: Presentamos a una mujer de 44 años, diagnosticada por primera vez de AR en 2008. En consulta con el personal, los médicos decidieron iniciar el tratamiento con Golimumab y MTX en 2021. La evaluación del coeficiente ACR es con mejoría en el ACR20.

Conclusión: El uso de Golimumab con MTX reduce los signos y síntomas clínicos en los pacientes con AR, mejorando así tanto la calidad de vida como el alivio del dolor.

Palabras clave: Artritis reumatoide, golimumab, tratamiento.

Introduction

According to "The Center for Disease Control and Prevention" Rheumatoid arthritis (RA) is an autoimmune and inflammatory disease, which means that the immune system attacks healthy cells in the body by mistake, causing inflammation (painful swelling) in the affected parts of the body[1]. RA mainly attacks the joints in the hands, wrists, and knees, and usually affects many joints at once. In a joint with RA, the lining of the joint becomes inflamed, causing damage to joint tissue. This tissue damage can cause long-lasting or chronic pain, unsteadiness (lack of balance), and deformity (misshapenness). RA can also affect other tissues throughout the body and cause problems in organs such as the lungs, heart, and eyes[2]. The total average prevalence of this disease in the world is about 1%, while in Mediterranean countries is 0.36%. It is more prevalent in women than men and is three to four times more common in men[3]. RA clinic is different among patients. In some patients, it appears with the onset of early signs such as fatigue, weakness, anorexia,

and late synovium or accompanying musculoskeletal symptoms[4]. The diagnosis of RA is mainly clinical[4], and is made by evaluating clinical signs lasting 1-2 years, with symmetrical synovitis, morning stiffness, or subcutaneous nodules. Laboratory procedures examine the joint fluid and evaluate the rheumatoid factor, while radiographs often show bone and cartilage damage[5]. The treatment of RA has been increasingly developed in recent years, although no treatment has yet been discovered that would give the patient the final solution to RA. The most commonly used drugs are NSAIDs, Glucocorticoids, and corticosteroids. Furthermore, specialists nowadays are also prescribing disease-modifying antirheumatic drugs (DMARDs) for most patients. Hydroxychloroquine, minocycline, and sulfasalazine are commonly prescribed for patients with mild to moderate disease or in combination with other medications. Cyclophosphamide is used in very severe cases, while Leflunomide is widely used in moderate to severe RA[4,6]. Over the last 3 decades, RA treatment has been administered with five different TNF-α inhibitors such as infliximab, etanercept, adalimumab, golimumab, and certolizumab-pegol. Hereby we describe a case of a middle-aged woman having a complicated RA. This case study provides further evidence that changes in treatment modalities for RA management leads to a significant improvement in disease activity in patients with severe disease.

Case report

Patients information

This case study presents a female patient, currently 44 years old, diagnosed with RA firstly in 2008. Thus, the following parameters were collected at study entry: age, comorbidity (other chronic diseases requiring long-term medical care), disease duration, patient's assessment of pain, number of swollen and tender joints, extra-articular manifestations, and also the functional status evaluated by an adapted version of Health Assessment Questionnaire (HAQ)[7]. Furthermore, we evaluated some of the laboratory finding such as erythrocyte sedimentation rate (ESR), C reactive protein (CRP) level, rheumatoid factor (RF) positivity, Anti-citrullinated protein/peptide antibodies (ACPA) positivity using second-generation anti-CCP assay (CCP2), plus anti-double-stranded DNA antibody (anti-dsDNA), etc.

For the period 2008-2013, the data were collected by patient anamnesis and medical files.

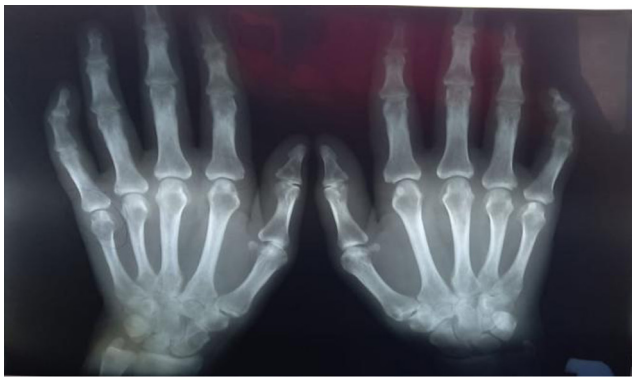
Clinical findings

This patient meanwhile has performed regular consultations with the Rheumatologist of the district. The management of the case included the physical therapy rehabilitation program when she was diagnosed and treatment with NSAIDs, analgesics, glucocorticoids, Methotrexate, folic acid, and Plaquenil (**Table I**).

