

ACADEMIC JOURNAL OF HEALTH SCIENCES

MEDICINA BALEAR

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- First-ever stroke patients in Suriname show more communication disorders than swallowing disorders and these depend on age and length of stay in hospital
- Inositol in Dermatologic Diseases
- Evaluate specificity and sensitivity of cone beam computed tomography for midfacial fractures:
A systematic review and meta-analysis
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- Pregnancy obesity, weight gain during pregnancy, and its association with birth outcomes
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- Analysis of the efficacy of the main dietary patterns in reducing cardiovascular risk
- Prevalence of Carpal Tunnel Syndrome(P-CTS) in Iran: An Updated Systematic Review
- Budd-Chiari Syndrome: An Unexpected Diagnosis in a Clinical Practice in Somalia

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Currently **Academic Journal of Health Sciences Medicina Balear** publishes in English, Spanish or Catalan original papers, review articles, letters to the editor and other writings of interest related to health sciences. The journal submits the originals to the anonymous review of at least two external experts (peer review).



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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. María 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 ROTACIÓ 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 Toulouse*, 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 Noemi 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 Piñero 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?”.
Autores: Paula Greciano Calero, Alicia Serra Sastre, Marta López García y Artur Sharluyan.
- 5.** “Una picadura inusual”.
Autor: Juan Martínez Andrés.

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Cáncer y trabajo. Una visión holística preventiva de una enfermedad compleja

Cancer and work. A holistic preventive view of a complex disease

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Resumen

Introducción: El cáncer y su prevención son en el momento actual una prioridad en Salud Pública en todos los países. En cáncer ocupacional, la Organización Mundial de la Salud estima que cada año al menos 200.000 personas en todo el mundo mueren de cáncer relacionado con su lugar de trabajo. Se considera al cáncer una enfermedad multifactorial que puede no deberse a una única causa sino a una secuencia de exposiciones a lo largo de la vida.

Metodología: Se realizó una búsqueda en julio de 2022 en las bases de datos de PubMed/Medline, utilizando como palabras clave y términos MeSH: *health promotion and cancer, Workplace and cancer, Environment and cancer, exposome and Cancer*.

Se seleccionaron 43 artículos originales, revisiones sistemáticas y artículos de revisión relacionados con cáncer y exposición laboral y medioambiental. Se excluyeron estudios con información no relevante, comentando los autores 11 de estos artículos con información relevante desde un punto de vista laboral.

Resultados: La etiología del cáncer requiere de estudios que incluyan las alteraciones genéticas, las exposiciones laborales y medioambientales así como la valoración de aspectos socioeconómicos en las personas afectadas para proporcionar una base de evidencia enfocada a la prevención. Algunas exposiciones medioambientales asociadas a las laborales incrementan el riesgo de cáncer: la contaminación del aire exterior e interior, los pesticidas, algunos disruptores endocrinos, metales y metaloides cancerígenos y las radiaciones entre otros.

Conclusiones: Los factores relacionados con el estilo de vida, el aumento del cribado y el envejecimiento no pueden explicar totalmente la actual incidencia global creciente del cáncer. La valoración conjunta de exposiciones medioambientales, laborales y sociales facilita la visión preventiva dentro del concepto de exposoma ocupacional, aunque requiere de costosos procedimientos no al alcance de todos.

Palabras clave: Cáncer laboral, exposoma ocupacional, salud laboral, riesgo laboral, riesgo medioambiental.

Abstract

Introduction: Cancer and its prevention is currently a public health priority in all countries. In occupational cancer, the World Health Organisation estimates that each year at least 200,000 people worldwide die of cancer related to their workplace.

Cancer is considered a multifactorial disease that may not be due to a single cause but to a sequence of exposures over a lifetime.

Methodology: A search was conducted in July 2022 in PubMed/Medline databases, using as keywords and MeSH terms: *health promotion and cancer, Workplace and cancer, Environment and cancer, exposome and Cancer*.

Forty-three original articles, systematic reviews and review articles related to cancer and occupational and environmental exposure were selected. Studies with non-relevant information were excluded, with the authors commenting on 11 of these articles with relevant information from an occupational point of view.

Results: The etiology of cancer requires studies that include genetic alterations, occupational and environmental exposures as well as the assessment of socio-economic aspects in affected individuals to provide an evidence base for prevention.

Some environmental exposures associated with occupational exposures increase the risk of cancer: indoor and outdoor air pollution, pesticides, some endocrine disruptors, carcinogenic metals and metalloids, and radiation among others.

Conclusions: Lifestyle factors, increased screening and ageing cannot fully explain the current increasing global incidence of cancer. The joint assessment of environmental, occupational and occupational exposures facilitates the preventive view within the concept of occupational exposome, although it requires costly procedures not available to all.

Keywords: Occupational cancer, occupational exposome, occupational health, occupational risk, environmental risk.

Introducción

El cáncer como enfermedad y su prevención ha sido y sigue siendo en el momento actual una prioridad en Salud Pública en todos los países. De forma general, los tumores pueden clasificarse en dos grupos: aquellos en los que las mutaciones impulsadas son causadas por factores ambientales y tumores en los que hay una gran proporción de mutaciones de genes impulsores relacionados con eventos genéticos aleatorios.

La estrategia de prevención en estos dos tipos de tumores debe ser diferente: en los relacionados en gran medida con factores ambientales, como el cáncer de pulmón, el melanoma de piel y el cáncer de cuello de útero, la prevención primaria es la mejor estrategia para reducir drásticamente la incidencia del cáncer mediante actuaciones tendentes a evitar los factores causales. En los tumores que presentan una proporción significativa de mutaciones, como los de próstata, mama, colon y páncreas, de los que sólo una parte de los casos puede relacionarse con los riesgos ambientales, la estrategia óptima consiste en la prevención secundaria, dirigida a la detección e intervención en un momento temprano durante la evolución de la enfermedad.

La Agencia Internacional de Investigación sobre el Cáncer (IARC, Lyon, Francia) estima que la incidencia anual de nuevos casos de cáncer aumentará de 18,1 millones en 2018 a 29,4 millones en 2040. El coste para los sistemas sanitarios nacionales de esta carga mundial de cáncer en continuo crecimiento es muy elevado, incluso para la mayoría de los países económicamente desarrollados.

Es evidente que la prioridad para hacer frente a este problema, incluso en términos económicos, consiste en desarrollar sistemas más eficaces y aceptados de prevención primaria y secundaria del cáncer a nivel de la población mundial. Este desarrollo necesitará una verdadera cooperación entre las autoridades científicas y políticas para converger en un propósito común en la salud mundial¹.

Si nos referimos al cáncer ocupacional, la situación es todavía más compleja. La Organización Mundial de la Salud estima que cada año al menos 200.000 personas en todo el mundo mueren de cáncer relacionado con su lugar de trabajo². En 2017, la Asamblea Mundial de la Salud aprobó la resolución WHA70.12 sobre la prevención y el control del cáncer en el contexto de un enfoque integrado, en la que se insta a los Estados Miembros y a la OMS a acelerar la aplicación de medidas encaminadas a alcanzar las metas detalladas en el Plan de Acción Mundial para la Prevención y el Control de las Enfermedades No Transmisibles 2013-2030 y la Agenda 2030 de las Naciones Unidas para el Desarrollo Sostenible a fin de reducir la mortalidad prematura por cáncer³.

Un gran número de exposiciones ocupacionales continúa afectando a la carga del cáncer en países de altos ingresos. La información sobre los tipos de exposiciones, los trabajos afectados, las industrias y los tipos de cáncer más frecuentes son clave para priorizar las políticas y las iniciativas de prevención⁴. A esto se ha de añadir la evaluación de todas las fuentes de exposición y de las contribuciones relativas de los elementos ocupacionales y no ocupacionales.

Se considera que el cáncer es una enfermedad multifactorial y de múltiples etapas que puede no deberse a una única causa suficiente, sino a una secuencia de exposiciones a lo largo de la vida. Por ejemplo, la exposición ocupacional a polvo de sílice, por sí sola puede no ser suficiente para causar cáncer de pulmón y es probable que quienes lo padecen hayan estado expuestos a varios carcinógenos pulmonares y posean otras características, como alguna forma de susceptibilidad hereditaria u otras exposiciones de riesgo. La implicación matemática de esto es que la suma de fracciones atribuibles para varias exposiciones puede ser >100%, y la cantidad que excede el 100% se debe en parte a las interacciones sinérgicas entre los factores de riesgo⁵.

Metodología

Se realiza una búsqueda en julio de 2022 en las bases de datos de PubMed/Medline, de artículos científicos publicados en línea desde enero de 2010 hasta febrero de 2022, utilizando como palabras clave y términos MeSH: *health promotion and cancer*, *Workplace and cancer*; *Environment and cancer*; *exposome and Cancer*.

Se seleccionaron 43 artículos originales, revisiones sistemáticas y artículos de revisión relacionados con cáncer y exposición laboral y medioambiental. Se excluyeron estudios con información no relevante, comentando 11 de estos artículos con información referente a este tema desde un punto de vista laboral y destacados por los autores para un comentario más amplio. Se incluyeron referencias con más de 5 años de antigüedad para describir la evolución que ha tenido este tema a lo largo del tiempo.

Comentarios de los artículos destacados por los autores

La compleja etiología del cáncer hace necesario recurrir a formas cada vez más complejas de análisis para proporcionar una base de evidencia enfocada a la prevención, siendo particularmente importantes para la epidemiología las referidas a evaluar la exposición; este requisito se ha destacado a través del concepto del exposoma. Además, la capacidad de observar alteraciones genéticas y epigenéticas en individuos expuestos a factores de riesgo brinda la

oportunidad de dilucidar los mecanismos subyacentes de la carcinogénesis, lo que a su vez puede permitir una detección más temprana y una clasificación molecular más precisa de la enfermedad. Este enfoque interdisciplinario es vital si se quieren aprovechar todos los beneficios de los avances en las ciencias de laboratorio y las inversiones en estudios de cohortes prospectivos a gran escala en relación con la prevención del cáncer⁶.

Se parte de la base de que, el medio ambiente contiene numerosas sustancias potencialmente tóxicas, algunas de las cuales han demostrado ser cancerígenas. Pueden llegar al organismo humano principalmente por vía respiratoria o digestiva. Aunque no siempre es fácil demostrar una relación causal en los estudios observacionales, cuya interpretación está limitada por numerosos factores de confusión, algunos compuestos del medio ambiente están claramente asociados a un mayor riesgo de cánceres, especialmente la contaminación del aire exterior e interior, los pesticidas, algunos disruptores endocrinos y las radiaciones. La identificación de los factores ambientales asociados a un mayor riesgo de cáncer permite aplicar estrategias de erradicación y, por tanto, de prevención eficaz⁷. **(Tabla I)**.

La bibliografía más reciente afirma que los factores relacionados con el estilo de vida, el aumento del cribado y el envejecimiento no pueden explicar totalmente la actual incidencia global creciente del cáncer. Además de los factores relacionados con el estilo de vida, los factores ambientales exógenos pueden desempeñar un papel más importante en la carcinogénesis de lo esperable y, por tanto, pueden explicar la creciente incidencia. Algunos de los factores ambientales calificados como potencialmente cancerígenos por la Agencia Internacional para la Investigación del Cáncer (IARC) son: los microorganismos (incluidos los virus), las radiaciones (incluida la radiactividad, los rayos UV y los campos electromagnéticos pulsados) y los xenotóxicos.

Las sustancias químicas relacionadas con la contaminación ambiental parecen tener una importancia fundamental, ya que pueden inducir cánceres profesionales y de otro tipo. Los principales motivos de preocupación son: la contaminación del aire exterior por partículas de carbono asociadas a hidrocarburos aromáticos policíclicos; la contaminación del aire interior por el humo de tabaco ambiental, el formaldehído y los compuestos orgánicos volátiles como el benceno

y el 1,3 butadieno, que pueden afectar especialmente a los niños; y la contaminación alimentaria por aditivos alimentarios y por contaminantes cancerígenos como los nitratos, los plaguicidas, las dioxinas y otros organoclorados.

Además, pueden estar implicados los metales y metaloides cancerígenos, los medicamentos, fármacos y los cosméticos. Aunque todavía se desconoce la fracción de riesgo atribuible a los factores ambientales, esta larga lista de factores carcinógenos y, sobre todo, mutagénicos, apoya la hipótesis de trabajo según la cual numerosos cánceres pueden estar causados, de hecho, por la reciente modificación de nuestro entorno⁸.

En los países occidentales, la expansión y el envejecimiento de la población, así como los avances en la detección del cáncer mediante nuevas pruebas de diagnóstico y cribado, no pueden explicar por sí solos la creciente incidencia de cáncer observada. Se considera que los factores ambientales desempeñan un papel más importante en la génesis del cáncer de lo que se suele considerar. Ejemplo de ello es el consumo de alcohol, el tabaquismo y la obesidad cuyo aumento es llamativo en muchos países y que se relaciona con un gran número de cánceres. Pero la creciente incidencia también afecta a aquellos cánceres no relacionados directamente con la obesidad ni con otros factores conocidos de estilo de vida. Por ello, cobra un interés creciente el medio ambiente, que ha cambiado durante las últimas décadas y que precede al reciente aumento de la incidencia del cáncer. Este cambio, que aún continúa, incluye la acumulación de nuevos factores cancerígenos medioambientales.

La susceptibilidad genética al cáncer, debida al polimorfismo genético, no puede haber cambiado a lo largo de una generación y, de hecho, favorece el papel de los factores exógenos a través de las interacciones gen-ambiente. La edad no es el único factor a tener en cuenta, ya que el aumento de la incidencia de los cánceres se observa en todas las categorías de edad, incluidos los niños y los adolescentes. De hecho, el feto es específicamente vulnerable a los factores exógenos, siendo esta exposición fetal una ventana temporal crítica. Se asume, por ello, que la exposición involuntaria a muchos carcinógenos en el medio ambiente, puede ser la causa de la reciente y creciente incidencia del cáncer⁹.

Tabla I: Asociación entre la exposición a carcinógenos y cáncer en los países desarrollados.

Exposición	Localización del cáncer
Asbesto: naufragios, minería, manufacturas, material geológico.	Pulmón, gastrointestinal, cavidad oral, tráquea, bronquios, mesotelioma
Arsénico: Agua de bebida, dieta, minería del carbón y minerales	Pulmón, hígado, renal, pelvis y uréter, riñón y vejiga
Polución en interiores: biomasa, carbón	Oral, pulmón, hipofaringe, laringe
Polución medio-ambiental: PM _{2.5} y SO ₂	Pulmón

Modificado de: Hashim D, Boffetta P. Occupational and environmental exposures and cancers in developing countries. *Ann Glob Health*. 2014 Sep-Oct;80(5):393-411.

Probablemente, entre los cánceres ocupacionales sea el de pulmón el más prevalente y, de forma concreta el mesotelioma. Los estudios realizados atribuyen un papel destacado a las exposiciones medioambientales y domésticas, además de las laborales, siendo los resultados más consistentes para el mesotelioma que para el cáncer de pulmón. En Europa, hasta un 10,7% de cáncer de pulmón podría ser atribuible a la contaminación atmosférica urbana, encontrándose una asociación entre el tabaquismo pasivo y el cáncer de pulmón del 1,6% en estos cánceres. El radón es otro carcinógeno presente en el aire interior, que puede ser responsable del 4,5% de los cánceres de pulmón. En cánceres como el de vejiga los subproductos de la cloración del agua podrían tener un peso importante. Las pruebas disponibles sobre el riesgo de cáncer tras la exposición a otros contaminantes ambientales, incluidos los pesticidas, las dioxinas y los campos electromagnéticos, no son concluyentes¹⁰.

En algunos estudios se aportan datos para evidenciar con medios biológicos el efecto de la exposición a contaminantes del aire interior y el riesgo de cáncer de pulmón analizando 14 contaminantes atmosféricos comunes en el líquido pleural de 39 casos de adenocarcinoma de pulmón y 40 controles no malignos mediante cromatografía de gases-espectrometría de masa, excluyendo a los fumadores y ajustando los resultados por edad. Los resultados muestran en el líquido pleural que los biomarcadores de exposición más importantes para el cáncer de pulmón son naftaleno, etilbenceno y o-xileno, destacando el papel de las exposiciones en ambientes interiores en el riesgo de adenocarcinoma de pulmón¹¹.

Los efectos de exposiciones medioambientales son considerados en su relevancia en la aparición del cáncer y es objeto de estudio el papel de la exposición a dosis bajas de contaminantes ambientales en la progresión del cáncer, pero además, existe evidencia que sugiere que los contaminantes ambientales como el bisfenol A (BPA), el benzo[a]pireno (BaP), los contaminantes orgánicos persistentes (COP), el cloruro de aluminio (AlCl₃) y las partículas suspendidas en el aire pueden reducir la eficacia de algunos fármacos quimioterapéuticos comunes utilizados en diferentes tipos de cáncer y se discute actualmente cuales son los posibles mecanismos moleculares subyacentes que conducen a la quimiorresistencia¹².

En cáncer, la epidemiología descriptiva identifica asociaciones entre exposiciones ambientales y los efectos sobre la salud, aunque por su complejidad se requieren estudios metodológicamente más sólidos para poder considerar la causalidad. El estudio Sentieri ejemplifica las limitaciones de los estudios descriptivos de epidemiología ambiental, en los que la mayoría de las hipótesis tienen un apoyo previo limitado y donde muchos de los resultados no muestran asociaciones, o no se dispone de datos sobre posibles factores de confusión y otras fuentes de sesgo y, por ello, no es posible llegar a establecer relaciones claras de causalidad e identificar situaciones críticas que requerirían investigaciones más complejas¹³. En la tabla se muestra la evaluación de la solidez de la evidencia sobre la exposición a la contaminación ambiental y sus efectos en la salud en el estudio Sentieri (**Tabla II**).

Tabla II: Evaluación de la solidez de la evidencia sobre la exposición a la contaminación ambiental y sus efectos en la salud. Estudio Sentieri.

Health effect	Exposure circumstance								
	Ch	PR	IS	PP	Mi	As	Ha	WL	In
Gastric cancer	L								L
Colorectal cancer	L								
Liver cancer									L
Lung cancer		L		L		L			L
Pleural cancer					S	S	L		
Soft tissue sarcoma									L
Ovarian cancer						L			
Lymphohematopoietic neopl.									L
Non Hodgkin lymphoma									L
Respiratory diseases	L	L	L	L			L		
Acute respiratory diseases		L	L	L					
Chronic respiratory diseases			L						
Asthma	L	L	L	L			L		
Congenital malformations		L						L	
Perinatal conditions	L	L						L	
Respiratory diseases (children)		L	L						
Asthma (children)	L	L	L	L					

L (light shading): limited evidence; S (dark shading): sufficient evidence
 Ch, chemical industry; PR, petrochemical plant and refinery; IS, iron and steel plant; PP, power plant; Mi, mining; As, asbestos industry; Ha, harbor; WL, waste landfill; In, incinerator

En cáncer ocupacional, probablemente uno de los estudios de referencia sea el realizado en poblaciones nórdicas de Dinamarca, Finlandia, Islandia, Noruega y Suecia recopilando hasta 45 años de datos de incidencia de cáncer por categoría profesional y abarcando 15 millones de personas de entre 30 y 64 años de los censos de 1960, 1970, 1980/1981 y/o 1990. Incluyó también a los 2,8 millones de casos de cáncer incidentes diagnosticados en estas personas en seguimiento hasta aproximadamente 2005¹⁴.

Este estudio, por su elevada cobertura, precisión y validez es considerado muy confiable y minimiza el papel de la variación del azar, incluso en el caso de formas de cáncer relativamente raras. Aun sabiendo que la ocupación en un momento dado puede no siempre corresponder a la historia ocupacional de toda la vida de una persona, facilita minimizar el riesgo de clasificación errónea.

En sus resultados se pudieron confirmar riesgos laborales bien conocidos como una alta incidencia de cáncer de labios en agricultores y pescadores, un alto riesgo de adenocarcinoma nasal entre los trabajadores de la madera, mesotelioma entre los trabajadores expuestos al asbesto y cáncer de pulmón entre los trabajadores expuestos al asbesto y al polvo de sílice.

Se observa que los trabajadores sedentarios tienden a tener un mayor riesgo de cáncer de mama, mientras que la asociación con el cáncer de colon no fue tan evidente. El melanoma de piel fue más común entre los trabajadores de interiores que no están acostumbrados a la radiación solar y, por lo tanto, se queman fácilmente debido a los intensos baños de sol durante las vacaciones.

En algunos casos, las asociaciones observadas deben confirmarse en otros estudios para descartar asociaciones causales. Por ejemplo, en el cáncer de ovario, especialmente los tumores borderline, había un grupo de ocupaciones expuestas a productos químicos con un alto riesgo. Incluso en una enfermedad tan rara como el cáncer de mama masculino hubo suficientes casos que indicaban un aumento del riesgo en las ocupaciones caracterizadas por el trabajo por turnos. La rara categoría ocupacional de deshollinadores, que están expuestos a carcinógenos conocidos, mostró un exceso significativo de riesgo de cáncer de faringe, esófago, pulmón, colon, páncreas y vejiga.

Los factores sociales relacionados con la ocupación parecen ser determinantes importantes en algunos riesgos de cáncer, incluso más que las exposiciones ocupacionales. Se detecta un alto riesgo de cánceres relacionados con el alcohol entre los trabajadores con fácil acceso a bebidas alcohólicas en su trabajo. Las ocupaciones también pueden crear un entorno protector contra el cáncer. Así, el efecto ejemplarizante de un

maestro de escuela primaria, un dentista o un sacerdote en consumo de tabaco en el trabajo (o en cualquier otro lugar), se refleja en una baja incidencia de cánceres relacionados con el tabaquismo.