The first hospitalization was in 2013 at the Rheumatology unit in "Mother Teresa University Hospital"(MTUH) in Tirana, a tertiary healthcare center. The main symptom she presented was joint pain. Further examination revealed the reduction of the arch of joint movement, edema, and fine crepitations.

The radiological assessment revealed osteoporosis of both hands in the form of bands, narrowing of the articular spaces, geode, and semi-ankylosis. Bilateral gonarthrosis was detected on radiographic examination of the genus joints. **Figure 1** presented the radiological view of the patient in 2013. The diagnosis was Arthritis Rheumatoid Stage III-IV.

Figure 1: Radiological view: Patients' hands in the year 2013.



She was treated for rheumatoid arthritis and started DMARDs therapy on a high dose of Leflunomide for three days, followed by a dose reduction for the next 27 days. Therapy with Plaquenil, Ranitidine, Prednisone, Naproxen, and Calciocarbonat + cholecalciferol, was applied concurrently. **Table I** shows the treatment scheme prescription of the patient in 2013.

Table I: Treatment scheme prescription in 2013.

Name of the drug	Dosage	Method of administration	Duration
Arava (Leflunomide)	20mg	5 tablets/ day	3 first days
Arava (Leflunomide)	20mg	½ tablet/ day	The next 27 days
Plaquenil	200mg	2x1 tablet/ day	30 days
Ranitidine	150mg	1 tablet/ day	30 days
Prednisone	5mg	2 tablets/ day	30 days
Naproxen	250mg	2x1 tablet / day	30 days
CADTRE (Calcio carbonato + colecalciferolo)	1000mg + 880 UI	1 bustine/ day	30 days

Looking at the chronicity of her problem, especially with just minimal improvement with the current treatment plan, the patient was subjected in 2021 for the third time at the Rheumatology unit at MTUH, with complaints of generalized joint pain of inflammatory character, fatigue, marked bodily weakness, marked difficulty in movement. Joints appeared infiltrated and painful in pressure. Both genu articulations presented hypertrophic synovium, and pain in flexio-extension. Deformities of hands were present too and the Squeeze test was positive bilaterally. The first formation was limited. Immunologic parameters were monitored RF was very high at 663.0 UI/ml, ERS 60 mm/h, and CRP 8.4 mg/dl. Based on this situation rheumatologist specialist decided to start the treatment with biological therapy Golimumab.

Table II shows the recommended treatment of the female patient during and after hospitalization in 2021.

Table III shows the results of the connective tissue screening profile that included erythrocyte sedimentation rate, C-reactive protein (CRP), anti-cyclic citrullinated peptide (anti-CCP), antineutrophil cytoplasmic antibody (ANCA) plus anti-double-stranded DNA antibody (anti-dsDNA) and rheumatoid factor (RF).

The patient was subject to DAS28 evaluation at the start of the new scheme of treatment with Golimumab, with a score of 5.5 (**Table IV**). After one year of treatment with Golimumab, was done a new evaluation of immunologic status (CRP, RF, ERS- **Table III**) and physical function of the patient using the DAS28 tool. Hematologic investigation results improved CRP from 8.4 mg/dl to 7.3 mg/dl, RH from 663.0 UI/ml to 255UI/ml, and the score of DAS28 were 4.8.

At the end of this case study, the patient underwent an interview on HAQ before and after treatment with Golimumab. The result obtained from the interview is shown in **table V**. An improvement in Pain rate and Health rate is noticed after 12 months of treatment.

Table II: The recommended treatment in 2021, including Golimumab.

Name of the drug	Dosage	Method of administration	Duration
Golimumab	50mg	2 pens SC/ month	
Prednisone	5mg	2 x1 tablet/ day	
CaVitD3	1000 UI	1 tablet/ day	
Omeprazole	20mg	1 tablet/ day	
Naproxen	500mg	2x ½ tablet/ day	In pain
Methotrexate	2.5mg	2x2 tablets / 1 day on week	
Folic acid	5mg	2 tablets/ day	After MTX

Table III: Laboratory parameters for 2013, 2019 to 2022.