El cáncer es socialmente discriminatorio, más para los hombres que para las mujeres. Se encontró que los cánceres altamente discriminatorios eran aquellos etiológicamente relacionados con la exposición al asbesto, la luz solar y el tabaco y/o el alcohol. Las categorías ocupacionales de alto riesgo para un cáncer pueden ser de bajo riesgo para otro y este estudio realizado en países nórdicos mostró una variación de 1,9 veces en el riesgo general de cáncer para los hombres y en una variación de 1,5 veces para las mujeres.

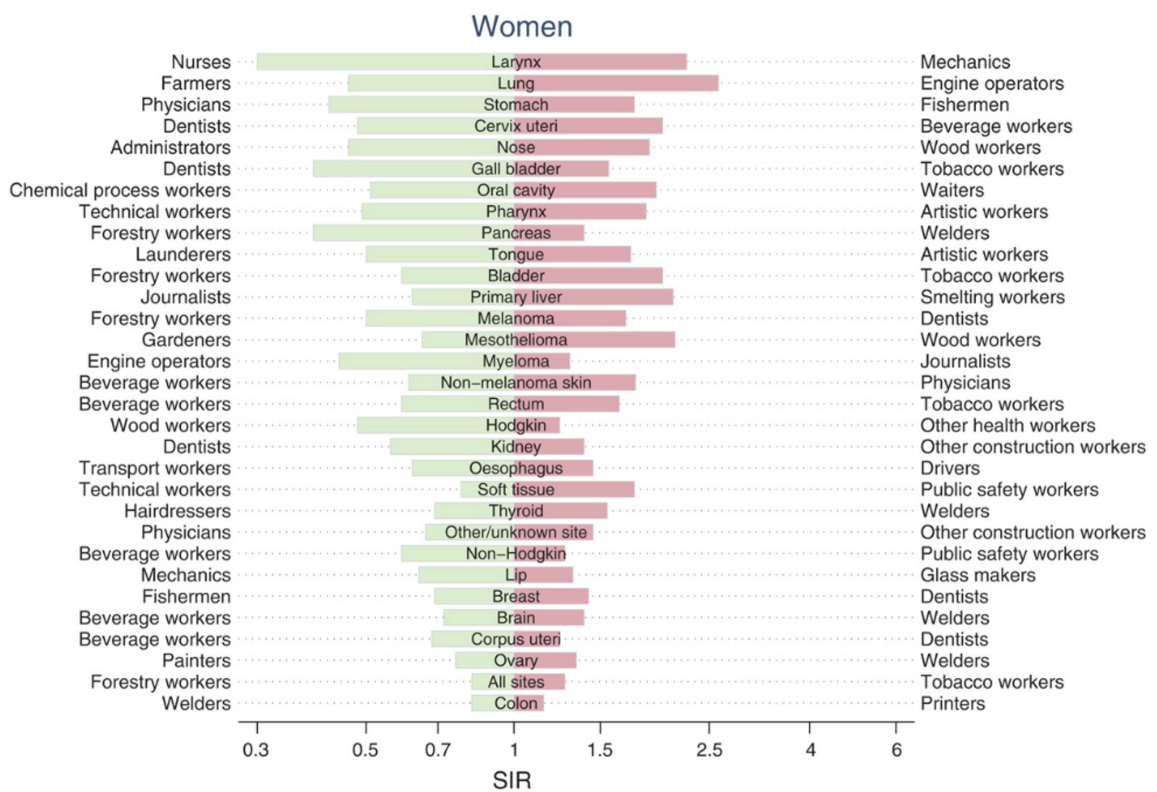
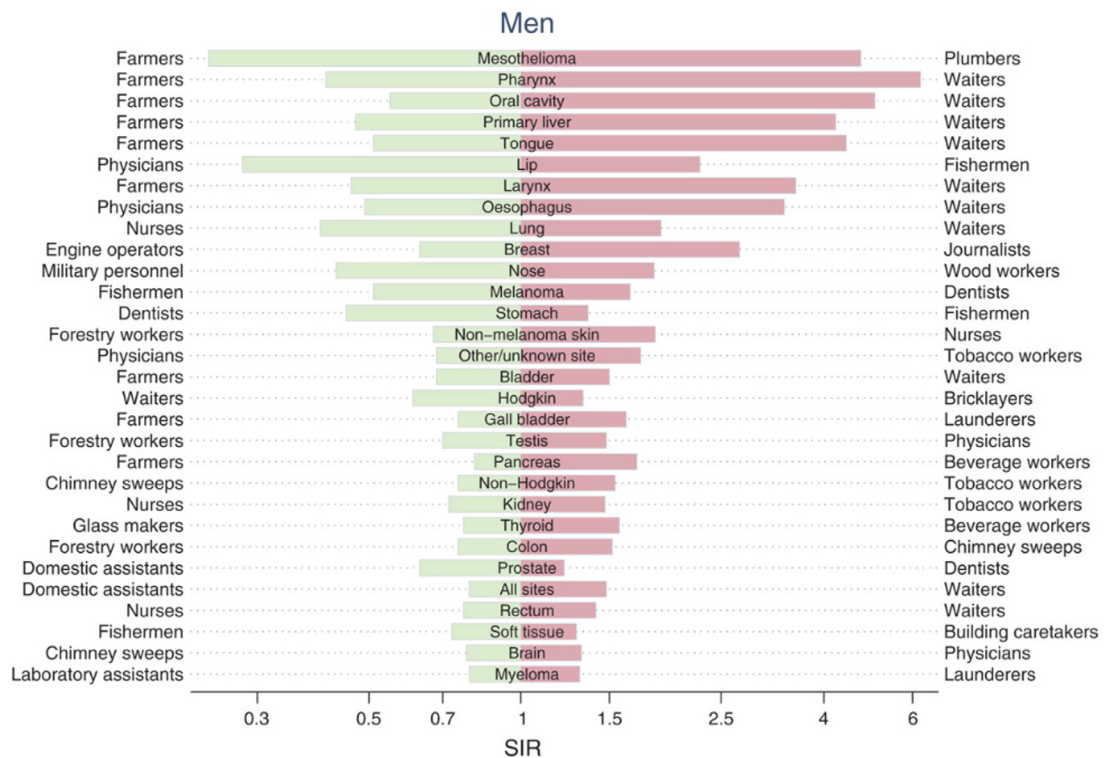
Se estimó que alrededor del 5 % de todos los cánceres, tanto en hombres como en mujeres, estaría relacionado con el trabajo, y alrededor del 35 % de la incidencia de cáncer en hombres y el 16 % en mujeres sería atribuible a la posición socioeconómica. Los resultados globales se muestran en la imagen (**Gráfico 1 y 2**).

Estudio de referencia es también el realizado en 2005 en Gran Bretaña estimando la carga del cáncer profesional midiendo la fracción atribuible (FA), es decir, la proporción de casos que no se habrían producido en ausencia de exposición ocupacional. Se obtuvieron datos sobre el riesgo de enfermedad debido a la exposición, teniendo en cuenta los factores de confusión y las exposiciones superpuestas, y la proporción de la población objetivo expuesta durante el periodo en el que se produjo la exposición pertinente. La estimación se realizó para las exposiciones profesionales clasificadas por la Agencia Internacional para la Investigación del Cáncer (IARC) como carcinógenos del grupo 1 (establecidos) y 2A (probables). Este trabajo fue financiado por el Health and Safety Executive (HSE).

El 5,3% de las muertes por cáncer fueron atribuibles a la ocupación (hombres: 8,2%; mujeres 2,3%). Las estimaciones atribuibles para el total de registros de cáncer son 13.694 (4,0%); y para los hombres: 10.074 (5,7%) y las mujeres 3620 (2,1%).

Las fracciones atribuibles ocupacionales son superiores al 2% para los cánceres de mesotelioma, sinusal, pulmón, nasofaringe, mama, cáncer de piel no melanoma, vejiga, esófago, sarcoma de tejidos blandos y estómago. El amianto, el trabajo por turnos, los aceites minerales, la radiación solar, el sílice, los gases de escape de los motores diésel, los alquitranes y las breas del carbón, la profesión de pintor o soldador, las dioxinas, el humo de tabaco en el ambiente, el radón, el tetracloroetileno, el arsénico y las nieblas inorgánicas fuertes aportan cada uno más de 100 registros. Las industrias/ocupaciones con elevados registros de cáncer incluyen la construcción, la metalurgia, los

Gráfico 1 y 2: Risk of cancer in occupations with the highest and lowest standardised incidence ratios (SIR), by gender. Only occupations with $\geq 1\ 000$ workers, ≥ 5 observed cases and ≥ 5 expected cases have been included.
 Ref: Occupation and cancer – follow-up of 15 million people in five Nordic countries. Eero Pukkala, et al. <https://doi.org/10.1080/02841860902913546>



servicios personales/domésticos, la minería, el transporte terrestre, la impresión/edición, el comercio minorista/hoteles/restaurantes, la administración pública/defensa, la agricultura y varios sectores manufactureros. El 56% de los registros de cáncer en los hombres son atribuibles

al trabajo en el sector de la construcción (principalmente mesoteliomas, cánceres de pulmón, de vejiga y de piel no melanoma) y el 54% de los registros de cáncer en las mujeres son atribuibles al trabajo por turnos (cáncer de mama). (Tabla III).

Tabla III: Estimated attributable fractions for agents and occupations classified as IARC group 1 with 'strong' evidence of carcinogenicity in humans.

Cancer Site	Attributable Fraction (%) (95% Confidence Interval)			Attributable Numbers (95% Confidence Interval)					
				Deaths (2005)			Registrations (2004)		
	Male	Female	Total (Based on Deaths)	Male	Female	Total	Male	Female	Total
Bladder	0.8 (0.7,3.0)	0.6 (0.5,2.9)	0.7 (0.6,2.8)	24 (20, 91)	10 (9, 39)	34 (29, 130)	55 (47, 211)	18 (16, 70)	73 (63, 280)
Bone	0	0	0	0	0	0	0	0	0
Brain	0	0	0	0	0	0	0	0	0
Breast		0	0		0	0		0	0
Cervix	0	0	0	0	0	0	0	0	0
Kidney	0	0	0	0	0	0	0	0	0
Larynx	2.3 (0.8,5.1)	1.5 (0.5, 3.4)	2.1 (0.8, 4.8)	14 (5, 31)	2 (1, 5)	16 (6, 37)	40 (15, 89)	6 (2, 12)	46 (17, 102)
Leukaemia ^a	0.1 (0, 2.0)	0.2 (0.1, 3.9)	0.2 (0, 2.6)	3 (0, 40)	2 (0, 36)	5 (1, 75)	5 (1, 70)	4 (0, 55)	8 (1, 124)
Liver	0.2 (0.1,0.3)	0.1 (0, 0.1)	0.1 (0.1, 0.2)	2 (1, 4)	1 (0, 2)	3 (1, 6)	2 (1, 4)	1 (0, 2)	3 (2, 6)
Lung	17.6 (15.5, 19.4)	4.4 (3.5, 5.4)	12.0 (10.2, 13.9)	3347 (2945,3687)	599 (527,660)	3946 (3472,4346)	3853 (3390,4244)	673 (592, 741)	4526 (3982, 4985)
Lympho-haematopoietic	0	0	0	0	0	0	0	0	0
Melanoma (eye)	0	0	0	0	0	0	0	0	0
Mesothelioma	97.0 (96.0, 98.0) ^b	82.5 (75.0, 90.0) ^b	94.9 (93.0, 96.9) ^b	1699 (1681, 1717)	238 (216, 260)	1937 (1898, 1976)	1699 (1681, 1717) ^c	238 (216, 260) ^c	1937 (1898, 1976) ^c
Multiple Myeloma	0	0	0	0	0	0	0	0	0
Nasopharynx	0	0	0	0	0	0	0	0	0
NHL	0	0	0	0	0	0	0	0	0
NMSC ^d	7.1 (1.3, 15.1)	1.1 (0.0, 2.9)	4.6 (0.8, 10.0)	21 (4, 44)	2 (0, 6)	23 (4, 50)	2576 (481, 5475)	352 (0, 900)	2928 (481, 6375)
Oesophagus	0	0	0	0	0	0	0	0	0
Ovary	0	0	0	0	0	0	0	0	0
Pancreas	0	0	0	0	0	0	0	0	0
Sinonasal	21.1 (11.8, 34.7)	13.6 (8.2, 22.5)	17.7 (10.2, 29.2)	13 (7, 22)	7 (4, 12)	20 (11, 34)	46 (26, 76)	22 (12, 36)	68 (38, 112)
STS	0	0	0	0	0	0	0	0	0
Stomach	0	0	0	0	0	0	0	0	0
Thyroid	0.12	0.02	0.05	0	0	0	1	0	1
Total Based on deaths	6.6 (6.0, 7.2)	1.2 (1.0, 1.4)	4.0 (3.6, 4.4)	5123 (4665, 5635)	862 (758, 1019)	5986 (5415, 6612)			
Total Based on registrations	4.7 (3.2, 6.8)	2.0 (1.3, 2.8)	3.4 (2.3, 4.8)				8277 (5642, 11886)	1313 (839, 2075)	9590 (6482, 13962)
Total cancers in GB in ages 15+				77912	72212	150124	175399	168184	343583

NHL = Non-Hodgkin's lymphoma; NMSC = non-melanoma skin cancer; STS = soft tissue sarcoma a AF applicable to all leukaemias b Includes cases described as due to paraoccupational or environmental exposure to asbestos. c Taken as equal to attributable deaths for this short survival cancer. d Based on registrations. Totals do not always sum across rows due to rounding error Confidence Intervals not estimated for cancers attributed to ionizing radiation, as they are not yet available for the excess relative risk models used (UNSCEAR 2006).

Si se parte de la base de que la esperanza de vida ha ido en aumento en todo el mundo, se puede comprender mejor la transición epidemiológica que ha ido desde los factores de riesgo en las enfermedades transmisibles hacia los factores de riesgo de las enfermedades no transmisibles (ENT). Este cambio implica nuevos enfoques preventivos en los sistemas de salud, hacia programas de manejo de enfermedades no transmisibles e inversión en recursos para la detección y el tratamiento tempranos. Esto es aplicable al cáncer para actuar tanto en prevención primaria como en detección y reducir la carga del cáncer y otras ENT, especialmente

si el progreso se monitorea con mediciones adecuadas y si los resultados se evalúan y retroalimentan para rediseñar adaptativamente los programas, manteniendo los beneficios de salud para las generaciones futuras. El objetivo debe ser la promoción de un marco integrado para intervenciones de control del cáncer, reconociendo que los sistemas, tanto para la prevención como para la detección temprana, son necesarios a nivel mundial. La historia de la salud pública ha demostrado que cuando los programas se desarrollan de forma aislada para problemas complejos, los resultados no son duraderos. El cáncer, como innumerables procesos patológicos,

requiere prevención, diagnóstico temprano, tratamiento y paliación para un control integral centrado en la persona afectada y, por ello requiere de una acción coordinada a nivel individual y poblacional¹⁵.

En cáncer laboral, como ocurre con otras enfermedades, se introduce el concepto de exposoma profesional para comprender la complejidad de las exposiciones en el lugar de trabajo y todos sus determinantes. Esto requiere un enfoque organizativo desde una perspectiva interdisciplinar, que amplíe los niveles de análisis de las exposiciones, cualquiera que sean, desde el riesgo individual a la situación laboral y las exposiciones individuales o colectivas, considerando de forma conjunta el entorno socioeconómico tanto del individuo como de la empresa.

Este enfoque organizativo del exposoma profesional contribuye a ampliar el espectro de la evaluación de riesgos para la salud y a promover un enfoque preventivo global e integrado del impacto en salud de las exposiciones y el desgaste laboral¹⁶. **(Gráfico 3)**

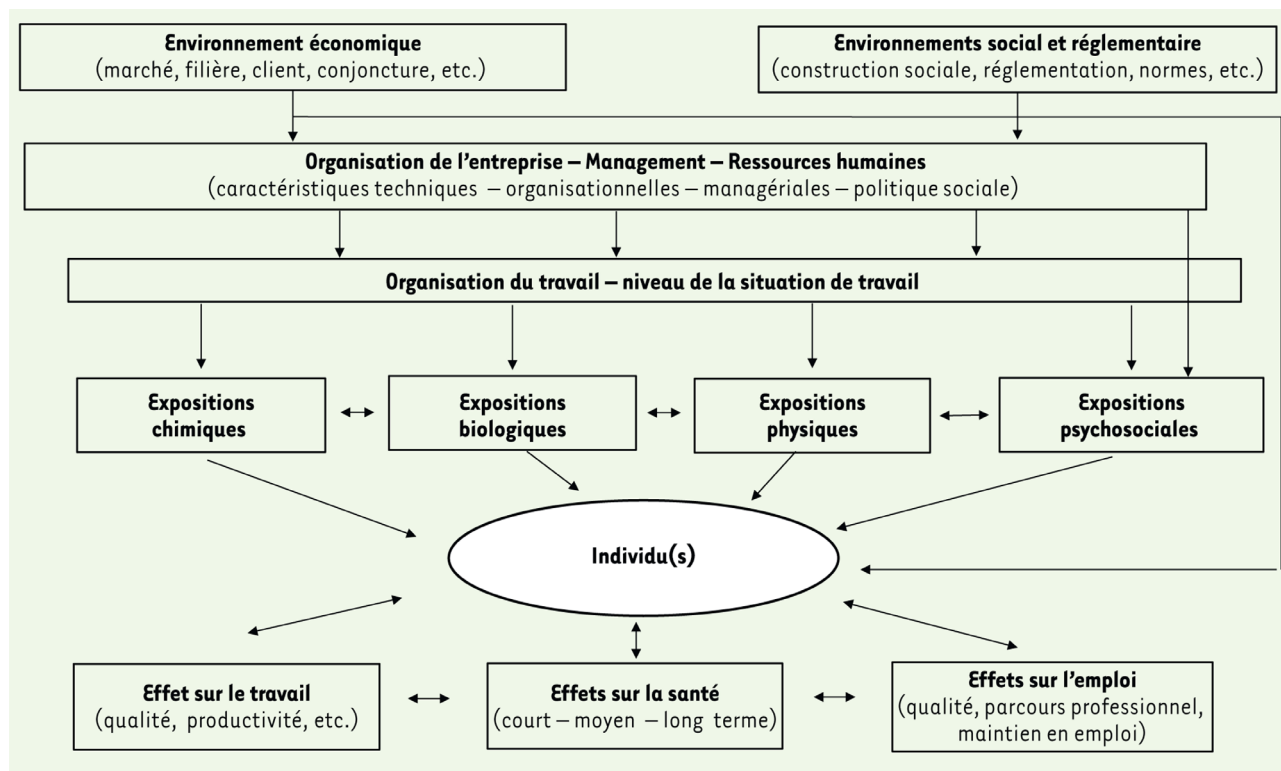
Conclusiones

- La etiología multifactorial del cáncer hace necesario recurrir a formas cada vez más complejas de análisis para proporcionar una base de evidencia enfocada a la prevención.

- Los factores relacionados con el estilo de vida, el aumento del cribado y el envejecimiento no pueden explicar totalmente la actual incidencia global creciente del cáncer.
- Algunos compuestos del medio ambiente están claramente asociados a un mayor riesgo de cánceres, especialmente la contaminación del aire exterior e interior, los pesticidas, algunos disruptores endocrinos, metales y metaloides cancerígenos y las radiaciones.
- Estudios de largo seguimiento, como los realizados en Países Nórdicos, estiman que alrededor del 5% de todos los cánceres, tanto en hombres como en mujeres, estaría relacionado con el trabajo, y alrededor del 35% de la incidencia de cáncer en hombres y el 16% en mujeres sería atribuible a la posición socioeconómica.
- En mortalidad, los trabajos realizados en Gran Bretaña consideraron que el 5,3% de las muertes por cáncer fueron atribuibles a la ocupación (hombres: 8,2%; mujeres 2,3%).
- En cáncer laboral se introduce el concepto de exposoma profesional para comprender la complejidad de las exposiciones en el lugar de trabajo y todos sus determinantes. Esto requiere un enfoque organizativo interdisciplinar, desde el riesgo individual a la situación colectiva, considerando de forma conjunta el entorno socioeconómico del individuo y de la empresa.

Conflicto de intereses: Ninguno.

Gráfico 3



Ref: Tomado de Roquelaure Y, Luce D, Descatha A, Bonvallot N, Porro B, Coutarel F. Un modèle organisationnel de l'exposome professionnel [Occupational exposome: An organisational model]. Med Sci (Paris). 2022;38(3):288-93.

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Relationship of severity of COVID -19 disease with lung-CT-scan imaging

Relación de la gravedad de la enfermedad COVID-19 con la tomografía computarizada de pulmón

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Abstract

Objectives: Lung-CT-scan imaging is known as important diagnostic technique for evaluation of the effectiveness and infectious involvement of the lungs. In this study, we evaluated and analyzed lung CT images in patients with Coronavirus Disease 2019 (COVID-19) and its relationship with some important clinical and laboratory factors as well as the patient's condition in the worst disease conditions.

Methods: In this retrospective descriptive-analytical study, 375 patients with complete information have been considered. Among these patients, CT scans of patients' lungs was carefully reevaluated. Other radiologist reviewed the images and recorded the final score of the patients' lung involvement.

Results: Data showed that lung and cardiac involvement have high prevalence among studies patients. Among demographic variables, there was significant relationship between age and recovery. Evaluating the relationship of recovery with CT variables showed that CT score, bilateral lung involvement, and Crazy paving had significant effect on recovery rate.

Conclusion: According to this study, evaluation of CT variables can be used as potent factors for evaluation of disease status and design of suitable treatment strategy.

Keywords: CT-scan imaging, Lung, COVID-19, Involvement, Recovery.

Resumen

Objetivos: La tomografía computarizada de pulmón es conocida como una técnica de diagnóstico importante para la evaluación de la efectividad y el compromiso infeccioso de los pulmones. En este estudio, evaluamos y analizamos imágenes de TC de pulmón en pacientes con enfermedad por coronavirus 2019 (COVID-19) y su relación con algunos factores clínicos y de laboratorio importantes, así como la condición del paciente en las peores condiciones de la enfermedad.

Métodos: En este estudio descriptivo-analítico retrospectivo se han considerado 375 pacientes con información completa. Entre estos pacientes, se reevaluaron cuidadosamente las tomografías computarizadas de los pulmones de los pacientes. Otro radiólogo revisó las imágenes y registró la puntuación final de la afectación pulmonar de los pacientes.

Resultados: Los datos mostraron que la afectación pulmonar y cardíaca tiene una alta prevalencia entre los pacientes del estudio. Entre las variables demográficas, hubo relación significativa entre la edad y la recuperación. La evaluación de la relación de la recuperación con las variables de la TC mostró que la puntuación de la TC, la afectación pulmonar bilateral y el pavimento loco tuvieron un efecto significativo en la tasa de recuperación.

Conclusión: Según este estudio, la evaluación de las variables de TC se puede utilizar como factores potentes para la evaluación del estado de la enfermedad y el diseño de una estrategia de tratamiento adecuada.

Palabras clave: Tomografía computarizada, pulmón, COVID-19, participación, recuperación.

Introduction

Since December 2019, a new coronavirus, named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was discovered in China¹. This novel virus lead to moderate to severe pulmonary involvement, Coronavirus Disease 2019 (COVID-19). Based on epidemiological studies, the main symptoms of COVID-19 include fever, dry cough and fatigue are. Other related clinical features of this disease include aches and pains, sore throat Diarrhea, conjunctivitis, headache, loss of taste or smell, and diarrhea². Due to the highly contagious nature of COVID-19 and the lack of specific proven therapeutic drugs, early detection of this disease is of particular importance. There are two main diagnosis tools for COVID-19: RT-PCR and CT scan of the lungs³. The incidence of false-negative RT-PCR is high due to insufficient cellular material or incorrect nucleic acid extraction⁴. According to current experience, CT imaging of the lung may show the diagnosis of pulmonary involvement earlier than RT-PCR test. At present, high-resolution CT is listed as one of the main tools for screening, early diagnosis and assessment of disease severity^{5,6}. So, chest CT imaging as a non-invasive imaging technique can be useful and a tool with high accuracy for early detection^{7,8}. Thus, the aim of this study was to evaluate and analyze lung CT images in patients with COVID-19 and its relationship with some important clinical and laboratory factors as well as the patient's condition in the worst disease conditions (death or recovery).

Materials and Methods

In this retrospective descriptive-analytical study, 1000 patients with at least one CT imaging were selected. All

Table I: The frequency of clinical features of disease (fever, cough, Shortness of breath, Plt, WBC, and other related symptoms).

Variable		Frequency	Percent
Fever	No	161	43.0
	Yes	209	55.9
	Total	370	98.9
Cough	No	129	34.5
	Yes	241	64.4
	Total	370	98.9
Shortness of breath	No	158	42.2
	Yes	210	56.1
	Total	368	98.4
Plt	< 50	1	0.3
	51-99	25	6.7
	100-149	100	26.7
	150-450	241	64.4
WBC	<4	57	15.2
	4.1-12	297	79.4
	>12.1	15	4.0
Other related symptoms	No	105	28.1
	Yes	265	70.9
	Total	370	98.9

selected patients has been performed pharyngeal test for PCR and laboratory diagnosis. Among these patients, 375 patients with complete information have been considered as the final statistical population. CT scans of patients' lungs was carefully reevaluated and recorded in designed questionnaires. Two independent researchers, without information about results of CT scan, recorded the clinical and laboratory information of the patients in the questionnaire. Then, the CT scan data was entered into the questionnaires by one of experienced radiologist. Other radiologist reviewed the images and recorded the final score of the patients' lung involvement. Acquired data were analyzed by SPSS-20.

Results

Totally, 375 patients were entered in this study. Based on data, Most of the studied patients were women (54.9%). In terms of age, most patients were over sixty years old (39.5%). The clinical features of disease including fever, cough, Shortness of breath, and other related symptoms were recorded in **table I**. Cough had the highest frequency among evaluated patients (64.4%). Frequency of underlying variables in patients were summarized in **table II**. Based on this table, lung and cardiac involvement have high prevalence among studies patients. Lung CT scan findings were summarized in **table III**. This table showed that highest CT score was 25-50. Bilateral lung involvement, Ground-glass opacification, Crazy paving, linear atelectasis, bronchies, and pleural was seen in 78.5, 84, 53.7, 21.7, 2.1, and 9.1%, respectively. Results showed that 42.8% of patients had involvement of five lobe. The relationship of recovery with

Table II: The frequency of underlying variables in evaluated patients.

Variable		Frequency	Percent
HTN	No	217	58.0
	Yes	115	30.7
DM	No	238	63.6
	Yes	94	25.1
Cardio disease	No	307	82.1
	Yes	25	6.7
Lung disease	No	297	79.4
	Yes	35	9.4
Cancer	No	329	88.0
	Yes	3	.8
Kidney disease	No	317	84.8
	Yes	15	4.0
Infection	No	332	88.8
	Yes	42	11.2
Smoking	No	256	68.4
	Yes	20	5.3
Opium consumption	No	275	73.5
	Yes	2	.5
Hookah consumption	No	250	66.8
	Yes	27	7.2
Alcohol consumption	No	275	73.5
	Yes	2	.5

demographic variables was analyzed (Table IV). There was significant relationship between age and recovery. Other demographic variables had no significant effect on recovery rate. The relationship of recovery with clinical features of disease was also analyzed (Table V). This table showed that there is significant relationship between recovery and shortness of breath, Platelet (Plt), and White blood cells (WBCs). The relationship of recovery with underlying variables was also analyzed (Table VI). Among these underlying variables, cardio and lung diseases had

significant correlation with recovery rate. Evaluating the relationship of recovery with CT variables showed that CT score, bilateral lung involvement, and Crazy paving had significant effect on recovery rate (Table VII).

Table III: The frequency of variables related to lung CT scan findings.

Variable		n	%	
CT score	0	35	9.4	
	< 25	98	26.2	
	25-50	150	40.1	
	50-75	66	17.6	
	>75	25	6.7	
Total involvement	Involvement of a lobe	51	13.6	
	Involvement of two lobe	48	12.8	
	Involvement of three lobe	39	10.4	
	Involvement of four lobe	28	7.5	
	Involvement of five lobe	160	42.8	
Bilateral lung involvement		256	78.5	
	Ground-glass opacification	314	84	
	Crazy paving	119	31.8	
	Linear atelectasis	81	21.7	
	Air bronchogram	92	24.6	
Bronchiectasia		8	2.1	
	Pleural effusion	No	336	89.8
		Right involvement	34	9.1
		Left involvement	1	0.3
		Bilateral involvement	3	0.8
Other involvements		6	1.6	

Table V: The relationship between clinical features of disease and recovery rate.

Variable		Recovery			P value
		complete	moderate	dead	
Fever	No	4	129	13	0.348
	Yes	2	166	23	
Cough	No	1	103	15	0.456
	Yes	5	192	21	
Shortness of breath	No	3	134	6	0.005
	Yes	3	160	29	
Plt	<50	0	0	1	0.014
	51-99	0	21	3	
	100-149	0	76	15	
	150-450	7	193	18	
WBC	<4	0	49	3	0.008
	4.1-12	0	94.2%	5.8%	
	>12.1	6	235	29	
	<4	2.2%	87.0%	10.7%	
	4.1-12	1	8	5	
		7.1%	57.1%	35.7%	

Table IV: The relationship between and recovery rate.

		Recovery			P value
		complete	moderate	dead	
age	18-40	1	88	1	0.0000
		1.1%	97.8%	1.1%	
	41-60	3	105	5	
		2.7%	92.9%	4.4%	
	>=61	3	101	29	
		2.3%	75.9%	21.8%	
Male	Female	6	174	24	0.197
	Male	1	123	11	
		2.9%	85.3%	11.8%	
		.7%	91.1%	8.1%	
Marital status	Married	7	274	33	0.292
	Single	0	17	0	
		2.2%	87.3%	10.5%	
		.0%	100.0%	.0%	

Table VI: The relationship between underlying variables and recovery rate.

Variables			Recovery			P value
			complete	moderate	dead	
HTN	No	Count	4	176	17	0.150
		% within HTN	2.0%	89.3%	8.6%	
	Yes	Count	2	87	17	
		% within HTN	1.9%	82.1%	16.0%	
DM	No	Count	3	196	19	0.067
		% within DM	1.4%	89.9%	8.7%	
	Yes	Count	3	68	14	
		% within DM	3.5%	80.0%	16.5%	
Cardio	No	Count	4	245	29	0.049
		% within Cardio	1.4%	88.1%	10.4%	
	Yes	Count	2	19	4	
		% within Cardio	8.0%	76.0%	16.0%	
Lung	No	Count	6	236	29	0.041
		% within lung	2.2%	87.1%	10.7%	
	Yes	Count	0	28	4	
		% within lung	.0%	87.5%	12.5%	
Cancer	No	Count	6	262	32	0.448
		% within cancer	2.0%	87.3%	10.7%	
	Yes	Count	0	2	1	
		% within cancer	.0%	66.7%	33.3%	
Kidney disease	No	Count	6	253	31	0.767
		% within kolyavi	2.1%	87.2%	10.7%	
	Yes	Count	0	11	2	
		% within kolyavi	.0%	84.6%	15.4%	
Infection	No	Count	6	264	33	1.000
		% within ofoni	2.0%	87.1%	10.9%	
Smoking	No	Count	5	213	20	0.416
		% within smoking	2.1%	89.5%	8.4%	
	Yes	Count	1	16	3	
		% within smoking	5.0%	80.0%	15.0%	
Opium consumption	No	Count	6	227	23	0.880
		% within opiom	2.3%	88.7%	9.0%	
	Yes	Count	0	2	0	
		% within opiom	.0%	100.0%	.0%	
Alcohol consumption	No	Count	6	228	23	0.938
		% within alcohol	2.3%	88.7%	8.9%	
	Yes	Count	0	1	0	
		% within alcohol	.0%	100.0%	.0%	

Table VII: The relationship between CT variables and recovery rate.

Variable		Recovery			P value
		complete	moderate	dead	
CT score	< 25	1	83	4	0.001
	25-50	4	125	11	
	50-75	2	45	12	
	>75	0	17	8	
Total involvement	Involvement of a lobe	0	44	1	0.063
	Involvement of two lobe	1	41	3	
	Involvement of three lobe	0	30	4	
	Involvement of four lobe	0	26	1	
	Involvement of five lobe	5	119	25	
Bilateral lung involvement		6	198	33	0.008
Ground-glass opacification		6	250	34	0.462
Crazy paving		4	87	20	0.004
Linear atelectasis		2	61	11	0.400

Discussion

Coronaviruses are RNA viruses with broad distribution in mammals, especially in humans⁹. A new member of these family, e.g. SARS-Cov2, similar to other related coronaviruses, lead to severe acute respiratory syndrome¹⁰. This new virus was assessed based on clinical records, laboratory tests, and lung CT test. Fever, cough, fatigue, sputum production and diarrhea are known as important clinical signs of SARS-Cov2 infection¹¹. Shortness of breath has been also shown as sign of disease¹². The imaging evaluation showed that patients had chest CT scans abnormalities¹³. The severity of abnormalities can related to disease severity¹⁴. So, it's suggested that chest CT scans can predict the severity of disease and after schedule of disease management. In this study, we evaluated the relationship between CT finding and disease outcome.

We also evaluation of relationship between demographic and clinical finding with disease outcome. Based on our results, among all evaluated demographic data, only age had significant effects on disease outcome. This result is similar to other published articles¹⁵⁻¹⁸. Our study, along with other related articles, showed that increased age can be considered as strong risk factor for COVID-19 severe outcomes. Mortality rates were significantly higher in the age group over sixty years. Among clinical data, Shortness of breath, Plt, and WBC had significant relationship with recovery rate. Blood clot formation has been occurred in some patients with COVID-19. This situation lead to artery dysfunction and enhancement of heart attack risk. All these situation can alter the recovery rate of patients¹⁹. Similar to these data, our data also showed the related variables, especially Plt, cane significantly alter the recovery rate. Our results showed that some finding of CT imaging had significant effect on recovery rate. Based on results, CT score, bilateral lung involvement, and Crazy paving had

significant effect on recovery rate. Pneumonic changes was seen in radiological evidence of most patients. Based on literature review, bilateral lung involvement and Small unilateral peripheral opacification are two main abnormality in radiological evidence of patients²⁰⁻²³. In our study, bilateral lung involvement and Ground-glass opacification had highest prevalence among all radiological symptoms. Similar to other studies, in our study, the most common symptoms is ground-glass opacification. The highest CT score belonged to 25-50 involvement. In involvement more than 75%, that was no complete recovery among patients. The recovery rate decreased with increasing lung involvement. This relationship was statistically significant. Peijie et al indicated that in patient with severe disease, involvement of lung segments and lobes, crazy-paving pattern and air bronchogram increased²⁴. Similar to Peijie et al study, crazy paving had high prevalence in our study. On the other hand, bronchogram had lower incidence in our study. In our study, similar to other related studies, the prevalence of crazy-paving pattern and air bronchogram had more incident in patients with moderate recovery or dead patients²⁵⁻²⁸. This data showed that there severity of these CT variable can predicted the severity of disease as well as recovery rate. Xiong et al acknowledged that COVID-19 infection usually lead to typical glass opacities and other related CT features. These variables had significant correlations with various clinical factors²⁹. So, most studies suggested that follow-up CT images can help the scientists for evaluation of disease outcome, recovery rate as well as treatment procedures. Among all related variables, lung involvement score, ground-glass opacification, crazy paving, and linear atelectasis had significant effects on disease outcome, recovery rate, and treatment procedures in most studies²⁵⁻²⁸. Our data showed that lung involvement score and crazy paving had significant effects on disease outcome and recovery rate. So, our study is consistent with other reported data to some extent. The severity of lung involvement can predict the disease outcome. Although not all CT-related variables had a significant effect on recovery rates, the data showed that for all variables, the incidence of more severe disease increased with increasing frequency of variables. But, pay attention to the lung involvement score and crazy paving is more important to evaluate the outcome of the disease.

Conclusions

According to this study, lung and cardiac involvement have high prevalence among patients with COVID-19. Evaluation of the relationship between recovery and CT variables showed that CT score, bilateral lung involvement, and crazy paving had significant effect on recovery rate. So, evaluation of CT variables can be used as potent factors for evaluation of disease status and design of suitable treatment strategy.

List of abbreviations

COVID-19: Coronavirus disease 2019

CT: Computerized Tomography

WBCs: White blood cells

Plt: Platelet

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences.

Consent to publish

Not applicable

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ORIGINAL

First-ever stroke patients in Suriname show more communication disorders than swallowing disorders and these depend on age and length of stay in hospital

Los primeros pacientes con accidente cerebrovascular en Surinam muestran más trastornos de la comunicación que trastornos de la deglución y estos dependen de la edad y la duración de la estancia en el hospital.

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Abstract

Objective: Research on the occurrence of communication and swallowing disorders in first-ever stroke patients in Suriname is scant. This study aimed to determine the (co-) occurrence of speech-language pathology disorders following a first-ever stroke. Furthermore, it examined the association between age and length of stay with various speech-language pathology disorders.

Methods: Forty-three first-ever stroke patients admitted to the neurological unit of the Academic Hospital in Paramaribo were enrolled in this prospective study. Speech-language pathology screenings were performed within one week after admission. Occurrence rates were calculated as frequencies. Associations between variables of interest were calculated using the Mann-Whitney U test.

Results: Aphasia, dysarthria, apraxia of speech and dysphagia were present in 41.9%, 39.5%, 23.3% and 20.9% respectively. A co-occurrence of 7 to 28%, 20.9% and 2.3% was seen for two, three and four disorders, respectively. Age was significantly associated with apraxia of speech ($p = .04$) and dysphagia ($p = .04$) whereas length of stay was significantly associated with only dysphagia ($p = .02$). Overall, the study showed the highest occurrence of aphasia, followed by dysarthria, AOS, and dysphagia.

Conclusions: Communication disorders are more common than swallowing disorders among first-ever stroke patients in Suriname. To serve these patients, there is an urgent need for standardized testing and rehabilitation.

Keywords: Aphasia, Dysarthria, Apraxia of Speech, Dysphagia, Stroke.

Resumen

Objetivo: La investigación sobre la aparición de trastornos de la comunicación y la deglución en pacientes con primer accidente cerebrovascular en Surinam es insuficiente. Este estudio tuvo como objetivo determinar la coocurrencia de trastornos de la patología del habla y el lenguaje después de un primer accidente cerebrovascular. Además, examinó la asociación entre la edad y la duración de la estancia con diversos trastornos de la patología del habla y el lenguaje.

Métodos: Cuarenta y tres pacientes con ictus ingresados en la unidad neurológica del Hospital Académico de Paramaribo se inscribieron en este estudio prospectivo. Los exámenes de patología del habla y el lenguaje se realizaron dentro de una semana después de la admisión. Las tasas de ocurrencia se calculan como frecuencias. Se calcularon una asociación entre variables de interés mediante la prueba U de Mann-Whitney.

Resultados: Afasia, disartria, apraxia del habla y disfagia estuvieron presentes en 41.9%, 39.5%, 23.3% y 20.9% respectivamente. Se observó una coocurrencia de 7 a 28%, 20.9% y 2.3% para dos, tres y cuatro trastornos, respectivamente. La edad se asoció significativamente con apraxia del habla ($p = 0,04$) y disfagia ($p = 0,04$), mientras que la duración de la estancia se asoció significativamente solo con disfagia ($p = 0,02$). En general, el estudio mostró la mayor incidencia de afasia, seguida de disartria, AOS y disfagia.

Conclusión: Los trastornos de la comunicación C son más comunes que los trastornos de la deglución entre los pacientes con primer accidente cerebrovascular en Surinam. Para atender a estos pacientes, existe una necesidad urgente de pruebas estandarizadas y rehabilitación.

Palabras clave: Afasia, Disartria, Apraxia del habla, Disfagia, Accidente cerebrovascular.

Introduction

Stroke is a sudden and abrupt loss of brain function following an ischemic or hemorrhagic cerebrovascular injury. It can temporarily or permanently affect skills such as communication and swallowing. Depending on the type, location, and severity of the stroke, a variety of speech-language pathology (SLP) disorders such as aphasia, dysarthria, apraxia of speech (AOS) and swallowing disorders like dysphagia, can occur as a prolonged complication of the stroke. Consequently, these disorders can cause an additional burden on health and economy and have an impact on patients' quality of life.

Previous studies found that there is a large variability in the occurrence of these various SLP disorders. In a systematic review of Meng et al the pooled occurrence rate of dysphagia in stroke patients was 36.3%¹. In other studies, this percentage ranged from 8.1% to 80%². For dysarthria and aphasia, the occurrence rate in subacute stroke patients was reported to be 54.9% and 31.7%, respectively³. Similar results of a lower incidence of aphasia compared to dysarthria were reported in acute stroke patients⁴⁻⁶. Moreover, SLP disorders often co-occur in stroke patients and at least a third of the participants concomitantly showed up to two of these disorders. For instance, about 30% of the patients develop both dysarthria and aphasia⁴ and this results in significantly less functional recovery than with the single occurrence of the two disorders⁷.

In addition to the (co)-occurrence of SLP disorders in stroke patients, studies also described the relationship between various factors and the presence or absence of these SLP disorders. For instance, extended hospitalization contributes significantly to a decreased quality of life in patients with dysphagia. Moreover, several studies point out that stroke patients with dysphagia have an extended hospital stay compared to stroke patients without dysphagia⁸⁻¹⁰. A recent review underscored this also for patients with aphasia¹¹. Thus, it can be safely assumed that the severity of aphasia is inversely correlated with the length of stay in hospital. Age is another factor contributing to the severity of SLP disorders. An advanced age is associated with a higher prevalence and increased risk of aphasia¹²⁻¹⁷. Patients presenting with dysphagia were averagely older than the rest^{18,19}.

Unfortunately, in Suriname, few if any scientific writings have been devoted to SLP disorders in stroke patients. In this study, we aim to close the gap by analyzing the (co)-occurrence of SLP disorders in Surinamese post-stroke patients. We also assess whether there is a relationship between age, or, length of hospital stay and the presence or absence of common SLP disorders in stroke patients. In line with current literature, we hypothesize different

types of SLP disorders will co-occur for at least 20%. In addition, there will be a relationship between higher age and increased LOS and the presence of especially dysphagia and aphasia.

Method

Participants

Recruitment of patients took place from April 1, 2019 to August 1, 2019 at the stroke unit of the Academic Hospital Paramaribo. Enrollment in the study was based on the following inclusion criteria: (1) a first-ever stroke as defined by the World Health Organization (WHO); (2) ≥ 18 years.

This study was approved by the Ministry of Health, "Commissie Mensgebonden Wetenschappelijk Onderzoek" (approval number DVG-055) for its feasibility as well as its ethical aspects. All patients or their legal representatives gave informed consent for the study and all procedures were carried out in accordance with the Declaration of Helsinki. Only de-identified data for those consenting to its use for research purposes are presented.

Study procedures

All study procedures were carried out by trained SLPs during the participants' hospitalization, aided by nursing personnel whenever necessary. Demographic information such as age, sex, and date of birth, as well as clinical information were mainly collected from the medical records followed by oral interviews. Furthermore, participants included in the study completed all four screenings (i.e., aphasia, dysarthria, AOS, and dysphagia) within one week after admission to the hospital.

Evaluation of aphasia

Aphasia was evaluated using the Token test. This validated and standardized tool consists of 36 items, which includes 20 tokens with different colors, sizes and shapes. For each item, the examinee must understand and respond to simple verbal commands by pointing out or moving tokens. The maximum score is 36 with a higher score indicating a better performance and a score less than 29 indicating the presence of aphasia²⁰.