Laboratory parameters	2013	2019	2020	2021	2022
CRP	103mg/dl	13.2mg/dl	233.9mg/dl	8.4 mg/dl	7.3 mg/dl
RF	200UI/ml		450 UI/ml	663.0 UI/ml	255UI/ml
T-score	-1.2				
Fibrinogens	491 mg/dl		630mg/dl	459 mg/dl	490 mg/dl
C3	109mg/dl				
C4	19mg/dl				
Anti-CCP	363 U/ml				
Anti-DNA	(-)				
ERS	39mm/h	70mm/h	105mm/h	60 mm/h	72mm/h
K+	7.9 mmol/l			4.1 mmol/L	
Uremia	27mg/dl	49 mg/dl	35mg/dl	41mg/dl	36mg/dl
Creatinine	0.7mg/dl	0.65 mg/dl	0.92 mg/dl	0.64mg/dl	0.53mg/dl
25-(OH) vitamin D			15.1 ng/ml		

Table IV: DAS28 in two times.

	Before treatment with Golimumab	After treatment with Golimumab
DAS28	5.5	4.8

Table V: HAQ used before and after treatment with Golimum.

	Before treatment with Golimumab	After treatment with Golimumab
HAQ	2.88	2.33
Supporting devices	Supporting stick Auxiliary equipment for the toilet Can opener	Support stick Equipment for opening cans
Categories that need help with	Dressing and grooming Arising Hygiene Gripping and opening things Errands and chores	Dressing and grooming Arising Hygiene Errands and chores
Pain rate (0-100) 0- without pain / 100- severe pain	92	87
Health rate (0-100) 0-very good / 100- very bad	95	89

Discussion

Rheumatoid arthritis is usually diagnosed based on the 2010 American College of Rheumatology-European League Against Rheumatism (ACR-EULAR) Classification[8]. The current treatment paradigm for patients with rheumatoid arthritis (RA) consists of disease-modifying antirheumatic drugs (DMARDs), including conventional synthetic DMARDs (csDMARDs) and biologic DMARDs (bDMARDs)[9]. The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) propose methotrexate as the first step in the treatment of patients with active RA. Although ~30% of patients achieve full clinical remission with methotrexate monotherapy, 70% require a step-up treatment that includes the addition of either csDMARDs or bDMARDs[10]. A study conducted by Keystone[11] in 2013 found an improvement in patients treated with Golimumab and MTX from 35% to 55%.

Estimates of efficacy rates of TNF-α inhibitors may depend on several factors, including patient characteristics, such as disease duration, prognostic factors, number of previously failed DMARDs, and disease activity, as well as the dose of TNF-α inhibitor and the designs of the studies from which they were obtained. Despite some variation attributable to these factors, estimates derived from randomized, controlled trials (RCTs) suggest that between 40% and 50%[12] of RA patients treated for at least 6 months with one of the three first-generation TNF-α inhibitors (etanercept, adalimumab, and infliximab) failed to achieve the American College of Rheumatology 50% (ACR50) improvement criteria[13], while the results from a large, registry-based study[14] indicated that over 70% of these patients fail to achieve Disease Activity Score 28 joint count (DAS28)-defined "remission" (DAS28 <2.6).

Contrasvely with the previous study, in the case we have presented the female patient presented an improvement of CRP from 8.4 mg/dl to 7.3 mg/dl, RH from 663.0 UI/ml to 255UI/ml, and the score of DAS28 were 4.8 after 12 months of treatment with biological therapy Golimumab. Additionally, based on the HAQ interview and before and after treatment with Golimumab, the patient has seen an improvement in Pain rate and Health rate. Those findings are the same as two other studies conducted by Shono, and Shimizu et al (15,16). So Shono in a study performed on Japanese patients[15], the primary endpoint, clinical remission, was attained in 83% of patients according to DAS28-CRP criteria ($p < 0.001$) and 69% according to SDAI criteria ($p < 0.001$) by week 24. Adverse events were reported in 11.6% of patients receiving golimumab. In a recent study (2020) by Shimizu et al.,[16] patients demonstrated significant improvement in the clinical signs and symptoms of rheumatoid arthritis at 24 weeks, as indicated by the reduction of DAS28-CRP (Δ0.87), DAS28-ESR (Δ0.85), SDAI (Δ7.32), and CDAI (Δ6.98) scores.