Evaluation of dysarthria

Dysarthria was evaluated using the 'Nederlandstalig Dysartrisch Onderzoek voor Volwassenen' (NDO-V), which is a validated and standardized Dutch scale that is used for screening of dysarthria²¹. This scale provides information on various aspects of speech such as spontaneous speech, reading of standardized text, diadochokinetic, slide tones, shouting and speech holding time. Also, the type and severity of dysarthria is determined. At last, a differential diagnosis of dysarthria is made by the SLP based on a two-point scale with yes or no.

Evaluation of AOS

AOS was evaluated using a self-developed perceptual evaluation based on direct and indirect characteristics. This evaluation included seven questions based on characteristics such as (1) initiation problems, (2) distortion of sounds, (3) sequence problems, (4) articulation problems, (5) slowed rate of speech, (6) prosodic impairments, and (7) problems in naming words²². These questions are rated on a two-point scale with yes or no. The presence of at least the necessary signs such as articulation problems, slowed rate of speech and prosodic impairments differentiated between patients with and without AOS.

Evaluation of dysphagia

Dysphagia was evaluated using the Gugging Swallowing Screen (GUSS), which is a quick and safe clinical bedside tool to identify patients with dysphagia²³. It consists of an indirect swallowing test followed by a direct swallowing test. The examinee should earn the maximum score of 5 for the indirect test in order to go further with the direct test. The total score of the GUSS is 20 with a score of ≤ 19 indicating the presence of dysphagia.

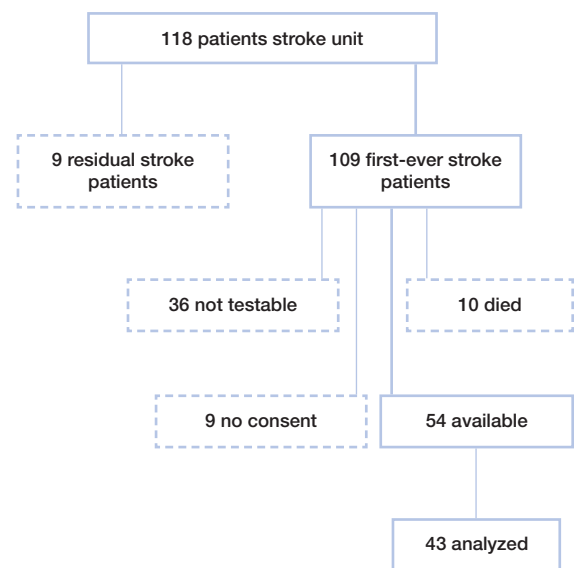
Data analysis

Demographics and clinical characteristics were reported as median (interquartile range) or frequencies based on continuous or categorical variables. Furthermore, the first outcome of interest included estimates for the incidence and co-occurrence of aphasia, dysarthria, AOS and dysphagia and was calculated using frequency estimates and their 95% confidence intervals (CIs). To address the second outcome of interest, the relationship between age, or, LOS and the absence/presence of a specific SLP disorder (aphasia, dysarthria, AOS and dysphagia), Mann-Whitney U tests were conducted. All calculated p values were considered significant if less than .05. All statistical analyses were performed using IBM Statistical Package for Social Science (SPSS) version 25 (SPSS Inc., Chicago, IL, USA).

Results

All 118 patients admitted to the stroke unit of the Academic Hospital Paramaribo between April 1, 2019 and August 1, 2019 were considered for inclusion in the present study (Figure 1). Nine patients were excluded because their symptoms were diagnosed to result from a residual stroke. From the remaining 109 first-ever stroke patients, 36 were excluded because they were not testable, while 10 died within the testing period. Finally, nine patients did not provide consent. As a result, a total of 54 first-ever stroke patients could be tested for their communication and swallowing skills. Of these, 11 patients did not complete the study procedure, and, therefore, were excluded for the analysis. Therefore, 43 patients were included in the final analysis. Patient demographics and

Figure 1: Flow chart of patient selection.



Note: Boxes with dotted lines indicate subjects excluded from the study removed from the analysis.

Table I: Demographics and clinical characteristics of participants.

Variable	Total participants, N = 43
Demographics	
Age in years, median (IQR)	61.74 (20.82)
Male, n (%)	22 (51.2%)
Ethnicity, n (%)	
Creole	18 (41.9%)
Hindustani	16 (37.2%)
Javanese	6 (14%)
Maroon	0 (0.0%)
Other	3 (7%)
Stroke pathogenesis, n (%)	
Cerebral infarction	25 (58.1%)
Intracerebral hemorrhage	2 (4.7%)
Not specified	16 (37.2%)
Side hemiparesis, n (%)	
Left	15 (34.9%)
Right	10 (23.3%)
Unknown	18 (41.9%)
Length of stay (days), median (IQR)	8 (11)

IQR, interquartile range

Table II: Incidence and co-occurrence of four disorders.

Disorder(s)	Total participants, N = 43
Incidence	
	% (n)
Aphasia	41.9% (18)
Dysarthria	39.5% (17)
AOS	23.3% (10)
Dysphagia	20.9% (9)
None	37.2% (16)
Co-occurrence	
Aphasia + dysarthria	27.9% (12)
Dysarthria + AOS	20.9% (9)
AOS+ Aphasia	16.3% (7)
Aphasia + dysphagia	9.3% (4)
Dysphagia + dysarthria	7.0% (3)
Dysphagia + AOS	7.0% (3)
3 combined	20.9% (9)
All 4	2.3% (1)

clinical characteristics are shown in **table I**. The mean age of the patients was 60 (SD 15; range 19-87) years and 51% were male. The mean LOS was 11 days (SD 10; range 2-47). Furthermore, most patients were from African (41.9%) or South Asian origin (37.2%). For approximately half of the patients (41.9%), the side of hemiparesis was not documented. The majority of patients (58.1%) suffered from an ischemic stroke while only a few patients (4.7%) had an intracerebral hemorrhage pathogenesis. For nearly 37.2%, the stroke pathogenesis was unknown.

First, the occurrence rates of the different SLP disorders, displayed in **table II**, were determined. The highest rate was aphasia with 41.9% of participants experiencing this SLP disorder following a first-ever stroke (95% CI [27.0%-57.8%]), followed by dysarthria with 39.5% of participants (95% CI [25%-55.9%]), AOS with 23.3% of participants (95% CI [11.8% - 38.6%]) and dysphagia with 20.9% of participants (95% [10.0%-36.0%]).

The co-occurrence of two disorders ranged from 7 to 28%, the latter percentage referring to the co-occurrence of aphasia and dysarthria. 20.9% of the patients showed a co-occurrence of three disorders, while only 2.3% showed a combination of all four disorders.

Second, the association between age and LOS with the different SLP disorders is seen in **table III**. Results of the Mann-Whitney U test showed significant differences in median age between patients with and without at least one of the examined SLP disorders ($U=124, p=.02$), with the SLP disordered patient group showing a higher median age than the patient group without any SLP disorder. Differences in median LOS between both patient groups were also significant ($U=126, p=.02$), with a higher median LOS in the SLP disordered patient group.

When focusing on the SLP disorders separately, results indicated that the median age of patients with AOS was significantly higher than the median age of patients without AOS ($U=92, p=.04$). The same patterns was observed for patients with dysphagia as compared to

patients without dysphagia ($U=83, p=.04$). No significant differences in median age were found for patients with/without aphasia ($U=161, p=.12$) and for patients with/without dysarthria ($U=166, p=.18$). For the median length of stay, only patients with and without dysphagia showed a significant difference ($U=78, p=.02$). No significant differences were found between patients with/without AOS ($U=161, p=.91$), patients with/without dysarthria ($U=181, p=.31$) and patients with/without aphasia ($U=180, p=.28$).

Discussion

In this study, we first assessed the (co)-occurrence of the different SLP disorders in first-ever stroke patients in Suriname. In our sample, the highest occurrence rate was found for aphasia, while the lowest occurrence rate was found for dysphagia. In other studies, dysphagia showed the highest occurrence followed by dysarthria and aphasia^{6,5,24,25}. This contrasting finding could have several reasons. First, in our sample, there could be an underestimation of dysphagia since assessments were carried out at one-week post stroke with patients already having spontaneous recovery. In other studies, assessment of dysphagia was mostly carried out within 72 hours. Second, the different occurrence pattern in our sample could potentially be linked to severity of stroke or lesion location. However, to date, no data are available on stroke severity and lesion location in Surinamese stroke patients. Indeed, currently, stroke severity is not consequently included in assessment protocols of the specialist and lesion location is not always specified. Thus, documentation of stroke severity and lesion location is extremely poor.

In addition, we observed the highest co-occurrence for aphasia with dysarthria. The co-occurrence of dysarthria with AOS and the co-occurrence of three SLP disorders accounted for the second highest co-occurrence rate. This indicates that communication disorders were very prevalent in our sample. These results are in line with other studies^{5,25}

Table III: Median age and length of stay for the various speech and swallowing disorders.

	N	Age	95%	CI	p	LOS	95%	CI	p
0 disorders	16	53.55	43.8	67.8		6	4	8	
> 0 disorders	27	67.42*	59.3	73.4	0.02	12*	8	16	0.02
Aphasia -	25	56.2	50	67		7	6	14	
Aphasia +	18	68.6	61.6	73.4	0.11	10.5	8	16	0.27
Dysarthria -	26	56.7	50	69.5		7	6	11	
Dysarthria +	17	67.4	59.3	71.3	0.18	12	6	16	0.31
AOS-	33	57.3	52.6	66.6		3	2	5	
AOS+	10	70.2*	53.1	85.5	0.04	4	1	6	0.91
Dysphagia-	34	58.3	52.6	67.8		7	5	12	
Dysphagia+	9	69.5*	57.2	85.5	0.04	14*	10	30	0.02

Note. The Mann-Whitney non-parametric unpaired two way t-test was used because of the small numbers.

* $p<0.05$

Secondly, our study examined the relationship between age and LOS with the presence or absence of (one of the) SLP disorders. For LOS, our results are partially in line with other studies. In these studies an extended LOS was associated with only dysphagia^{26,8,9,10,11}. We only found that relationship between LOS and the presence/absence of dysphagia.

In line with other studies, in our sample there was also a significant association between the age of stroke patients and SLP disorders^{14,15,16,17}.

This study is the first in Suriname to document the (co-)occurrence of SLP disorders after a first-ever stroke using standardized measurements as part of a well-founded diagnostic protocol.

One of the limitations of this study, however, was that the evaluation of dysphagia could not be carried out within 72 hours after the stroke. Another limitation was that basic (medical) information such as stroke severity, type and location of stroke was not well documented. This makes it difficult to interpret some of the differences with previous studies in the same domain, however, other contexts.

Conclusion

Results from this study identified communication disorders to be prominent compared to swallowing disorders in first-ever stroke patients in Suriname.

Aphasia seems to be the most common SLP disorder. Moreover, our study confirmed an association of LOS with aphasia and dysphagia. Given the fact that aphasia has a major impact on one's quality of life, future studies in Suriname should further document the severity of aphasia patients.

At the same time, standardized assessment and treatment methods, i.e. clinical guidelines, adapted to the local context should be further optimized with the potential to facilitate future treatment advances for stroke patients in Suriname. Given the key role of SLPs in rehabilitation services after stroke, other known barriers such as a national policy to support SLP provisions should also be targeted.

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Declaration of conflicting interest

The author(s) declare(s) that there is no conflict of interest.

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ORIGINAL

Inositol in Dermatologic Diseases

El Inositol en enfermedades dermatológicas

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Abstract

Background: Inositol is a natural ingredient widely used to treat metabolic conditions, hormonal regulation, and neurodegenerative diseases. However, there is a lack of discussion about the importance of inositol in the treatment of dermatological disorders.

Objectives: To systematically review the literature on the efficacy and safety of systemic inositol use for dermatologic diseases.

Methods: PubMed, Ovid/MEDLINE, and Embase in the Cochrane Library databases were searched. We included clinical trials studies and case reports of systemic inositol use among patients diagnosed with skin disorders of all ages (16 studies and 2 case reports).

Results: Inositol and its derivatives including myo-inositol (MI), d-chiro-Inositol (DCI), glycerophospho-Inositol (GPI), and inositol hexaphosphate (IP6) demonstrated potential use for the treatment of acne, hirsutism, atopic dermatitis, seborrheic dermatitis, hidradenitis suppurativa, psoriasis, Raynaud's disease, ischemic ulcer, calciphylaxis, and melanoma. Mild gastrointestinal side effects were reported in 21 patients, which all resolved without modifying the original regimens.

Limitations: Small sample sizes, variations in treatment protocols and lack of standardized outcome measurements.

Conclusions: Inositol is a promising treatment for various dermatological disorders. Dermatologists should consider inositol as a combined therapy in their medication arsenal given its promising results, good tolerability, and relatively few side effects.

Keywords: Inositol, myo-inositol, D-chiro-inositol, metabolic diseases, dermatology.

Resumen

Antecedentes: El inositol es un ingrediente natural ampliamente utilizado para tratar afecciones metabólicas, la regulación hormonal y las enfermedades neurodegenerativas. Sin embargo, no se discute la importancia del inositol en el tratamiento de los trastornos dermatológicos.

Objetivos: Revisar sistemáticamente la literatura sobre la eficacia y seguridad del uso del inositol sistémico para las enfermedades dermatológicas.

Métodos: Se realizaron búsquedas en las bases de datos PubMed, Ovid/MEDLINE y Embase de la Biblioteca Cochrane. Se incluyeron estudios de ensayos clínicos y reportes de casos sobre el uso de inositol sistémico entre pacientes diagnosticados con trastornos de la piel de todas las edades (16 estudios y 2 reportes de casos).

Resultados: El inositol y sus derivados, incluidos el mio-inositol (MI), el d-chiro-inositol (DCI), el glicero-fosfato-inositol (GPI) y el hexafofosfato de inositol (IP6), demostraron un uso potencial para el tratamiento del acné, el hirsutismo, la dermatitis atópica, la dermatitis seborreica, la hidradenitis supurativa, la psoriasis, la enfermedad de Raynaud, la úlcera isquémica, la calcifilaxis y el melanoma. Se notificaron efectos secundarios gastrointestinales leves en 21 pacientes, que se resolvieron sin modificar los regímenes originales.

Limitaciones: Tamaños de muestra pequeños, variaciones en los protocolos de tratamiento y falta de mediciones estandarizadas de los resultados.

Conclusiones: El inositol es un tratamiento prometedor para diversos trastornos dermatológicos. Los dermatólogos deberían considerar el inositol como terapia combinada en su arsenal de medicamentos, dados sus prometedores resultados, su buena tolerabilidad y sus relativamente escasos efectos secundarios.

Palabras clave: inositol, mio-inositol, D-chiro-inositol, enfermedades metabólicas, dermatología.

Capsule summary

- Inositol is a natural ingredient widely used to treat metabolic conditions, hormonal regulation, and neurodegenerative diseases, but their safety and efficacy have not been systemically reviewed in dermatological disorders.
- Most data supported Inositol as an effective alternative for treating a wide range of dermatological diseases, with relatively few side effects.

Abbreviations

AE: Adverse effect; ATP: adenosine triphosphate; BID: twice a day; BMI: Body mass index; BWAT: Bates-Jensen Wound Assessment Tool; CGI-I: clinical global impressions-improvement scale; DCI: D-chiro-Inositol; DHEAS: Dehydroepiandrosterone; FTU: fingertip unit; GAGS: global acne grading system; GI: gastrointestinal disturbance; GPI: Glycero-phospho-Inositol; HM: Myo-inositol hexaphosphate; HTN: hypertension; HS: Hidradenitis suppurativa; IGA: investigator global assessment; IGF-1: Insulin growth factor-1; IP6: Inositol hexaphosphate; IV: Intravenous; MeSH®: Medical Subject Headings; Hexopal®: Inositol nicotinate; HD: hemodialysis; mCS: modified Cook's scale; mFGHS: Ferriman-Gallwey hirsutism score; MI: Myo-inositol; NOS: Newcastle-Ottawa Scale; OCD: Obsessive-compulsive disorder; OR: Odds ratio; PASI: psoriasis area and severity index; PI: Phosphoinositides; PIP2: Phosphatidylinositol 4,5-bisphosphate; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PCOS: Polycystic ovarian syndrome; PSI: plaque severity index; QoL: quality of life; ROS: Reactive oxygen species; RP: Raynaud phenomenon; (R)TG: (reactive) therogradient; SD: Seborrheic dermatitis; SE: side effect; SRI: Serotonin-reuptake inhibitor; TH: trehalose; TID: thrice a day; TIW: thrice a week; VAS: visual analogue scale.

Introduction

The beneficial effect of dietary supplementation in clinical medicine has gained great attention in recent years and led to the development of the “functional medicine” field. In particular, physicians and scientists started to investigate vitamin/mineral/natural product supplements as an alternative to standard medication. One example is the family of inositols, which is a carbocyclic sugar consisting of nine stereoisomers of naturally occurring cyclohexanehexol (myo-, scyllo-, muco-, neo-, and D-chiro-Inositol) or its derivatives (L-chiro-, allo-, epi-, cis-Inositol)^{1,2} Inositols were first identified in 1850 from muscle cells by Johann Joseph Scchere, a German physician and chemist, and named it from the Greek terms [ἰς (is, in-, “sinew, fiber”), -ose (indicating a carbohydrate), -ite (“ester”), -ol (“an alcohol”)] to describe its sugar alcohol configuration^{3,4}. Inositols are important components of eukaryotic cell membranes and they are involved in biological signal transduction, osmoregulation, and phosphate storage^{1,5,6}. It has received much attention in medicine in recent years as a plant-based supplementation for metabolic syndrome, reproduction, and pregnancy development⁷⁻¹¹. Myo-inositol (MI) being the most bioavailable and the most popular isoform, it is used in topical, oral, and intravenous (IV) forms for various clinical practices.

To date, it is often used with metformin to treat women with polycystic ovarian syndrome (PCOS). MI has similar biological properties to insulin and is widely used for its insulin-sensitizing property on various tissues, including

the ovary¹². It is mainly catabolized by the kidneys or converted to D-chiro-inositol (DCI) by the NADH-dependent epimerase under insulin stimulation^{13,14}. Both MI and DCI increase glucose uptake and conversion to glycogen in cells and reduce the release of free fatty acids from adipocytes^{11,14}. Given the intricate link of skin health to hormones and metabolism, it is interesting to explore the possible utility of inositols in dermatology.

Methods

Literature Search

This study was done in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)¹⁵. A primary literature search was conducted with PubMed, Ovid/MEDLINE, and Embase in the Cochrane Library databases on December 20, 2021, without limitation as to dates. Medical Subject Headings (MeSH®) controlled vocabulary, text words, and database-specific wildcards were utilized to develop the search terms.

Study selection and appraisal

All reviewers independently screened all article titles and abstracts to include clinical trials, cohort studies, case-control studies, retrospective analyses, case series, cross-sectional studies, or case reports, written in English, of inositol-related interventions in human subjects in the field of dermatology. Animal studies,

reviews, and articles not written in English or Chinese were excluded. Subsequently identified studies were then subjected to full-text review. Rationales for exclusion and article appraisals were recorded at every stage. The final decision on study selection was reached by discussion. References of included and excluded studies were reviewed for potential studies not identified through the initial search strategy and added according to the criteria mentioned above.

Data extraction and analysis

Included studies were summarized using a data extraction form. Authors were contacted for missing data. Studies were graded using the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence. Bias risk and methodological qualities were assessed using the Risk of Bias tool for randomized controlled trials, and the Newcastle-Ottawa Scale (NOS) for observational studies. Results of included studies were described in synthesized narratives and are presented in **table I**.

Table I: Recommended use of systemic inositol.