Conclusion

The use of Golimumab with MTX reduces clinical signs and symptoms in patients with RA, thereby improving both qualities of life and pain relief.

Conflict of Interest and Informed Consent

No conflict of interest was identified during data collection and analysis. The patient was acquainted in advance with the terms of the study and obtained written consent.

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CASE REPORT

A case of intravascular leiomyomatosis, a pathology of infrequent diagnosis

Un caso de leiomiomatosis intravascular, una patología de diagnóstico infrecuente

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Abstract

A case of intravascular leiomyomatosis is presented in a 45-year-old woman, a benign pathology of very infrequent diagnosis. The clinical circumstance of its diagnosis and its histological characteristics are described.

Key words: Intravascular, Leiomyomatosis.

Resumen

Se presenta un caso de leiomiomatosis intravascular en una mujer de 45 años, una patología benigna de diagnóstico muy infrecuente. Se describe la circunstancia clínica de su diagnóstico y sus características histológicas.

Palabras clave: Leiomiomatosis intravascular.

Intravascular leiomyomatosis is a benign alteration caused by the proliferation of smooth muscle cells of the myometrial vessels or uterine fibroids. Its diagnosis should be considered when faced with uterus-dependent pelvic masses, especially if it occurs in women with previous or current uterine fibroids. It's important to keep in mind that it can spread to the cava vein and also to the right heart chambers.

A 45-year-old woman (LGB), with menarche at 12 years of age, menstrual type 4/28, with no history of interest, who consulted for the first time on 12/21, providing a a magnetic resonance imaging (**Figures 1, 2**). that depicted: "Increased uterus with leiomyomas and occupation of most of the pelvis by a large solid-cystic or solid left pelvic mass with necrosis and to a lesser extent a predominantly cystic or necrotic right para-uterine mass, which although they raise doubts due to their size and heterogeneity, they are suggestive of large pedunculated leiomyomas with degeneration or necrosis. Both ovaries normal".

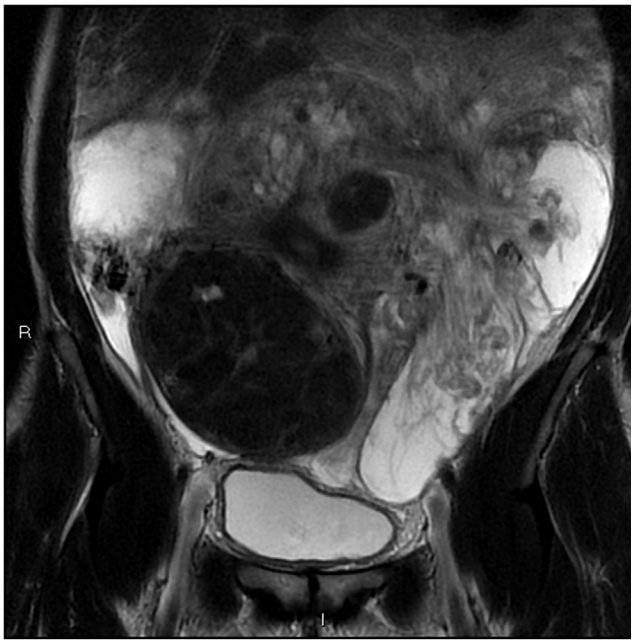
Surgical intervention was scheduled, which was performed on 01/22. It was found a large uterus with a polimyomatous appearance occupying the entire pelvis and a tumour of about 6cm with a cystic appearance. Also, in the left para-adnexal area and retroperitoneally a 40 cm tumour with a predominantly cystic appearance and a highly vascularized cystic not adherent to deep layers or intestine occupying the bottom of the pouch of Douglas. It was decided to perform a total hysterectomy with double adnexectomy and retroperitoneal lumpectomy.

Histological report

Total hysterectomy piece with right adnexectomy and left salpingectomy. It weighs 1002 g as a whole and has a polylobulated appearance with multiple myomatous lesions, the largest measuring 8 cm. At the level of the left horn, a poorly defined 6 x 5 cm area with an edematous and vesicular appearance was identified in relation to several small myomatous lesions. Collapsed endometrial cavity with smooth-surfaced mucosa 0.1 cm thick. Right ovary and tube without macroscopic alterations.