Study	Study type	Subject	Regime	Trial duration (month)	Route	Primary outcome measure	Results	AEs
Hyperandrogenism – acne, hirsutism								
Fruzzetti, 2017 ³²	RCT	50 PCOS women (inositol: 24, metformin: 22) + 30 healthy controls	MI, 4g, daily plus folic acid, 400mcg, daily; or metformin, 1500mg, daily	6	Oral	On patient-self assessment, 1. 20% of inositol group and 12% of metformin group felt a slight improvement in hirsutism, 0% and 12% reported worsening, the remaining reported no change 2. 38% of inositol group and 43% of metformin group felt a slight improvement in acne, 12% and 7% reported worsening, the remaining reported no change		None
Pezza, 2015	RCT	100 PCOS women with acne	Inositol, 2g, BID (50) or placebo (50)	6	Oral	Decreased number of papulopustular lesions		None
Fabbrocini, 2017	Uncontrolled clinical trial	40 women with adult female acne	4% MI and 1% trehalose-loaded liposomes, overnight every other day	2	Peel-off facial mask	1. Significantly reduced mean count of comedones (-3.9), papule (-6.1), pustule (-2.0), and nodular (-0.5) lesion (P<0.001) 2. GAGS scale scores reduced from 16.8±5.3 to 9.8±4.6 (P<0.001) 3. Sebutape score decreased from 3.4±0.6 to 1.8±0.2 (P<0.001)		None
Minozzi, 2008	Uncontrolled clinical trial	46 women with mild to moderate hirsutism	MI, 2g, BID	6	Oral	Hirsutism score decreased by -2.3±0.9 (P<0.001)		None
Advani, 2020	Uncontrolled clinical trial	Obese (35) or lean (16) PCOS women*	Trazer F Forte™, BID: Inositol (MI:DCI) 600 mg, NAC 300mg, Biotin 5mg, 10% Lycopene 5mg, Chromium picolinate 200 mcg, Folic Acid 120 mcg, Vitamin D 400 IU	3	Oral tablet	In the obese and lean group, 1. Acne score scores -10.05 (P<0.001) and -4.38 (P<0.01), respectively 2. Hirsutism score scores -0.45 (P<0.01) and -0.25 (P<0.05), respectively		None
Ramanan, 2020	Uncontrolled clinical trial	32 females with mild-to-moderate acne and hirsutism	Tracnil™, BID: MI, 2g; folic acid 1mg, vit D3 1000IU	6	Oral powder sachets	1. IGA scores on acne reduced from 4.34±0.33 to 1.3±0.14 by Weeks 24 2. mFGHS reduced by 8.6, 7.4, and 5.8 by Weeks 4, 12, and 24, respectively		Mild GI in some patients
Inflammatory dermatosis – atopic dermatitis, seborrheic dermatitis, hidradenitis suppurativa, psoriasis								
Allan, 2004	Crossover RCT	Patients on lithium who developed chronic plaque psoriasis (15) or patients not on lithium with psoriasis (8)	Inositol, 6g, daily	2.5	Oral	1. Patients on lithium: PASI scores -1.7 in the inositol group compared to +1.9 in the placebo group (P>0.05) 2. Patients not on lithium: PASI scores +0.7 in the inositol group compared to -0.75 in the placebo group (P=0.015)		None
Owczarczyk-Saczonek, 2021	RCT	46 patients with mild plaque psoriasis (PASI<10, BSA<10%); 10 healthy controls	1% (B) or 0.25% (C) DCI, 1 FTU, BID, or placebo applied to three different psoriatic plaques	1.5	Topical cream	1. VAS scores reduced by 22% and 33% in the B and C group; and 23% in the placebo group (P<0.05) 2. PSI scores reduced by 30% and 45% in the B and C group; and 28% in the placebo group (P<0.05)		Not reported

Study	Study type	Subject	Regime	Trial duration (month)	Route	Primary outcome measure	Results	AEs
Dall' Oglia, 2017	Uncontrolled clinical trial	25 patients with mild-to-moderate SD	GPI, piroctone olamine, lactoferrin, and Aloe vera, BID	1.5	Topical gel	1. Excellent response (IGA = 4) in 47.9% of patients and no case of worsening (IGA = 0) 2. Significant reduction in desquamation, erythema, and pruritus (P<0.001)		None
Donnarumma, 2020	RCT	20 patients with HS	Antibiotics with (10) or without (10) MI 2g, liposomal magnesium and folic acid, BID	6	Oral	Reduction of Sartorius scores from 38.3±7.5 to 27.3±13.53 (P<0.04), compared to non-significant reduction in the control group		None
Vascular and circulation – Raynaud's disease, ischemic ulcer, calciphylaxis								
Sunderland, 1987	RCT	23 patients with primary RP	Hexopal @, 4g, daily (11) or placebo (12)	3	Oral	1. Significantly reduced frequency (P=0.032) and duration (P=0.058) of attack in Hexopal group; non-significant increase in duration of attack in placebo group 2. Higher subjective improvement in the Hexopal group vs placebo group (80% versus 50%)		None
Ring, 1981	Uncontrolled clinical trial	18 patients with secondary RP	Hexopal @, 1g, QID	9	Oral suspension or tablet	Progressive improvement in TG and RTG, with the latter reaching significance at Weeks 36 (P<0.05)		None
Holti, 1979	Uncontrolled clinical trial	30 patients with primary (14) or secondary (16) RP	Hexopal @, 4g, daily	3	Oral	1. Significantly higher "on arrival" finger temperatures at Weeks 4, 8, and 12 with no difference in "after heating" temperatures (P<0.01) 2. Non-significantly lower thermal clearance readings (indicates more rapid blood flow) towards Weeks 12 3. Significantly longer time to induce RP at Weeks 4, 8, and 12 (P<0.001)		None
Mishima, 1997	RCT	227 patients with ischemic ulcers	Inositol, 400mg, TID (116) or pyridinol-carbamate, 500mg, TID (111)	1-1.5	Oral	57% and 49% of the patients achieved clinical improvement in the inositol group at Weeks 4 and 6 respectively, compared to 50% and 68% in the pyridinol-carbamate group		Mild AEs (10), severe 6.8% slight to moderate GID 1.3% severe GID requiring termination
Brandenburg, 2019	Uncontrolled clinical trial	14 HD patients with calciphylaxis	SNF472, 7mg/kg, TIW	3	Intravenous infusion	1. BWAT improved from 33.6±9.6 to 25.6±7.3 (P<0.001) 2. Reduction in pain VAS from 71.8±29.2 mm to 48.1±28.6 mm (P=0.015) 3. Wound-QoL improved from 2.44±0.89 to 1.54±0.90 (P=0.003)		4 (28.6%); unspecified
Perelló, 2018	RCT	8 HD patients with calciphylaxis; 20 healthy volunteers	SNF472, 9mg/kg, every 48 hours	1.5	Intravenous infusion	No significant change in serum calcium levels		Paraesthesia oral (1), moderate HTN (1)
Psychodermatoses – skin picking, trichotillomania								
Seedat, 2001	Case series	3 patients with trichotillomania and compulsive skin picking	Inositol, 6g, TID (primary treatment in two and adjunct to SRI in one)	2-3	Oral powder dissolved in water or juice	Two patients reported a CGI-I score of 2 (much improved), and one (adjunct to SRI) reported CGI-I of 1 (very much improved)		Mild GID (2) and headache (1)
Neoplasm								
Khurana, 2019	Case report	A patient with stage IVB melanoma	IP6+inositol (800 mg/220 mg), 5 tablets, BID	24	Oral tablets	Restaging scans showed significant improvement after 6 months, complete clinical and radiological remission after 2 years		None

AEs: adverse events; PCOS: polycystic ovarian syndrome; MI: myo-Inositol; DCI: d-chiro-Inositol; BID: twice a day; FTU: fingertip unit; PSI: plaque severity index; VAS: visual analogue scale; TH: trehalose; GAGS: global acne grading system; TIW: thrice a week; BWAT: Bates-Jensen Wound Assessment Tool; QoL: quality of life; HD: hemodialysis; SEs: side effects; PASI: psoriasis area and severity index; TID: thrice a day; GID: gastrointestinal disturbance; CGI-I: clinical global impressions-improvement scale; IP6: inositol hexaphosphate; mCS: modified Cook's scale; mFGHS: modified Ferriman-Gallwey hirsutism score; SD: seborrheic dermatitis; GPI: glycerophospho-Inositol; IGA: investigator global assessment; HS: hidradenitis suppurativa; RP: Raynaud's disease; (R)TG: (reactive) thermogradient [temperature difference between the phalanges and the dorsum of the hand]; HTN: hypertension; SRI: serotonin reuptake inhibitor; Hexopal @: inositol nicotinate.

*Obese/overweight: BMI >23 non-obese/lean: BMI ≤23

Results

Literature search

The literature search yielded 1181 non-duplicate articles. After title and abstract screening, 280 articles met the criteria for inclusion. These articles were subjected to full-text screening and 17 studies were included in this systematic review as depicted by the PRISMA flow diagram (Figure 1). This included eight randomized controlled trials, eight uncontrolled trials, and two case reports.

Inositol in dermatology

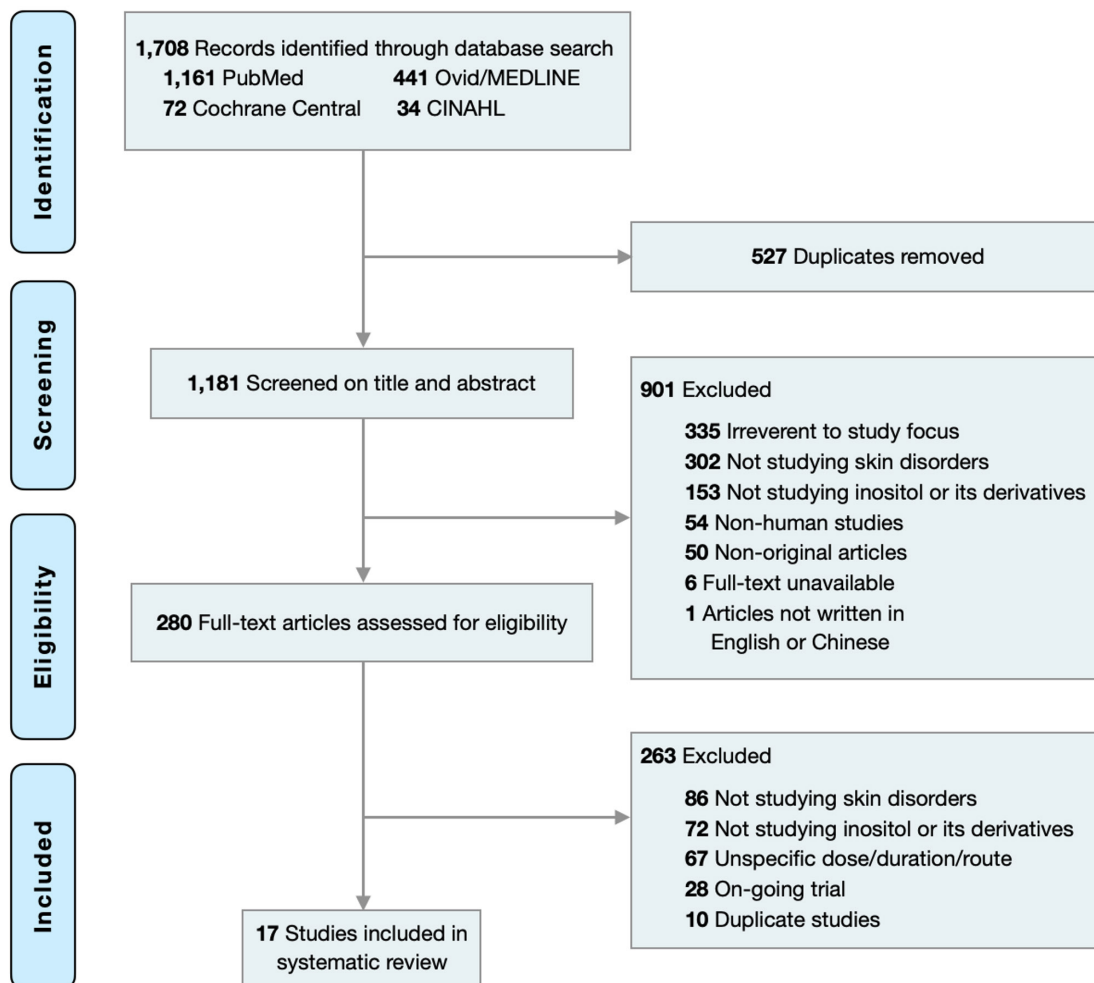
This review highlighted the existing utilities of inositol in a wide range of skin diseases with various mechanisms of pathogenesis. Inositol is thought of as an insulin-mimetic through multiple modes of action. MI promotes GLUT4 translocation to the plasma membrane, while DCI facilitates glycogen synthesis, enhances insulin signal transduction, and boosts major enzymes in the Krebs cycle to increase glucose utilization and

adenosine triphosphate (ATP) production^{10,11,13,16-18}. MI also reduces the release of free fatty acids, which promotes a pro-inflammatory state, from adipose tissue, decreases reactive oxygen species (ROS), and reduces white blood cell recruitment^{17,19-22}. Given the gut-skin connection, inositol's effects make it a promising therapy to treat cutaneous disorders. Below we further discuss the mechanism and utility of inositol according to clinical subcategories

Hyperandrogenism – acne, hirsutism

At the ovarian level, MI may indirectly increase aromatase activity by follicular stimulating hormone (FSH) modulation. On the other hand, DCI-based second messengers regulate androgen production through the cytochrome P450 system^{18,23-25}. Simultaneous alterations in hormonal balance and inflammatory cytokines synergistically improve acne in PCOS women and explain its efficacy in diseases arising from either mechanism. It is hypothesized that besides their individual effects, the ratio of MI and DCI determines the balance of steroidogenesis. Higher

Figure 1: PRISMA flowchart for study selection.



MI:DCI ratios increase estrogen secretion, and lower MI:DCI ratios result in a hyperandrogenic state. Therefore, some research used combined inositol with MI:DCI ratios ranging from 10:1 to 100:1 to address the state of hyperandrogenism such as acne and hirsutism with or without concomitant PCOS²⁶.

Acne

Acne arises from the interplay among sebaceous glands, *Propionibacterium acnes*, and sex hormones²⁷⁻³¹. Proposed as an additive insulin sensitizer in women with PCOS, inositol has been found to reduce acne of all stages. Fruzzetti et al³² and Pezza et al³³ assessed the effect of oral inositol on acne severity in 25 and 50 PCOS females, respectively. Thirty-eight percent of patients in the first study reported improvement in acne symptoms, and the latter found decreased numbers of papulopustular lesions. Interestingly, although these PCOS women had a higher average testosterone level, the former study found no change in the androgen levels Pezza's study reported a decrease in serum dehydroepiandrosterone (DHEAS) concentration. Another study on PCOS women with normal (≤ 23) or high (>23) body mass index (BMI) revealed a larger decrease in acne scores in overweight or obese subjects compared to lean individuals (-10.05 versus -4.38)³⁴. Both groups achieve significant acne clearance within a 12-week course of combined inositol 600mg, twice a day. It is likely that inositol clears acneiform eruptions through multiple mechanisms apart from hormonal regulation. Fabbrocini et al³⁵ reported a 45-69% reduction in mean acne counts in women with adult female acne and no endocrine abnormalities after 60 days of 4% MI peel-off mask application. In addition, Ramanan et al,³⁶ after excluding patients with comorbid endocrine and metabolic diseases, revealed a significant reduction on the modified Cook's scale from 4.34 ± 0.33 to 1.3 ± 0.17 after 24 weeks of MI with 2g MI twice daily.

Hirsutism

Hirsutism is the excessive male-pattern hair growth in women. It affects 5-10% of women, depending on age, menopausal status, and race³⁷. About 50% of cases are idiopathic while the other half is associated with PCOS (OR = 2.22 [1.30-3.81] or other sex hormones (OR = 1.78 [1.00-3.18])^{38,39}. Similarly, PCOS women with hirsutism respond to Inositol, despite to a lesser degree than acne^{32,34}. Minozzi, Andrea, and Unfer⁴⁰ conducted an uncontrolled clinical trial in hirsute women with or without PCOS using MI 2g, twice a day, for 6 months. The authors found a significant decrease in hirsutism scores (-2.3 ± 0.9 , $p < 0.001$) and total androgens (-13 ± 2.6 , $p < 0.002$) from the baseline. Likewise, the modified Ferriman-Gallwey hirsutism score (mFGHS) decreased from 10 to 5.8 in the study by Ramanan et al³⁶ using the same regime. Besides, 60% less of patients were complaining of hair loss at the end of the study.

Inflammatory dermatosis – psoriasis, seborrheic dermatitis, hidradenitis suppurativa

Psoriasis

Psoriasis is a chronic inflammatory dermatoses characterized by IL-23/IL-17 activation and Th17/Treg imbalance^{41,42}. First reported in 2004 as a remedy for psoriasis in patients taking lithium, oral Inositol replenished lithium-induced Inositol depletion in psoriatic lesions without decreasing its efficacy in patients treated for bipolar disorders⁴³. However, such improvement was not observed in patients taking inositol without lithium, suggesting that the endogenous production of inositol can be easily disturbed²². Another group of researchers investigated the effect of 1% or 0.25% d-chiro-Inositol (DCI) on chronic plaque psoriasis. Both concentrations, as well as placebo, showed statistically significant subjective and clinical improvement of psoriasis. It was speculated that placebo-related improvement may be related to the topical vehicle base improving the skin condition. The high-dose DCI showed better biophysical measurements and the low-dose regime had a larger reduction in psoriasis severity on clinical evaluation²². The contradictory results in these two studies may arise from different patient characteristics, routes of administration, or other non-specific mechanism. More research is required to understand the role of inositol in psoriasis treatment.

Seborrheic dermatitis

Seborrheic dermatitis (SD) affects people of all ages but is most common in infants and in adults aged 30-60 years. The adult form is often precipitated by stress or sleep deprivation and its pathogenesis is likely multifactorial, including hormone levels, skin flora composition, fatty acid metabolism, and neurogenic factors⁴⁴. Dall' Oglio et al⁴⁵ applied a new cosmetic topical gel containing glycerol-phospho-Inositol (GPI) to 25 patients with mild-to-moderate facial SD. They found a significant reduction on the investigator global assessment scale and an excellent response ($>80\%$ improvement) was reported in near 50% of the cases. Although it is reasonable that inositol improves SD through hormonal and metabolic regulation, there is limited data on this hypothesis. Besides, it was unclear whether the effect was due to GPI or other ingredients in the product.

Hidradenitis suppurativa

Hidradenitis suppurativa (HS) is a relapsing-remitting inflammatory dermatoses characterized by painful nodules, abscesses, and sinus tract formation⁴⁶. It can cause significant disfigurement due to fibrosis and scarring. Interactions between innate immunity and skin microbiota as well as genetic factors have all been linked to HS development⁴⁷. Donnarumma and colleagues performed a randomized controlled trial to estimate the effectiveness of oral MI (2g daily) supplementation. The average Sartorius Score in the experimental group decreased from 38.3 ± 7.75 to 27.3 ± 8.02 ($p < 0.04$), while

the control group showed a reduction from 38.4 ± 7.88 to 31.1 ± 8.02 ($p = 0.55$). There were no similar studies found on HS treatment with inositol.

Vascular and circulation – Raynaud phenomenon, calciphylaxis

Hexopal, or inositol nicotinate, has both immediate and delayed impacts on distal perfusion. Holti et al⁴⁸ found that there was a trend toward further improvement in RP patients at¹² weeks of treatment, suggesting other mechanisms such as enhanced fibrinolysis of Hexopal, besides vessel dilation.

Raynaud phenomenon

Raynaud phenomenon (RP) is a complex entity due to abnormal vascular reactions to temperatures. It can be a primary disease or secondary to other connective tissue diseases. Treatment includes vasodilators such as nitric oxide, calcium channel blockers, and alpha-blockers^{49,50}. Three studies conducted during 1979-1987 used Hexopal[®] in patients with primary or secondary RP. Hexopal (inositol nicotinate) is a compound made of inositol and niacin (vitamin B3). Although niacin is the major active ingredient, the inositol component may reduce side effects from nicotinic acid alone and facilitate vasodilation through the Ca^{2+} -dependent phosphatidylinositol 4,5-bisphosphate (PIP2) signaling pathway⁵¹. No adverse event associated with Hexopal[®] was reported in these studies.

Calcinosis cutis

Calcinosis cutis is a rare, life-threatening complication of end-stage renal disease. Its pathophysiology is still poorly understood, but occlusion of microvessels in the dermis and subcutis is frequently observed, resulting in painful necrotic skin ulcers⁵². Sodium thiosulfate, bisphosphonate, and hyperbaric oxygen therapy are the mainstay treatment, where none of above is approved by the FDA. SNF472, an intravenous preparation of myo-inositol hexaphosphate (HM), has received much attention as a crystallization inhibitor. In the phase 1 trial by Perelló and colleagues, they found a dose-dependent decrease in serum ionized calcium levels in healthy individuals while no significant changes were observed in hemodialysis patients⁵³. A follow-up phase 2 open-label, single-arm study, however, showed significant improvement in wound healing and pain scores. One study used 2% HM cream to prevent dystrophic calcinosis cutis in 14 male Wistar rats. The investigators induced plaque formation with 0.1% $KMnO_4$ and found a significant reduction in plaque size and weight⁵⁴. Supplementing HM during hemodialysis hypothetically replenishes endogenous crystallization inhibitor phytate and prevents calciphylaxis. Overall, HM may be a potential treatment for calcinosis cutis, whose management is often frustrating.

Psychodermatoses – skin picking, trichotillomania

Inositol is an important component of neuronal cells as

well. Hydrolysis of phosphoinositides (PI) is the first step of signal transduction for multiple neurotransmitters. MI regenerates hydrolyzed PI, making it an emerging therapeutic option for psychiatric disorders like depression and the obsessive-compulsive disorder (OCD) spectrum^{55,56}.

A case series by Seedat S, Stein DJ, and Harvey BH reported successful treatment of refractory trichotillomania and compulsive skin picking with inositol⁵⁷. Inositol has been shown to improve anxiety, depression, and obsessive-compulsive disorder.⁵⁸ These three patients were treated with a total daily dose of 18g inositol for 8-12 weeks. They reported noticeable improvement in mood and control over their compulsive behaviors. Although the dosage used in this series was much higher than that for other cutaneous disorders, side effects were mild and well-tolerated. Of note, two of them had inositol as primary treatment while one had inositol as an adjunct to a serotonin-reuptake inhibitor (SRI). Interestingly, adjunct treatment with SRI led to “very much improved” symptoms compared to “much improved” symptoms with sole inositol treatment based on CGI-I severity scores.

Neoplasm – melanoma

MI has been shown to modulate both PI3K/AKT and Wnt/ β -catenin pathways.^{59,60} It may also prevent insulin growth factor-1 (IGF-1) receptor-mediated tumor growth by decreasing insulin resistance⁶¹. Trials on lung and breast cancer chemoprevention or treatment with MI have been reported with promising results^{62,63}.

Significant inhibition of melanoma line HTB68 by inositol hexaphosphonate (IP6) was first reported in 2006.⁶⁴ It was hypothesized that IP6 exerts its anti-proliferative effect through the regulation of apoptosis and angiogenesis. IP6's anti-proliferative effect was supported by another *in vitro* study done by Schneider and colleagues.⁶⁵ An interesting case report of a stage IV melanoma successfully treated with IP6+inositol (800 mg/220 mg) was published in 2019. The patient had had a diagnosis of stage IIIc melanoma on the left foot with in-transit metastasis to the left shin. One year after, he presented with a new *BRAF V600E* mutant stage IVB melanoma on the left medial thigh. He received a total dose of 8g IP6 and 2.2g inositol daily for 2 years when complete clinical and radiological remission was achieved. He continued with the regime with no signs of relapse nor side effect attributable to the treatment⁶⁶. Nevertheless, although inositol has been shown to inhibit the proliferation of many types of cancer, this is the only report on melanoma in humans so far.