Resection piece of 20 x 20 x 7 cm multinodular with a vesicular appearance that presents an ovary adhered to one of its faces of 5 x 2 cm without alterations. The rest is made up of edematous material with small cystic areas and some hemorrhagic areas. Scattered myomatous-looking nodules are seen.

Figure 1, 2: Magnetic resonance imaging.



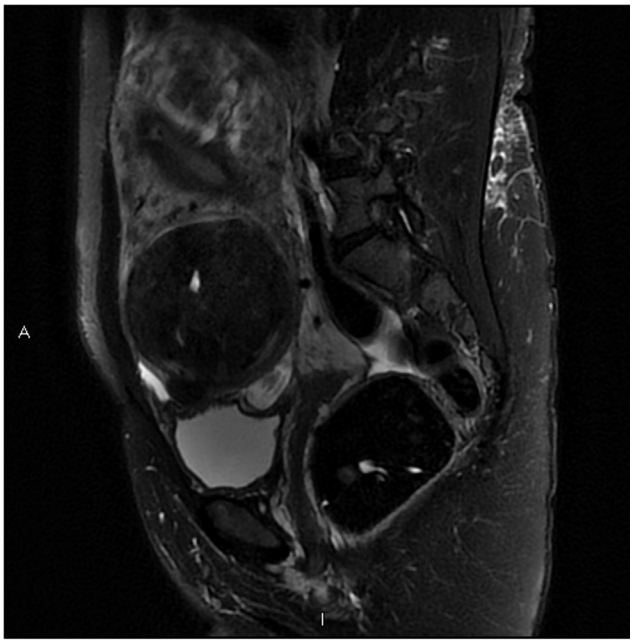


Figure 3: Hematoxylin-eosin. x16.

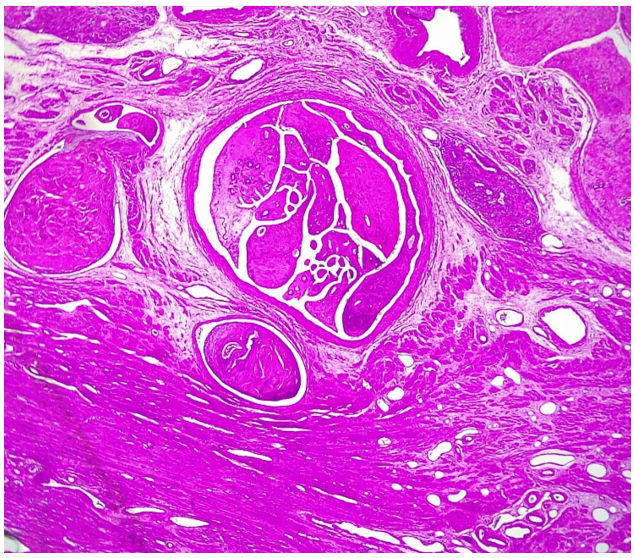
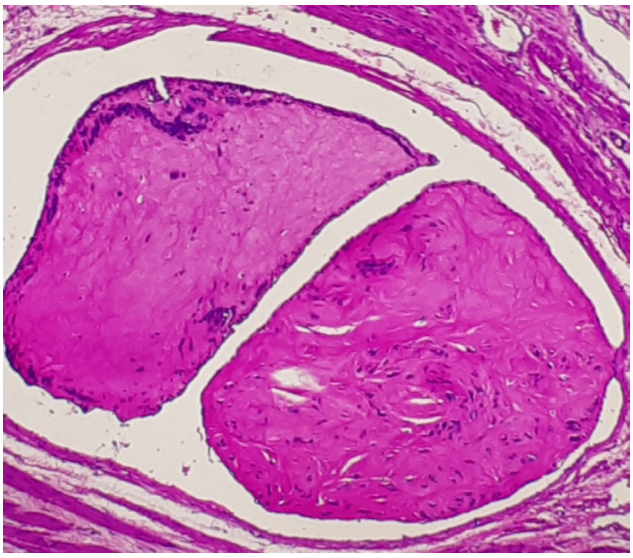


Figure 4: Hematoxylin-eosin. x200.