Other Adverse Effects (AEs)

The LD50 of oral MI is 1000mg/kg in mice, which is way below the usual therapeutic ranges of 2-6g daily⁶⁷. Most commonly reported side effects were gastrointestinal disturbance including gastritis and vomiting (14), perioral

paresthesia (1), headache (1), moderate hypertension (1), and four cases were non-specified. Although uncommonly administered, limited case studies support the safety of inositol even at a very high dose of 18g per day, and side effects, if any, are usually mild. In the 570 patients reviewed in this article, only 21 patients developed an adverse reaction to inositol. The most common complaint is gastrointestinal disturbance including gastritis and vomiting (14). Others include perioral paraesthesia (1), headache (1), moderate hypertension (1), and non-specified in four cases. It was reported that psychiatric patients can have some mild neurological discomfort including headaches seen in one of the cases in the OCD series⁶⁸. These side effects could be ameliorated by altering the pharmaceutical form and using lower doses⁶⁹.

There are a few limitations in this review, the exact composition and dosing of inositol in each study varied significantly. Isoforms used included MI, DCI, GPI, Hexopal, SNF472, and IP6, and the dosage ranged from 600mg to 18g/day over 4 weeks to more than 3 years. There was significant heterogeneity in the quality and varied outcome assessment presented from available studies. In addition, all RCT had small sample sizes and reports on inflammatory dermatoses, psychodermatoses, and skin neoplasms were limited.

In conclusion, inositol is a promising natural ingredient with anti-androgen, anti-inflammatory, anti-cancer, and many other mechanisms of action. It is proven to be effective as an alternative treatment for a wide range of dermatological diseases with very few side effects. Although data on its long-term safety after 2-6 months was limited, increasing tolerance with continual application and articles reporting extended use over 2 years indicated inositol is suitable for long-term maintenance therapy. Dermatologists should consider including oral inositol as a combination therapy in their medication arsenal given its promising results and good tolerability.

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Availability of data and material

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Evaluate specificity and sensitivity of cone beam computed tomography for midfacial fractures: A systematic review and meta-analysis

Evaluar la especificidad y la sensibilidad de la tomografía computarizada de haz cónico para las fracturas del tercio medio facial: una revisión sistemática y un metanálisis

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Abstract

Objectives: The present study aims to evaluate the specificity and sensitivity of cone beam computed tomography compared to physical examination for medial fractures.

Methods: In this study, international databases such as PubMed, Scopus, Science Direct, ISI, Web of Knowledge, and Embase were reviewed to select articles related to the purpose of this study from January 2012 to July 2022. Effect size with 95% confidence interval (CI) with fixed effect modal and inverse-variance done. STATA.V16 software was used for data analysis.

Results: In the initial review, the abstracts of 283 studies were reviewed, two authors reviewed the full text of 32 studies, and finally, eight studies were selected. The sensitivity of the Intra-oral assessment was 17% (ES: 95% CI, -0.34 to 0.74); the subgroup meta-analysis showed Sensitivity to Laceration, and the intraoral assessment was 19% (ES: 95% CI, -1.77 to 2.15); Sensitivity of Tooth avulsion assessment was 9% (ES: 95% CI, -1.04 to 1.22).

Conclusions: Diagnostic sensitivity of individual physical examination was low compared to imaging methods, Based on the findings of the present meta-analysis, which shows that individual physical examination cannot be accurately relied upon to identify intra-oral assessment in mid-face fractures.

Keywords: Cone-Beam Computed Tomography, Sensitivity and Specificity, Tomography, X-Ray Computed.

Resumen

Objetivos: El presente estudio tiene como objetivo evaluar la especificidad y la sensibilidad de la tomografía computarizada de haz cónico en comparación con el examen físico para fracturas mediales.

Métodos: En este estudio se revisaron bases de datos internacionales como PubMed, Scopus, Science Direct, ISI, Web of Knowledge y Embase para seleccionar artículos relacionados con el propósito de este estudio desde enero de 2012 hasta julio de 2022. Tamaño del efecto con 95 % de intervalo de confianza (IC) con modal de efectos fijos y varianza inversa realizada. Para el análisis de datos se utilizó el software STATA.V16.

Resultados: En la revisión inicial, se revisaron los resúmenes de 283 estudios, dos autores revisaron el texto completo de 32 estudios y, finalmente, se seleccionaron ocho estudios. La sensibilidad de la evaluación intraoral fue del 17 % (ES: IC del 95 %, -0,34 a 0,74); el metanálisis del subgrupo mostró Sensibilidad a la laceración y la evaluación intraoral fue del 19 % (ES: IC del 95 %, -1,77 a 2,15); La sensibilidad de la evaluación de la avulsión dental fue del 9 % (ES: IC del 95 %, -1,04 a 1,22).

Conclusiones: la sensibilidad diagnóstica del examen físico individual fue baja en comparación con los métodos de imagen, según los hallazgos del presente metanálisis, que muestra que no se puede confiar con precisión en el examen físico individual para identificar la evaluación intraoral en fracturas de la parte media de la cara.

Palabras clave: tomografía computarizada de haz cónico, sensibilidad y especificidad, tomografía computarizada de rayos X.

Introduction

In the emergency department, most of the referrals are related to traumas, of which mid-facial trauma is one of them that has a high prevalence; According to the available statistics, mid-face fractures can be caused by sports, accidents, daily activities, or fights; Therefore, its prevalence varies according to the geographical region, culture and living environment^{1,2}. This type of fracture has different degrees; depending on the type of accident, their severity is different, and the most common one is nose fracture³. When a trauma patient enters the emergency room, midface fractures are checked. Middle-face anatomy is complex, so it is important to pay attention to it. This part can be considered similar to a framework that supports and provides functional support for the teeth^{4,5}. Studies have reported a wide variety of midface fractures that affect physical examination and are challenging; among these cases, we can refer to fractures of the maxillary alveolar tooth complex, nasal fracture, and frontal sinus^{1,6,7}. Identifying fracture patterns is very important because radiological imaging is required for these types of fractures and cannot be detected by physical examination. Among the gold standard methods that have been of great interest in recent decades and are used to diagnose mid-face fractures we can mention cone beam computed tomography (CBCT) and computed tomography (CT)⁸⁻¹¹. Based on the findings of the studies, the effective dose of both mentioned methods depends on the scan range, system type, and scan protocol parameters¹²; For CBC, a dose of 0.08 to 0.21 mSv is usually considered. The risk of exposure to ionizing radiation is a concern, and there is a need to use less risky methods¹². If performed with greater accuracy, physical examinations can minimize unnecessary imaging procedures and reduce the risk of exposure to ionizing radiation^{13,14}. Therefore, prediction and diagnosis of mid-face trauma using the physical examination method are challenging, and if this method can be done well, it can be considered a good alternative for imaging methods. Considering the importance of the issue and that faster diagnosis by emergency physicians or oral and maxillofacial surgeons can help the patient in treatment, the present study aims to evaluate the specificity and sensitivity of cone beam computed tomography compared to physical examination for medial fractures.

Methods

The present study is a systematic review and meta-analysis based on PRISMA guidelines¹⁵. In this study, international databases such as PubMed, Scopus, Science Direct, ISI, Web of Knowledge, and Embase were reviewed to select articles related to the purpose of this study from January 2012 to July 2022. Mesh keywords were used for searching in PubMed, and similar keywords were searched in other databases. In

the current study, **table I** shows the response to PICO; the Google Scholar search engine was also used.

MeSH terms keywords: (((((((("Wounds and Injuries"[Mesh] OR "injuries" [Subheading]) AND "Fractures, Bone"[Mesh]) AND ("Oral and Maxillofacial Surgeons"[Mesh] OR "Maxillofacial Injuries"[Mesh] OR "Oral Surgical Procedures"[Mesh] OR "Surgery, Oral"[Mesh] OR "Orthognathic Surgery"[Mesh])) AND ("Maxillofacial Injuries/classification"[Mesh] OR "Maxillofacial Injuries/complications"[Mesh] OR "Maxillofacial Injuries/diagnosis"[Mesh] OR "Maxillofacial Injuries/diagnostic imaging"[Mesh] OR "Maxillofacial Injuries/etiology"[Mesh] OR "Maxillofacial Injuries/statistics and numerical data"[Mesh] OR "Maxillofacial Injuries/surgery"[Mesh] OR "Maxillofacial Injuries/therapy"[Mesh])) AND "Cone-Beam Computed Tomography"[Mesh]) AND "Tomography, X-Ray Computed"[Mesh]) AND "Sensitivity and Specificity"[Mesh].

Table I: PICO strategy.

PICO strategy	Description
P	Population: patients with mid-facial trauma
I	Intervention: physical examination
C	Comparison: CBCT, CT
O	Outcome: Sensitivity and Specificity

Inclusion and exclusion criteria

Randomized controlled clinical trials (RCT) and clinical trial studies, cohort studies, patients with mid-facial trauma, Studies other than RCT and cohorts, other trauma, conflicting data with objective, and studies without full text were excluded from the study.

Reporting and extracting study data

Using a checklist that included the author's name, year of publication, type of study, number of patients, and the average age of patients, the data of the studies were extracted and reported in **table II**; Also, the data required for meta-analysis including Sensitivity, Specificity, and Diagnostic accuracy were extracted from the studies.

Evaluating the quality of studies

In the current study, randomized control clinical trial studies were included, and the quality of these studies was evaluated using the Cochrane Collaboration's tool¹⁶. The scores of this tool are between 0 and 6, and the higher score showed a higher quality of study; the scoring of each item is 1 for low risk and 0 for high and unclear risk.

Newcastle-Ottawa Scale (NOS)¹⁷ was used to the assessed quality of the cohort and cross-sectional studies, case-control, and case series studies; this scale measures three dimensions (selection, comparability of cohorts, and outcome) with a total of 9 items. Any studies with NOS scores of 1-3, 4-6, and 7-9 were defined as a low, medium, and high quality, respectively.

Table II: Summary of demographic and clinical data of studies selected.

No.	Study. Years	Study design	Number of Patients		Prevalence of fracture	Mean of age (years)
			Male	Female		
1	Sun et al., 2019 (18)	Retrospective	41	6	74.5	40
2	Harrington et al., 2018 (19)	Retrospective	105	62	59.3	50
3	Huang et al., 2017 (20)	Retrospective	918	713	13.8	53
4	Scolozzi et al., 2017 (21)	Retrospective	632	280	77	46
5	Timashpolksy et al., 2016 (22)	Prospective	44	13	91.2	40
6	Sitzman et al., 2015 (23)	Retrospective	132	47	64	31
7	Büttner et al., 2014 (24)	Retrospective	1102	574	68	51
8	Yadav et al., 2012 (25)	Prospective	1544	718	16	38

Data analysis

STATA.V16 software was used for data analysis. Estimating Sensitivity and Specificity was done with Effect size with a 95% confidence interval (CI) with a fixed effect modal and inverse-variance method. The level of heterogeneity was evaluated using the I² index test (I² < 50% = low levels, 50 < I² < 75% = moderate and I² > 75% = high levels).

Result

The search was conducted based on the mentioned keywords, and 283 studies were found in the introduced databases; After entering the studies into the EndNote.x8 software, duplicate studies were removed, and finally, the abstract of 256 studies was reviewed, and the studies that met the inclusion criteria were left out for the full-text

review; at this stage, 225 studies were removed. The full text of 31 studies was carefully reviewed, and studies that had incomplete data, very low quality, or did not include the inclusion criteria and matched the exclusion criteria were excluded from the study (23 articles); finally, eight articles were selected, and their data were extracted for meta-analysis (**Figure 1**).

Characteristics

Six retrospective studies and two prospective studies have been included in the present article. The number of male and female patients was 4518 and 2413, respectively; a total of 6931 patients were examined; a summary of the data of the selected studies is reported in **table II**.

Evaluation of diagnostic accuracy of physical examination compared to CBCT and CT Intra-oral assessment

Sensitivity of Intra-oral assessment was 17% (ES: 95% CI, -0.34 to 0.74) (I²<0%; P=1.00; low heterogeneity). According to **figure 2**, the subgroup meta-analysis showed Sensitivity to Laceration; the intraoral assessment was 19% (ES: 95% CI, -1.77 to 2.15); Sensitivity of Tooth avulsion assessment was 9% (ES: 95% CI, -1.04 to 1.22).

The sensitivity of the Malocclusion assessment was 13% (ES: 95% CI, -1.25 to 1.52). The sensitivity of Functional and palpation assessment was 45% (ES: 95% CI, -1.51 to 2.41). The sensitivity of Facial pain assessment was 18% (ES: 95% CI, -0.70 to 1.06).

Specificity of Intra-oral assessment was 94% (ES: 95% CI, 0.38 to 1.51) (I²<0%; P=1.00; low heterogeneity). According to **figure 3**, the subgroup meta-analysis showed Specificity of Laceration; the intraoral assessment was 95% (ES: 95% CI, -1.01 to 2.91); Specificity of Tooth avulsion assessment was 98% (ES: 95% CI, -0.15 to 2.11). The specificity of the Malocclusion assessment was 97% (ES: 95% CI, -0.42 to 2.36). Specificity of Functional and palpation assessment was 70% (ES: 95% CI, -1.26 to 2.66). The specificity of Facial pain assessment was 95% (ES: 95% CI, -0.07 to 1.83).

Figure 1: PRISMA flowcharts.

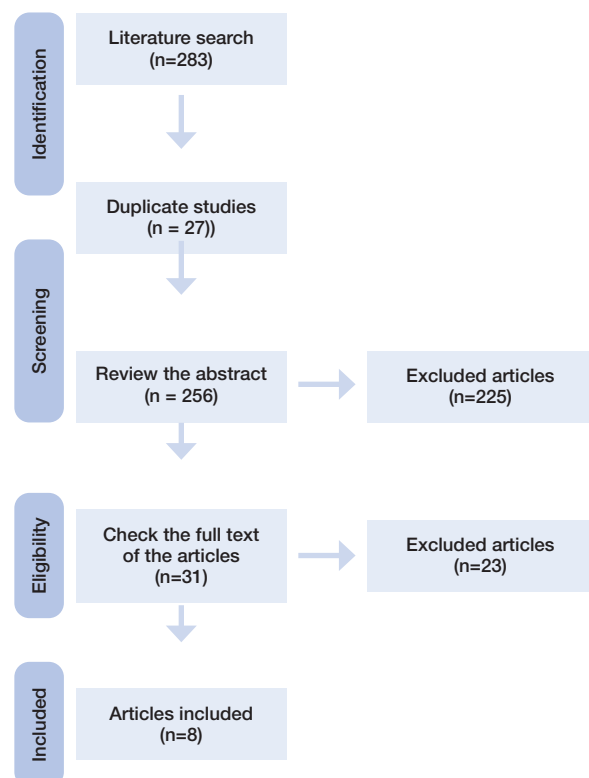


Figure 2: The Forest plot showed the Sensitivity of Intra-oral assessment.

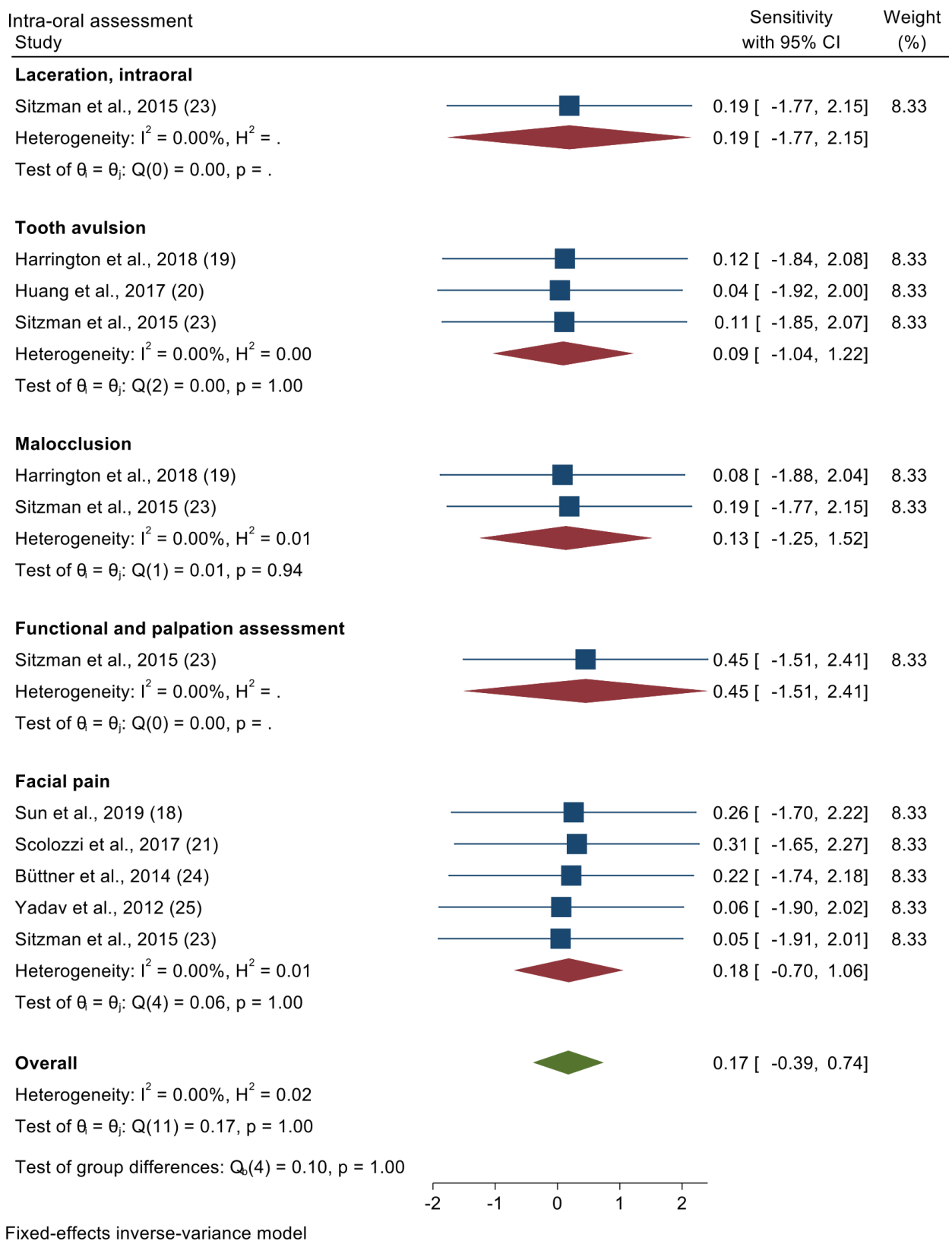
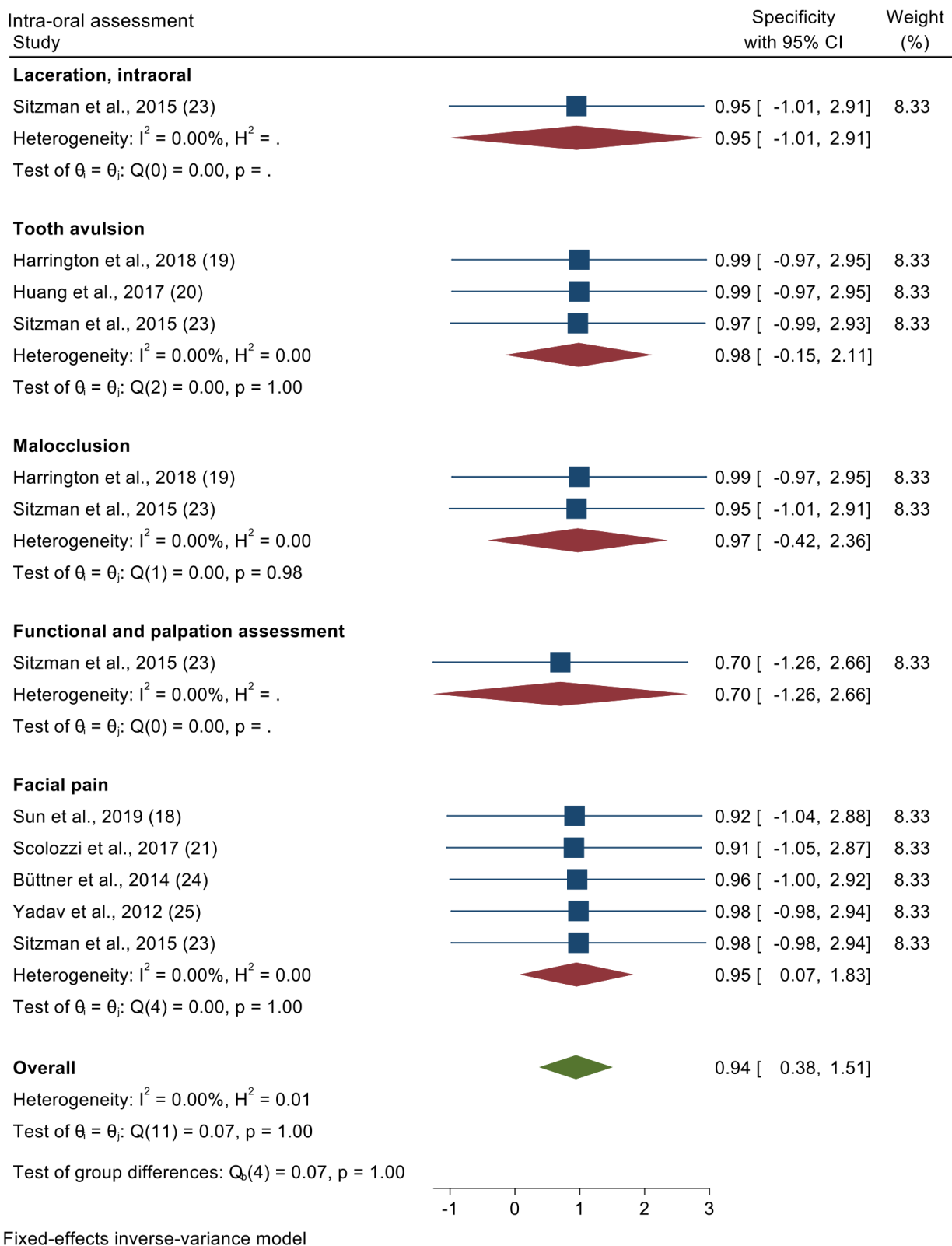


Figure 3: The Forest plot showed the Specificity of Intra-oral assessment.