Both at the uterine and extra-uterine levels, a myomatous proliferation associated with ectasia of the vascular walls, with intraluminal growth, is observed (**Figures 3,4**). Extensive areas with marked edema. The nuclei are oval and norm-chromatic, with no tumor necrosis, atypical mitoses, or signs of aggressiveness proliferative endometrium. Tubes and ovaries without alterations.

Based on these observations, INTRAVENOUS LEIOMYOMATOSIS is diagnosed.

In March 2022 (03/14/2022) the Aortic CT Angiography revealed venous occupation by a single mass that extended from the right gonadal vein to the artery of the lower lobe of the right lung, consistent with his pathology.

Cardiac surgery was performed on 03/14/2022, observing normal-appearing lungs and heart. A white mass is observed inside the inferior vena cava. A hard, lobulated, pearly white tumor was completely removed (**Figure 5**). With extension of the superior and inferior lobar branches of the right pulmonary artery, a branch of the Left Pulmonary Artery crosses the right cavities outflow tract RV, RA and inferior vena cava (about 20 cm in IVC) with rest of old clots probably related to previous surgery.

The macroscopic description of pathological anatomy describes an elongated fragment of 40cm in length, beaded and made up of whitish tissue of a firm and well-defined consistency. The microscopic description defines fragments corresponding to a well-differentiated

Figure 5: lobulated, pearly white tumor.

tumor made up of bundles of spindle cells of smooth muscle lineage. Presence of deposits of abundant hyaline substance in the stroma. No necrosis or hemorrhage is evident. Absence of signs of malignancy. Diagnosis: intravenous leiomyomatosis.

In May 2022, a whole body CT angiography was performed to rule out endovascular satellite fibroids, with a negative result.

Comment

If "endovascular leiomyomatosis" and 2022 as the search period are entered in PubMed as the keywords, three publications are displayed[1], 163 if the word is "leiomyomatosis"[2]. This great difference reflects the diagnostic rarity of the case discussed here. This fact is clearly expressed in the publication that the Gynecology group of the MD Anderson Hospital in Madrid published in 2016[3] describing it as an "exceptional entity" and pointing out the difficulty of diagnosis and the need for its diagnosis to be suspected when, as in the case that we present here, the evaluation of uterine pathology is addressed in women with pelvic masses of polimyomatous appearance and especially if it is also suspected that there may be associated abdominal or thoracic vascular pathology.

It is a benign pathology but it needs to be addressed in a multidisciplinary way in its surgical approach, as was done in the case discussed here. The recommendation also includes long-term follow-up with adequate imaging techniques to control the possible recurrence of the pathology in the areas that may be affected, of special relevance for diagnosis, therapy and prognosis of possible pulmonary or cardiac involvement[4,5].

Conflict of interest

All authors declare no conflict of interest for this publication.

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CASE REPORT

Patient with recurrent Kikuchi-Fujimoto disease associated with adult Still desease

Paciente con enfermedad de Kikuchi-Fujimoto recurrente y enfermedad de Still del adulto asociada

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Sumary

We report a patient with Kikuchi-Fujimoto disease (KFD) with a history of a similar process thirty years earlier. She concurrently presented clinical and analytical manifestations of adult Still's disease (AOSD).

Key words: Recurrent Kikuchi-Fujimoto disease, Adult Still's disease.

Resumen

Presentamos una paciente con enfermedad de Kikuchi-Fujimoto (EKF) con antecedentes de un proceso semejante treinta años antes. De forma concurrente presentaba manifestaciones clínicas y analíticas de enfermedad de Still del adulto.

Palabras clave: Enfermedad de Kikuchi-Fujimoto recurrente. Enfermedad de Still del adulto.

Case report

A 51-year-old woman diagnosed with Kikuchi-Fujimoto disease (KFD) by biopsy 30 years ago that progressed satisfactorily with nonsteroidal anti-inflammatory drug (NSAID) treatment. She was admitted to our department with a 2-month intermittent history of acute spiking fever (40ºC) and profuse sweating, without a clear focus. She also presented progressive pain and swelling in the left axilla, wrists, metacarpophalangeal joints and shoulders.

The general physical examination was normal, except for the palpation of lymphadenopathy in the left axilla and neck as well as inflammation signs in both hands and shoulders. Repeated blood and urine microbiological studies tested negative and so did the infectious serology and autoimmunity screenings. General blood tests revealed an anemia of inflammation (9,5g/dl), leukocytosis (15,7x10^9 L) with neutrophilia (98%) and lymphopenia (2%). The acute phase reactants were high: VSG 77, PCR 114. The rise of ferritin level up to 3135 ng/ml was striking. The rest of blood and urine determinations were normal except for a slight increase in liver enzymes.

Mantoux test was negative.
Chest X-Ray didn't show any significative alteration.
Echocardiography was normal.

A positron emission tomography-computed tomography (PET/CT) (**Figure 1**) revealed metabolically active disease in the lymph nodes especially in the supra-diaphragmatic area and left axilla. Lymph node biopsy (**Figure 2**) shows necrotic area, phagocytic histiocytes, dendritic cells, eosinophilic granular material and karyorrhectic debris. Immunohistochemistry showed CD3, CD4, CD8-positive T cells with CD68 histocytes. Mixed with lymphoid areas of smalls cells with blasts and absence of neutrophils or plasma cells. These findings correspond to a histiocytic necrotizing lymphadenitis compatible with KFD.

Given the poor response to the initial treatment with ibuprofen 600 mg every 8 hours, a new treatment was initiated with daily prednisone 30 mg combined with weekly methotrexate 12,5 mg and supplementary folic acid. The fever quickly resolved and there was an obvious improvement of the articular affectation and general condition.

Figure 1: PET/CT imagen.

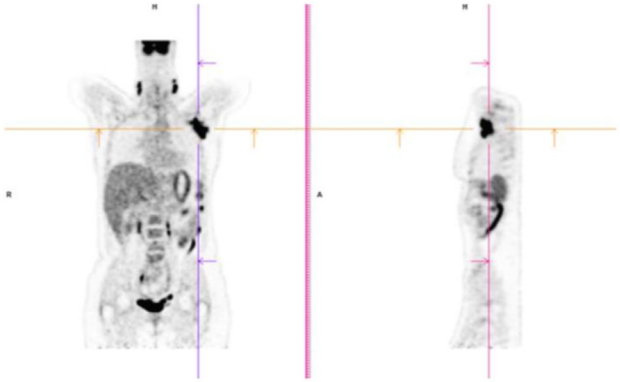
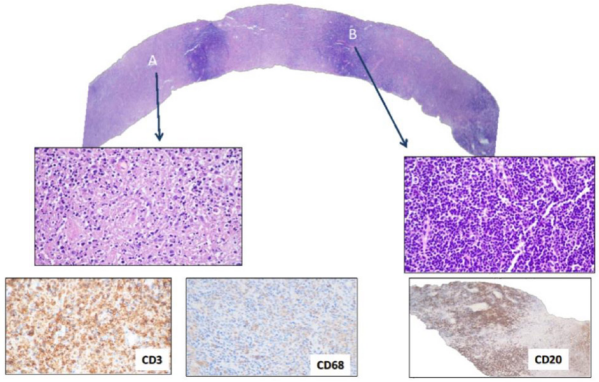


Figure 2: Lymph node biopsy. Histiocytic necrotizing lymphadenitis.



Discussion

Although Kikuchi-Fujimoto disease (KFD) and adult Still's disease (AOSD) were described during the 1970s, the number of published cases of both pathological processes is very scarce. Its simultaneous presentation (overlap syndrome) is exceptional and provokes varied manifestations[1,2].

The case we are reporting is exceptional given that the patient had already suffered from KFD 30 years earlier. It was thought that the recurrence of this disease was below 5%, however an important revision made in 13 French hospitals[3] proved a relapse in 21,3% of the cases, in a timeframe of 1 to 11,5 months, in contrast with other described cases which presented a gap of up to 8 years[4]. Consequently, it is remarkable that our patient suffered KFD thirty years later which also was associated with AOSD symptoms.

This overlapping is to be expected given that both diseases have an idiopathic inflammatory origin. The most accepted theory is that both KFD and AOSD are the result of an abnormal immune response to several infections, especially viral ones (Epstein- Barr Virus, herpesvirus 6, parvovirus B19, cytomegalovirus). The prevalence of KFD seen in young Asian women is related to haplotypes of the HLA (human leukocyte antigens) system, however more cases have been diagnosed in other races and geographic regions[1,3].