Discussion

Based on the findings of the present study, comparing the diagnostic sensitivity of physical examination versus imaging methods, the diagnostic sensitivity of intra-oral assessment in mid-face fractures was very low and 17%. Also, by examining the diagnostic feature of physical examination versus imaging methods, the diagnostic sensitivity of intra-oral assessment in mid-face fractures was 94%. Very little heterogeneity was observed between studies, indicating that the findings of the present study provide strong evidence, and high specificity and low sensitivity were reported for the diagnostic accuracy of physical examination related to patient appearance. The studies showed that the diagnostic accuracy for the areas around the mouth, lips, and face using physical examination and CBCT methods is similar to the present findings^{23,26,27}. Based on the findings of the studies^{19,20,23,27}, physical examination can be suitable in diagnosing malocclusion, falling teeth, and intraoral laceration, and its specificity is reported to be around 92 to 98%; in the current study, the specificity was 94%, which is similar to previous findings. Also, the sensitivity in studies has been reported to be around 10 to 21%, which is in line with the findings of the present study.

The findings of the present study conclude that, along with imaging methods, examination through physical examination is suitable for deciding on the treatment of the mid-face fracture. Based on subgroup meta-analysis, it was observed that there is a high diagnostic chance ratio in tooth extraction and malocclusion. In other cases, subgroup meta-analysis showed that physical examination is not a suitable diagnostic method, and it is better to use radiological imaging. Although there was no high heterogeneity between the studies and the findings of the studies were almost close to each other, few studies participated in this meta-analysis, which could be a high risk of bias, and the results should be interpreted with caution. Studies have published findings consistent with the results of the present study, which show that physical examination has low sensitivity in diagnosis^{19,21,23}. According to the results of CT and CBCT

studies, they have high diagnostic advantages, and it is suggested to use imaging methods in diagnosis^{28,29}.

It is suggested that future studies be conducted with higher quality and use CBCT as a reference. Also, the interpretation of CT and CBCT results should be done by a radiologist or maxillofacial surgeon to provide stronger evidence. Clinical trial studies were not found to be consistent with the purpose of the present study, and most of the selected studies were retrospective, so it is suggested to conduct prospective multicenter trials. Since the purpose of physical examination is to help speed up clinical decision-making and to minimize the patient's exposure to imaging rays, considering the diagnostic sensitivity of this method, it is suggested that it be used for intra-oral assessment in intermediate fractures if imaging methods are used.

Conclusion

Based on the findings of the present meta-analysis, it was observed that the diagnostic sensitivity of individual physical examination was low compared to imaging methods, which shows that individual physical examination cannot be accurately relied upon to identify intra-oral assessment in mid-face fractures. On the other hand, the high characteristic in the diagnosis of individual physical examination shows that this method is used to distinguish between patients with mid-face fractures and other traumas. Using individual physical examination and imaging methods for appropriate clinical decision-making is better. There were few studies in this field, so it is suggested that more studies be done to confirm the evidence.

Conflict of Interest

The authors declared that there is no conflict of interest.

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Cross-cultural adaptation and validation of a Moroccan arabic version of the american preoperative anxiety and information scale

Adaptación transcultural y validación de una versión árabe marroquí de la escala americana de ansiedad e información preoperatoria

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Abstract

Background: Anxiety is a common and difficult sensation whose source is often non-specific with deleterious effects on anesthetic management and postoperative outcomes. To effectively prevent and treat preoperative anxiety, patients' anxiety levels must be assessed using reliable measuring instruments. One of these tools is the Amsterdam Preoperative Anxiety and Information Scale (APAIS), which does not yet have a validated Moroccan version. Although the extent and consequences of preoperative anxiety are well documented in the developed world, there are few studies in Morocco.

Objectives: This study aimed to adapt APAIS to measure preoperative anxiety in adult Moroccan patients undergoing surgery. **Methods:** We produced an Arabic version of APAIS and administered it to a sample of 100 adult patients. A forward/backward translation was carried out to ensure a reliable Moroccan cultural adaptation. A pre-test was conducted and the final dialectal Arabic version of APAIS was administered to a sample undergoing elective surgery at the regional hospital of SoussMassa in Agadir. We explored its reliability through Cronbach's alpha and analyzed its validity.

Results: The reliability of the Moroccan APAIS was high with internal consistency and a Cronbach's alpha coefficient is 0.738. The Intraclass correlation coefficient (ICC) for this score is 0.880 (CI95%: 0.817 to 0.928), which corresponds to a good fidelity.

Conclusion: This version of APAIS is valid and can be used reliably in Morocco to appreciate the preoperative anxiety and the desire for information felt by future surgeons. It is a useful screening tool for anxiety and the need for information in clinical practice, particularly because of its brevity and simplicity.

Keywords: Anxiety, Amsterdam preoperative anxiety and information scale (APAIS), crosscultural adaptation, validation.

Resumen

Antecedentes: La ansiedad es una sensación común y difícil cuyo origen es a menudo inespecífico con efectos deletéreos sobre el manejo anestésico y los resultados postoperatorios. Para prevenir y tratar eficazmente la ansiedad preoperatoria, los niveles de ansiedad de los pacientes deben evaluarse mediante instrumentos de medición fiables. Uno de estos instrumentos es la Escala de Ansiedad e Información Preoperatoria de Ámsterdam (APAIS), que aún no cuenta con una versión validada en Marruecos. Aunque el alcance y las consecuencias de la ansiedad preoperatoria están bien documentados en el mundo desarrollado, hay pocos estudios en Marruecos.

Objetivos: Este estudio tenía como objetivo adaptar la APAIS para medir la ansiedad preoperatoria en pacientes adultos marroquíes sometidos a cirugía.

Métodos: Se elaboró una versión en árabe del APAIS y se administró a una muestra de 100 pacientes adultos. Se realizó una traducción hacia adelante/atrás para garantizar una adaptación cultural marroquí fiable. Se realizó un pre-test y se administró la versión final en árabe dialectal del APAIS a una muestra sometida a cirugía electiva en el hospital regional de SoussMassa en Agadir. Se exploró su fiabilidad mediante el alfa de Cronbach y se analizó su validez.

Resultados: La fiabilidad del APAIS marroquí fue alta, con una consistencia interna y un coeficiente alfa de Cronbach de 0,738. El coeficiente de correlación intraclass (CCI) para esta puntuación es de 0,880 (IC95%: 0,817 a 0,928), lo que corresponde a una buena fidelidad.

Conclusión: Esta versión del APAIS es válida y puede utilizarse de forma fiable en Marruecos para apreciar la ansiedad preoperatoria y el deseo de información que sienten los futuros cirujanos. Se trata de un instrumento útil de cribado de la ansiedad y la necesidad de información en la práctica clínica, sobre todo por su brevedad y sencillez.

Palabras clave: Ansiedad, escala de ansiedad e información preoperatoria de Ámsterdam (APAIS), adaptación transcultural, validación.

Introduction

Approximately 60% of patients undergoing surgery are anxious¹. Treating anxiety is a serious concern for improving the patient's experience during the perioperative period. In addition, preoperative anxiety can lead to adverse effects, such as autonomic fluctuation and resistance to anesthetic induction. These problems justify the widespread prescription of sedative premedication worldwide^{2,3}; they are not necessarily related to the actual level of anxiety felt by patients, which depends on several factors that are difficult to assess objectively⁴. Most of the time, nurse anesthetists try to assess their patients' anxiety themselves, which leads to variable results⁵.

There are several instruments to measure preoperative anxiety in patients. One of the most widely used is the Amsterdam Preoperative Anxiety and Information Scale (APAIS). It is a self-report scale which consists of six questions that have been developed and validated to assess a patient's preoperative anxiety. This global index includes three distinct domains: anxiety about anesthesia, anxiety about surgery, and desire for information. Items are scored on a five-point Likert scale ranging from "not at all" to "extremely"⁶. The APAIS has been validated in preoperative patients, whereas the STAI scale has been validated in the general population⁷. Thus, using only six items, the APAIS may become the standard for assessing anxiety in perioperative patients if it is available and validated in all languages⁸. It has been suggested that the APAIS may be associated with pain levels in the early postoperative period⁹.

Today, hospitalization for a scheduled surgical procedure is a common practice for a large part of the population. The entry into the particular "world" of the hospital is not trivial from the lens of the patient who reportedly undergo an unknown experience, full of misrepresentations and awful consequences such as pain, the announcement of diagnosis, the loss of bodily integrity and independence¹⁰.

In developing countries, the assessment of preoperative anxiety is becoming an increasingly relevant issue. The use of validated Anglo-Saxon scales in these countries could alleviate the problem of the remarkable lack of anxiety measurement tools. This approach is most often subject to criticism and poses enormous cross-cultural difficulties¹¹.

Most of the instruments circulating across the globe have been developed by teams of Anglo-Saxon culture, very rarely in French, and almost never in Arabic. The use of a scale in a population requires its adaptation to the mother tongue of the patients and to their social context. This rendering process from and into another language may prove inadequate and a real adaptation is therefore necessary¹².

The purpose of this study was to translate the APAIS into the Moroccan dialectal Arabic (i.e. darija) and to evaluate the psychometric properties of the Moroccan version of APAIS while respecting the latest recommendations of Guillemin and his colleagues.

Methods

The process consisted of two phases. The first phase involved the production of a Moroccan dialectal Arabic version of the APAIS that was semantically equivalent to the original version. In the second phase, we evaluated the psychometric properties of the Moroccan dialectal version, including the internal consistency and reliability, the differential item functioning, and the external validity.

Cross-cultural adaptation: development of an Arabic dialect version of the APAIS:

Forward translation: The original version of the APAIS was translated into dialectal Arabic by two Moroccan citizens, one of whom is a health professional (nurse in anaesthesia and resuscitation) who knows the questionnaire and its applications, and the other is a professor of the English language who does not.

Synthesis: A meeting was held on the Google Meet Platform between the two translators (T1 and T2) in the presence of a professor in anesthesia and intensive care in order to have a common translation taking into account the differences between the two initial translations.

Back-translation: The common T-12 Moroccan Arabic dialect version of the APAIS was back-translated into English by a back-translator without having access to the original questionnaire.

Expert committee review: A meeting was held on Google Meet between the members of the expert committee which includes professionals in the fields of health (nurse anesthetists and a professor of anesthesia and intensive care), methodology, translators and back translators. With the view to develop a pre-final version of the APAIS, and to achieve equivalence between the original and target versions.

Pre-Testing: To ensure that T-12 was understandable to the majority of patients and did not pose translation problems, we had patients from the population interviewed item by item. The 30 patients who were recruited for this test were all patients operated on, at the Hassan 2 Hospital in Agadir; they were all asked to participate in this project and to contribute to it. All patients were volunteers.

Validation process: evaluation of the psychometric properties

The psychometric evaluation covered three domains: content validity, reliability, and acceptability.

Content Validity: It aims to analyze the content of the questionnaire and to ensure that it is representative.

Reliability: internal validity (Allows us to ensure that the items are consistent with each other. Within the

questionnaire, it was explored using cronbach's alpha). Reproducibility (From the results of patients who completed the questionnaire twice and whose mental state did not subjectively change between the two administrations, an intraclass correlation coefficient (ICC) was calculated). Internal Validity (The factor analysis was performed by principal component analysis followed by factor extraction). **Acceptability:** To verify the acceptability of this test, the investigators compared the percentage of patients who completed the questionnaire with the number of patients who were asked to take it.

Study subjects:

A non-probabilistic random sampling at the Hassan II Souss Massa hospital was carried out to validate the results of this study with a sample size $n=100$, which will be constituted of Moroccan patients over 18 years old having a non-emergency surgery whatever the type of anaesthesia (general anaesthesia, locoregional anaesthesia, local anaesthesia),. Each individual should be able to understand Moroccan dialectal Arabic and fill in a self-evaluation questionnaire.

We excluded patients, under 18 years old and/or having emergency surgery, who are unable to understand Arabic and fill out a questionnaire, along with patients who refused to participate in the study.

Data collection

After they had shown consent to participate in the study, the patients answered individually in the presence of the student nurse anesthetist (investigator 1). They were given a questionnaire sheet and had to write down their responses by ticking the proposition of each item that applied most to them. Some characteristics were also collected: gender, age, type of anesthesia, ASA classification, level of education and type of surgery. The data collection was anonymous.

In order to test the reproducibility of the test, patients were asked to answer the questionnaire again in the presence of another student nurse anesthetist (investigator 2) just before accessing the operating room.

Ethical issues:

Because APAIS is copyrighted by Dr. Nelly Moerman and Dr. Frits Van Dam, the principal investigators of this project received full permission to use it for the transcultural adaptation process by email.

The project is approved by the Bioethics Consultative Commission Faculty of Sciences Agadir.

Statistical analysis:

Quantitative variables were described by means and standard deviations; however, qualitative variables were described by numbers and percentages. Statistical analysis was performed using SPSS version 22 software.

Cronbach's Alpha: A statistical tool used in psychometrics to measure the internal consistency (or reliability) of questions asked in a test. Many authors consider an alpha value above 0.7 to be satisfactory.

The intra-class correlation coefficient ICC: Note that the ICC is used for test-retest (repeated measures of the same individual) and intra-rater (multiple scores from the same raters) reliability analysis.

Factor analysis: a statistical method used to describe variability among observed, correlated variables in terms of a potentially lower number of unobserved variables called factors. Its purpose is to extract and visualize important information from a multivariate data table. PCA synthesizes this information into only a few new variables called principal components.

A correlation matrix: It is used to evaluate the dependency between several variables at the same time. The result is a table containing the correlation coefficients between each variable and the others.

The Kaiser–Meyer–Olkin (KMO) test: a statistical measure to determine how suited data is for factor analysis. The test measures sampling adequacy for each variable in the model and the complete model.

Results

Recruitment of translators and experts:

The original version of APAIS has been adapted to the Moroccan culture by Moroccan translators and experts of different occupations: a professor in anesthesia and resuscitation, two permanent instructors at the Higher Institute of Nursing Professions and Health Techniques (ISPITS) with the profile of a nurse in anesthesia and resuscitation, a professor of English Studies, a teacher of English language, a logistician pharmacist, a professor of higher education in the United States and a health statistician and temporary instructor of biostatistics, epidemiology and methodology at the Higher Institute of Nursing and Health Professions (ISPITS) Agadir.

Forward translation reconciliation

The original version of APAIS was translated into dialectal Arabic by two Moroccan speakers, one of whom is a health professional (nurse in anesthesia and resuscitation) who knows the questionnaire and its applications and the other is an English language teacher who does not, yet, he has a mastery of the original language (English) and target language (Arabic). A meeting was held on Google Meet Platform between the two translators in the presence of a Professor in Anesthesia and Resuscitation. The translators tried to stay faithful to the meaning of the written questionnaire but also to keep the designation of each item from 1 to 5. The discussion between the members of the committee gave rise to a translation (T-12) resulting from a consensus between them for each translation discrepancy, or with new, more relevant adaptations in order to best adapt the scale and reach an

intermediate translation.

The online meeting made it possible to better detect translation errors, mistranslations, inaccuracies, and/or flawed interpretations, to resolve any disagreement between the translators, and to eventually accommodate the questionnaire to the Moroccan culture and lifestyle.

Back translation review

The common T-12 Arabic dialect version of the APAIS was back-translated into the English language by an English language teacher, without having access to the original questionnaire. This step aims to ensure that the translated version reflects the same semantic and pragmatic content as the original version. This stage is intended to highlight unclear wording and inaccuracies in the translation.

After a long debate among the members of the expert committee and their remarks about the linguistic choices in terms of translation, the T1/2 version and the first back translation of the latter, the committee emphasized the importance of a second back translation to fully assimilate the goal of having a more reliable draft version that best represents the Moroccan culture. Hence, the need to involve another version which was reviewed by a doctor of pharmacy, a professor of higher education in the United States who is neither aware nor informed of the questionnaire.

Synthesis and obtaining an experimental version by the committee

After consolidating all versions of the questionnaire against the original APAIS and after checking the equivalences between the source and target languages and the accuracy of the medical terminology, a consensus was attained by the members of the expert committee, with the intention to validate the equivalences of items (the clinical manifestations evaluated are significant in both cultures), conceptual (the importance of the term evaluated in each of the two cultures) and semantic (conservation of the same meaning).

The expert committee focused on content and appearance and considered the pre-final version to be valid, which was confirmed by the test patients during the individual qualitative interviews.

Pre-test of the experimental version:

The population

The population consisted of 100 future operated Moroccan patients with a mean age of 43.5 years +/- 18.76 years with extremes ranging from 18 to 95 years. The patients included were of both gender with a clear male predominance, (55% of men and 45% of women) of different educational levels. 64% of the patients were ASA1, 25% are ASA2, 9% ASA3 and the rest are ASA4.

To ensure that the Moroccan APAIS measures what it is supposed to measure, it must meet the criteria of reliability and validity.

The validation of the Moroccan APAIS and the evaluation of its psychometric properties

• Reliability (Reproducibility):

Beginning with the internal consistency which ensures that the items are consistent with each other and it is evaluated by the cronbach's alpha which is 0.738 which shows that the Moroccan APAIS is homogeneous and measures the same construct.

In order to assess the reproducibility of the Moroccan APAIS, it was necessary to measure and assess the concordance between the investigators for each item and for the total score using the intra-class correlation coefficient.

The average CCI shows excellent repeatability at 0.880.

• Validity:

Validity of content and appearance: The panel focused on the content and appearance and considered the final version to be good. This was confirmed by the patient-tests in the qualitative individual interviews.

Acceptability: The questionnaire did not have any acceptability problems as all patients responded with no exceptions.

Internal construct validity: The test allows us to verify how variables describing the same dimension have consistent groupings.

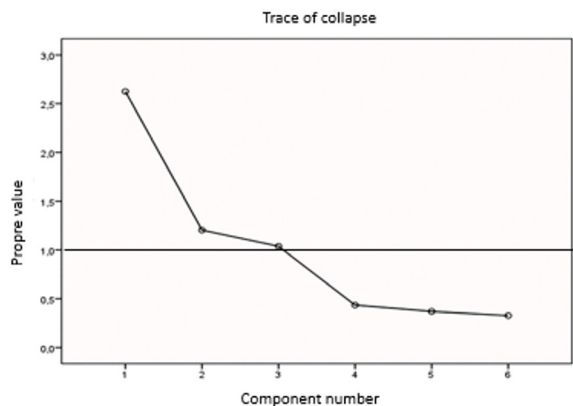
The establishment of this validity calls for descriptive statistical methods in the form of factorial analysis by principal component analysis, the first step of which is to calculate the KMO index, which is 0.65, so that significant sample (quality sample) will be created.

Then we move on to the correlation matrix, where we observe that the most correlated items are items 1 and 2, with a correlation of 0.582, items 3 and 6, with a correlation of 0.563, and items 4 and 5 with a correlation of 0.55, while the other items are mainly less correlated (e.g., the correlation between items 4 and 1 is 0.289).

Extraction of factors: From the table summarizing the total variance explained, three principal components can be extracted by looking for eigenvalues greater than 1, in fact we can reduce the six items into three components.

When studying the links between several variables, there is a risk of losing information. According to this table, the three components generate 81.14% of the total score information (normally more than 70% of the information should be extracted).

Figure 1: Graph representing the factor extraction.



According to the figure, we have three components with an eigenvalue greater than 1, so, graphically, we can represent the six items in three components (factors).

Interpretation of the factors: What are the items that make up each component? To answer this question, it was necessary to make a component diagram in space after rotation and a table of component matrix.

In accordance with the coefficients of the items at the formation of the components, presented in the Table of components matrix, it can be seen that the first component can present the items 4 and 5, the items 3 and 6 are summarized by the second component while the third component can define the items 1 and 2. These results are similar to those of the component diagram in the space after rotation.

In fact, the naming of the principal components is:

- Component 1: anxiety related to surgery.
- Component 2: desire for information.
- Component 3: anxiety related to anesthesia.

Discussion

Preoperative anxiety is usually experienced by future operated patients and its incidence, although not exactly determined, seems to be very high, ranging from 60 to 80%.

The objective of this study was to produce a Moroccan version of the APAIS. The method used was consistent with the guidelines established in the literature.

This study was carried out in two main stages: the translation of the APAIS questionnaire into dialectal Arabic and its validation. The first step consisted of the translation and back-translation of the questionnaire according to the international recommendations for the cross-cultural

adaptation of questionnaires in the health field. The pre-final version was then revised by a committee of experts, then tested out on a group of 30 participants, before arriving at the final translated version.

The second step was the validation of the translated version. The analysis of the psychometric properties of the translated version included reliability and validity. The validation process revealed the strong psychometric properties of the Moroccan Arabic version regarding reliability and validity.

The statistical analysis of the Moroccan version of the APAIS showed good accuracy in terms of equivalence and correspondence. Indeed, acceptability was noted, with no refusals, missing data, nor discrepancies observed. Linguistic validity was confirmed to transform the meaning from the English language to the Arabic language it is translated into. In this study, the back-translation method was used and the scale was translated according to the literature by expert researchers who were familiar with both languages and the specificities of the Moroccan culture.

To ensure the metric qualities of the translated instrument, Cronbach's alphas was performed to obtain internal consistency indices. These analyses allowed us to verify the homogeneity of the scale. A good internal consistency was found, Cronbach's alpha = 0.738. This value shows that the Moroccan Arabic version of the APAIS is homogeneous and measures the same construct. The test-retest reliability measured by the intra-class correlation coefficient (ICC) was good with ICC = 0.880 (95% CI: 0.817-0.928); thus, the Moroccan Arabic version of the APAIS has a fair confidence level.