The key sign for KFD is adenopathy, cervical lymph nodes are the most affected (92%) followed by axillary nodes (50%), even though half of the patients can present polyadenopathies. Along with mild fever (62%), sweating and asthenia and weigh loss in almost the totality of the patients. A non-specific and brief exanthema can appear (21%) as well as hepatosplenomegaly in very few cases (10%).

In the analysis, acute phase reactants and hepatic enzymes slightly increase in half of the patients and in some cases lymphopenia and thrombopenia can appear. Given that there are no pathognomonic clinical or analytical findings, the diagnosis should be based in an affected lymph node biopsy[3].

A 18F-FDG PET/CT could be useful for a differential diagnosis with a lymphoproliferative syndrome[5].

The KFD is a self-limited disease in 61,5% of the cases. If the symptoms are severe the treatment of choice is corticosteroids, in high doses initially (0,5 mg/kg) with progressive reduction according to the patient's response. There were cases that demanded the prescription of hydroxychloroquine or methotrexate in order to lower the steroids dose[3,4].

Unlike KFD, AOSD is more frequent, with an incidence of 0,16 for every 100.000 people and an average age of 25. It presents a bimodal distribution with one peak of incidence between 15-25 and another one between 36-46 years old. Amongst many published case series there is no proof of it being a female predominant disease[6].

The clinical and analytical manifestations of AOSD clearly differ from KFD[6,7,8]. The onset is acute with fever spikes of 39ºC, in 21% of the cases the temperature remains slightly elevated. The most common skin manifestation is an evanescent salmon-pink maculopapular rash that appears with the fever spikes. Its incidence ranges from 51-87% of the cases and sometimes can be misconceived as an allergic reaction. The joint involvement is present in 94% of the patients. Its described as polyarticular, migratory and symmetric, affecting knees, ankles and small articulations. Myalgia is also frequent (56-84%). In approximately half of the patients soft

Table I: Yamaguchi et al. criteria. Diagnosis is made when there are 5 or more criteria which include at least 2 major criteria.

MAJOR CRITERIA	MINOR CRITERIA
Arthralgia lasting 2 weeks or longer	Sore throat
Fever of 39ºC or higher lasting 1 week or longer	Lymphadenoapthy and/or splenomegaly
Typical rash	Liver dysfunction
Leukocytosis >10.000 including 80% or more of granulocytes test	Negative Rheumatoid Factor (RF) and negative Antinuclear antibody (ANA)

and mobile adenomegalies can be found, located in the cervical, submaxillary, supraclavicular and inguinal areas. Hepatosplenomegaly with slight liver biochemical alteration is less frequent. Pulmonary infiltrates and minor pleural effusion can occasionally appear. Exceptionally perimyocarditis can appear too.

The analytical study in 80-90% of the patients with AOSD presents an anemia of inflammation that can be intense in patients with severe disease. Thrombocytosis is usual and precedes and goes with inflammatory flares. Leukocytosis with neutrophilia is very common. Ferritin levels above 1000ng/L are considered to be a very characteristic feature of this disease with a sensibility of 80% and a specificity of 41%[9]. We have to underline the negativity of antinuclear and anti-citrullinated peptide antibodies. The result of the lymph node biopsy is unspecific as well as the imaging studies. The exclusion of differential diagnoses is essential in this rheumatic process, especially regarding infectious diseases. To make diagnosis easier several criteria have been published, amongst them the Yamaguchi et al. criteria[6] (**Table I**) which are considered to be the ones with a higher degree of sensibility (95,5%). The latter increases even more when ferritin levels are very high[9].

The AOSD treatment is based on the use of non-steroidal anti-inflammatory drugs (NSAIDs), although corticosteroids are necessary in 12% of the cases. In order to reduce the steroids dose, hydroxychloroquine, methotrexate, azathioprine and lastly anti-TNF agents have been used, even though there are no controlled trials of it[9].

In our patient, recurrent KFD diagnosis is unquestionable given the characteristic findings from the lymph node biopsies carried out during each episode.

The AOSD comorbidity is obvious given that it meets the Yamaguchi criteria, as well as the remarkable elevation of acute phase reactants and the strikingly high ferritin level.

Ethical approval

Patient's consent has been obtained before writing this manuscript.

Declaration of interest

The authors have no conflicts of interest to declare

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