The factor analysis extracted three factors with an eigenvalue greater than 1, which explains 81.14% of the total variance. hence, this three-dimensional structure was found as demonstrated by the French version of the APAIS: anxiety related to anesthesia (two items), anxiety about surgery (two items), and desire for information (two items).

The validity and reliability results conducted in this study indicate that the Moroccan Arabic version of the APAIS can be used easily to detect the presence and severity of preoperative anxiety symptoms and the need for information. It can be a useful alternative to measure the level of preoperative anxiety in patients who will undergo surgery.

Thanks to this empirical study, we were able to make Morocco join the list of countries where the cross-cultural adaptation and validation of the APAIS has been developed.

This study could contribute to the improvement of the management of future Moroccan surgical patients by correctly assessing their level of anxiety and demand

for information, thus preventing anxiety-related complications and improving their experience during the perioperative period.

Disclaimer

No funding was received for this study.

Conflict of interest

The authors declare that they have no conflict of interest.

Informed consent

The study is not an experimental research, and no personal information is used

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Hyperuricemia and shift work: A systematic review and meta-analysis

Hiperuricemia y trabajo por turnos: Una revisión sistemática y metanálisis

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Abstract

Objective. Update the available scientific evidence on the association between shift work and the appearance of hyperuricemia in workers.

Methods: The PICOS strategy was used to conduct a systematic review and meta-analysis of studies found in Pubmed, Web of Science, EBSCOhost, Scopus, and Cochrane Library databases which were published between January 2009 and September 2019 in English or Spanish. We used the CASPe and PRISMA-P 2015 systematic review analysis tools. Study quality was assessed using the STROBE and CONSORT statements. The GRADE-Pro tool was used to evaluate the evidence and the quantitative synthesis was produced with RevMan.

Results: Eight articles were used for the review and five for the meta-analysis. The average difference in uric acid between shift work and non-shift work was not significant. The meta-analysis showed an overall mean difference of -0.04 95% CI (-0.11, 0.04) $p=0.32$. The heterogeneity of the analysis was low ($I^2= 40\%$) $p=0.15$.

Conclusions: Evidence from the results shows that shift work is not associated with hyperuricemia. However, more research with greater control of bias is needed to support the results found.

Key words: Hyperuricemia; shift work schedule; uric acid; workers; systematic review; meta-analysis.

Resumen

Objetivo: Actualizar la evidencia científica disponible sobre la asociación entre el trabajo por turnos y la aparición de hiperuricemia en trabajadores.

Métodos: La estrategia PICOS se utilizó para realizar una revisión sistemática y un metanálisis de los estudios que se encuentran en las bases de datos Pubmed, Web of Science, EBSCOhost, Scopus y Cochrane Library que se publicaron entre enero de 2009 y septiembre de 2019 en inglés o español. Se utilizaron las herramientas de análisis de revisión sistemática CASPe y PRISMA-P 2015. La calidad del estudio se evaluó mediante las declaraciones STROBE y CONSORT. Se utilizó la herramienta GRADE-Pro para evaluar la evidencia y la síntesis cuantitativa se realizó con RevMan.

Resultados: Se utilizaron ocho artículos para la revisión y cinco para el metanálisis. La diferencia promedio en el ácido úrico entre el trabajo por turnos y el trabajo sin turnos no fue significativa. El metanálisis mostró una diferencia media global de -0,04 IC del 95 % (-0,11; 0,04) $p=0,32$. La heterogeneidad del análisis fue baja ($I^2= 40\%$) $p=0,15$.

Conclusiones: La evidencia de los resultados muestra que el trabajo por turnos no está asociado con la hiperuricemia. Sin embargo, se necesita más investigaciones con mayor control de sesgos para respaldar los resultados encontrados.

Palabras clave: Hiperuricemia; trabajo a turnos; ácido úrico; trabajadores; revisión sistemática; metanálisis.

Introduction

According to the International Labour Office (ILO), working in shifts is “a method of organization of working time in which workers succeed one another at the workplace so that the establishment can operate longer than the hours of work of individual workers at different daily and night hours”¹. This way of working is increasing. In Spain in 2017, 12.5% of the workers worked shifts, in 2018 this number increased to 13.2%. Among sectors, the chemical, along with the metal, health and social sectors cover 40% of these^{2,3}.

Shift work negatively influences not only a person's physical and mental health but also their social, work and family life⁴. In shift workers there is a higher prevalence of risk factors such as smoking, dyslipemia and obesity, and the risk of cardiovascular disease is increased⁵⁻⁷.

However, due to the multitude of factors affecting shift work, it has not been possible to decide which are relevant. Moreover, in the literature, there is not consensus in the findings of variably designed studies conducted to date. There are studies which confirm the relationship between shift work and higher cholesterol, triglycerides, and glucose^{8,9}, which either totally or partially contradict other similar studies^{10,11}, in which this relationship is not evident.

One of the markers that has been assessed as an independent marker of cardiovascular diseases and has been proposed as a possible risk factor is uric acid¹²⁻¹⁴.

There are few studies on the relationship between this marker and shift work. It has recently been reported that shift work acts as a protective factor against hyperuricemia¹⁵, but this theory cannot be taken as conclusive since other authors have either found no such link¹⁰ or have found one, but with serious limitations^{16,17}.

It is, therefore, necessary to evaluate studies that relate shift work and the occurrence of hyperuricemia in the workplace. Our aim was to know if shift workers have higher uric acid levels than non-shift workers.

Materials and methods

Protocol

In September 2019, a systematic review of the literature was performed according to the PRISMA-P 2015 methodology¹⁸. Two external reviewers evaluated the protocol separately. The review procedure was recorded in the PROSPERO systematic review database (reference number CRD42020180188).

Databases and Search Strategy

The PICOS strategy was used to identify studies on the presence of hyperuricemia in shift workers compared to

non-shift workers to test the claim that shift workers have higher uric acid levels (Population: Workers; Intervention: Shift work; Comparator: Shift workers compared to non-shift workers; Outcome: Hyperuricemia). An independent search was conducted by two of the authors (DPJ, MRS) in the following databases and platforms: Pubmed, Web of Science, EBSCOhost, Scopus and Cochrane, including all types (study type) of full-text documents published over the last ten years (January 2009 to September 2019), in English and Spanish. In addition, the search was also carried out in the grey literature. Searches were performed in the System for Information on Grey Literature in Europe (OpenGrey) and the Grey Literature Report (all types of documents).

The search strategy was based on identifying the terms to be searched according to three categories. The first group of terms was connected to the independent MeSH variable “shift work schedule” and the free terms “shift work”, “rotating shifts”, “night work”, “rotative work”, “shift work disorder” and “shift worker”. The second group of terms to the dependent MeSH variables “hyperuricemia” and “uric acid”. The third group related to the population, with the MeSH term “workers”. The combinations of terms for the three categories in the fields “Title”, “Abstract” and “Keywords” determined the searches to be carried out.

Table I shows these combinations and the number of studies selected.

Eligibility criteria

The criteria for selecting the items were: workers aged 18 and over who were subjected to any form of shift work where uric acid was measured. Those studies whose original language was not Spanish or English; which were more than 10 years old; or where shift work was not directly or indirectly related to uric acid were excluded, as well as opinion articles, editorials, or other non-scientific forms of communication. Eligibility was ensured by applying both inclusion and exclusion criteria.

Studies Selection

Two authors (M.R.S. and D.D.P.J.) separately examined the 238 records obtained from the searches for duplicates. Afterwards, three researchers (R.J.M., A.M.M. and R.M.L.) read the titles and abstracts separately to match the eligibility criteria, eliminating those in which one of the variables was missing in these fields. The gray literature search did not retrieve any new studies. After the full-text review of the 20 selected articles, 10 were removed because, although shift work and uric acid were mentioned in the title, abstract or keywords, they were not relevant. One was not deemed relevant because although the selection had been filtered to only include articles in English or Spanish, it appeared in another language (Japanese). Another was eliminated because it was the transcribed oral communication of a previously selected article. Finally, eight articles remained for the qualitative

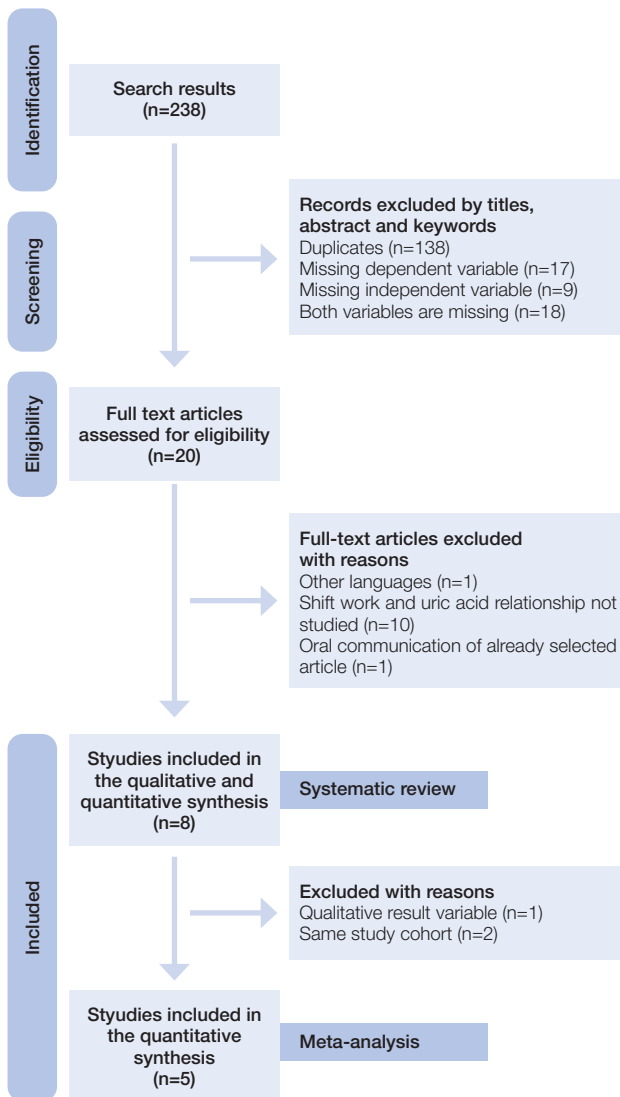
synthesis (systematic review). Of these, five were left for quantitative analysis (meta-analysis), one was excluded because the outcome variable is qualitative and two

because they were based on the same cohort as another study (Figure 1).

Table 1: Search keywords used for the different databases.

Database	Keywords	Result	Pre-selected	Selected	Pre-selected total	Selected total
Pubmed	"shift work Schedule" AND ("uric acid" OR hyperuricemia)	5	5	3	16	3
	"shift work" AND ("uric acid" OR hyperuricemia)	8	8	0		
	"night work" AND ("uric acid" OR hyperuricemia)	2	2	0		
	"rotative work" AND ("uric acid" OR hyperuricemia)	0	0	0		
	"rotating shifts" AND ("uric acid" OR hyperuricemia)	0	0	0		
	"shift work disorder" AND hyperuricemia	1	1	0		
	"shift work disorder" AND "uric acid"	4	0	0		
Web of Science	"shift work schedule" AND "uric acid"	8	8	1	40	2
	"shift work Schedule" AND hyperuricemia	1	1	0		
	"shift work" AND "uric acid"	10	10	1		
	"shift work" AND hyperuricemia	3	3	0		
	"rotating shifts" AND "uric acid"	1	1	0		
	"rotating shifts" AND hyperuricemia	0	0	0		
	"night work" AND "uric acid"	1	1	0		
	"night work" AND hyperuricemia	0	0	0		
	"rotative work" AND "uric acid"	0	0	0		
	"rotative work" AND hyperuricemia	0	0	0		
	"shift work disorder" AND hyperuricemia	5	0	0		
	"shift work disorder" AND "uric acid"	10	7	0		
	"shift worker" AND "uric acid"	14	8	0		
"shift worker" AND hyperuricemia	1	1	0			
EBSCOhost	"shift work schedule" AND "uric acid"	4	4	0	35	0
	"shift work schedule" AND hyperuricemia	0	0	0		
	"shift work" AND "uric acid"	10	10	0		
	"shift work" AND hyperuricemia	3	3	0		
	"night work" AND "uric acid"	3	3	0		
	"night work" AND hyperuricemia	0	0	0		
	"rotative work" AND "uric acid"	0	0	0		
	"rotative work" AND hyperuricemia	0	0	0		
	"rotating shifts" AND hyperuricemia	0	0	0		
	"rotating shifts" AND "uric acid"	0	0	0		
	"shift work disorder" AND "uric acid"	10	7	0		
	"shift work disorder" and hyperuricemia	0	0	0		
	"shift worker" AND "uric acid"	10	7	0		
	"shift worker" AND hyperuricemia	2	1	0		
Scopus	"shift work schedule" AND "uric acid"	0	0	0	111	3
	"shift work schedule" AND hyperuricemia	0	0	0		
	"shift work" AND hyperuricemia	3	3	0		
	"shift work" AND "uric acid"	11	11	1		
	"night work" AND "uric acid"	37	37	2		
	"night work" AND hyperuricemia	4	4	0		
	"rotating shifts" AND hyperuricemia	6	6	0		
	"rotating shifts" AND "uric acid"	29	29	0		
	"rotative work" AND "uric acid"	0	0	0		
	"rotative work" AND hyperuricemia	0	0	0		
	"shift work disorder" AND "uric acid"	8	6	0		
	"shift work disorder" AND hyperuricemia	0	0	0		
	"shift worker" AND hyperuricemia	2	2	0		
"shift worker" AND "uric acid"	22	13	0			
Cochrane	"shift work schedule" AND "uric acid"	0	0	0	0	0
	"shift work schedule" AND hyperuricemia	0	0	0		
	"shift work" AND "uric acid"	0	0	0		
	"shift work" AND hyperuricemia	0	0	0		
	"night work" AND "uric acid"	0	0	0		
	"night work" AND hyperuricemia	0	0	0		
	"rotating shifts" AND "uric acid"	0	0	0		
	"rotating shifts" AND hyperuricemia	0	0	0		
	"shift work disorder" AND "uric acid"	0	0	0		
	"shift worker" AND uric acid	0	0	0		
	"shift work disorder" AND hyperuricemia	0	0	0		
	"shift worker" AND hyperuricemia	0	0	0		
	"rotative shift" AND hyperuricemia	0	0	0		
	"rotative shift" AND "uric acid"	0	0	0		

Figure 1: Flow chart of study selection.



Quality Assessment

The Spanish critical reading skills program analysis tool, CASPe, was used¹⁹⁻²¹. For the quality analysis, recommendations from the STROBE statement (maximum 22 points for observational studies)²² and the CONSORT statement (maximum 25 points for randomised cross-over trials) were followed²³. The sub-sections of each item in the declarations were assessed independently, and if any of the sub-sections did not reflect the recommendation, it was considered not to comply.

Moreover, the GRADE-Pro tool was used to create the evidence profile, and summary of findings. The risk of bias was evaluated using the Cochrane and Revman 5.3 tool, which included the selection bias, performance bias, attrition bias, reporting bias and other biases.

Data Extraction

From each article, one reviewer (D.D.P.J.) was in charge of extracting the data, which was subsequently

verified by another reviewer (C.V.E.). The following data was gathered: author and year, country, study design, number of participants, occupation, ages, minimum time worked, sociodemographic variables, life factors and anthropometric measurements, forms of data collection, the definition of hyperuricemia, description of the shift, characteristics of the shift (the type and frequency of rotation, working hours per shift, number of days per month), main type of statistical analysis, main findings/conclusions and limitations. The main characteristics of the studies analysed are shown in **table II**. As no discrepancies were found between the two authors who carried out the searches (kappa index = 1), it was not deemed necessary for a third author to intervene.

Statistical analysis

For the meta-analysis, three authors (D.D.P.J, MRS and RML) used the Cochrane Review Manager software (RevMan 5.3) to perform the statistical analyses and create the forest and funnel plot figures. Due to the effect size variation in the different studies, a meta-analysis was carried out using the Mantel-Haenszel random-effects method and the DerSimonian and Laird model. The difference between the means (mg/dL), with a 95% confidence interval, was used to assess the effect size of shift work on uricemia. Heterogeneity was assessed using the Chi-square test and the inconsistency index (I²). According to the Cochrane Collaboration tool, heterogeneity is classified as: unimportant (0-40%), moderate (30-60%), substantial (50-90%) and considerable (75-100%). A sensitivity analysis was performed for the results of the meta-analysis, in which more than two studies were included, to determine the effect of each trial on the results obtained.

Results

Qualitative Synthesis

In relation to the geographical scope, six of the articles reviewed were Asian (China, Korea and, Japan) and two were European (Netherlands and Austria). According to their design, three had a cross-sectional design, one was a prospective randomised cross-over trial, and the rest were cohort studies. Moreover, three studies came from the same cohort, where 6,886 or 7,104 workers participated, so the total number of workers studied between these and the rest of the studies ranged from 14,863 to 15,081 workers.

The workers were from the energy, automobile, and steel industries and the health services. One study did not detail this aspect; it only referred to shift workers from a cohort study funded by the Dutch National Institute of Public Health and Environment. The ages ranged from 18 to 60 and time spent in the role varied from 1 to 13.9 years (on average).

Several sociodemographic variables, anthropometric measurements and biological samples were taken in all the studies (Table II). Some of the less commonly studied variables included chronotype and time spent awake and asleep, all of which appeared in only one study.

Table II: Summary of the studies included in the review and quantitative synthesis: 2009-2019 (N=8).

Author and year	Country	Study design	No of workers	Worksite	Ages	Minimum time in the workplace	Variables (socio-demographic, life factors and anthropometric measurements)	Data collection procedure	Definition of hyperuricemia	Shift description	Shift characteristics (type of rotation, rotation speed, working hours per shift, number of days per month)	Main type of statistical analysis	Main findings or conclusions	Limitations
Shen et al. (2019) *	China	Cross-sectional	4180	Employees of 23 different workplaces belonging to an electric power industry above 2600 m of altitude	18-60	2 years	Age, sex, educational level, occupation. Smoking, alcohol consumption, fruit and vegetable intake and dietary pattern. Weight and height, BMI, blood pressure Cholesterol, triglycerides, uric acid, glucose.	Self-administered questionnaire (measurements by trained health care professionals in hospital).	≥ 416 μmol/L (7 mg/dl) in men, 357 μmol/L (6 mg/dl) in women	Daytime work/ Shift work	Not collected	Multilevel logistic regression model and restricted cubic spline	Shift workers had a higher prevalence of hyperuricemia in men, not women. After multivariate regression, hyperuricemia was negatively associated with shift work in men (protective factor).	No specific data related to intake were collected (only reporting whether or not they ate little fruit or vegetables). No drug treatments were also collected. No kidney function was measured.
Hulsegge et al. (2019)*	Netherlands	Cohort	1061 workers form the first period (1987-91).	Not detailed	20-59	1 year	Cardiometabolic risk factors (anthropometry, blood pressure, lipids, non-fasting glucose, diabetes, gamma-glutamyltransferase, C-reactive protein, uric acid, cystatin C, creatine and estimated glomerular filtration rate). Education, lifestyle, use of antihypertensive and cholesterol medication, smoking, drinking, leisure time physical activity and occupational physical activity.	Questionnaire, anthropometric measurements and biological samples	>7.0 mg/dl in men, >6 mg/dl in women	Worked evening shifts (i.e. shifts ending before midnight), night shifts (i.e. shifts that continued or started after midnight), sleep shifts and rotating shifts	The year of the beginning and end of the shift work , number of years and months in total. The frequency was classified as: shifts without nights, 1 to 4 nights per month and ≥5 nights per month. Compare between day and shift work ≥= ten years or <10 years.	Linear mixed models	No relation was found.	No details were given on types of work, nor on the direction and speed of rotations
Oh et al. (2014)*	Korea	Cross-sectional	1029 men, 753 shift workers	Steel Company workers	Less than 20 to over 50, but not in detail	In shifts 13.9 years on average	Smoking status, alcohol consumption, physical activity, and others; medical history of hypertension, diabetes mellitus, hyperlipidemia, and current medications. Glucose, total cholesterol, triglycerides, HDL cholesterol, AST, ALT,γ-GTP, blood urea nitrogen, creatinine, and serum uric.	Self-administered questionnaires, anthropometric measurements and biological samples.	≥7.0 mg/dl	Daytime work/ Shift work	Daytime from 9 to 17, other hours are considered shifts. No further specification is given.	Logistic regression	After regression, an association was found between shift work and hyperuricemia. Daytime workers were more active.	Auto-questionnaires, lack of data on shift work. Dietary patterns were not monitored.
Rauchenzauner et al. (2009)*	Austria	Prospective randomized cross-over trial between 2005 and 2006.	30	Departments of Internal Medicine, Neurology, and Otorhinolaryngology at the Medical University Innsbruck	33,5 (31-36)	76 months (58 -106)	Sleep and wake time, number of awakenings, time to wake up, Glucose, urea, creatinine, total cholesterol, triglycerides, HDL, C-reactive protein, IL-6 and TNF-α, urine parameters for adrenalin and noradrenalin, 24 hours ECG. (Uric acid is not detailed).	Self-administered questionnaires and biological samples.	Not detailed	24 h on-call duty and 8 h not on-call duty.	On-call duty: 8 to 16,30 + 16 h. Not on-call duty: 8 to 16,30. 4 on-call duty per month.	Wilcoxon's signed Rank test and Spearman's correlation coefficient.	Decreased uric acid values during 24-hour shifts. Higher concentrations after 24-hour shifts compared to non-shifts	Low sample size. Variable shift duration.
Kawada and Otsuka. (2014)**	Japan	Prospective cohort study between 2008 and 2011	1677. Daytime work 868, 2-shift workers 686, 3-shift workers 99, and others, 23.	Car manufacturing company	Daytime work 44.4 (5.5), 2-shift work 44.3 (5.8) and 3-shift work 44.5. (5.2)	Not detailed	HDL, triglyceride, glucose, uric acid, serum insulin. Smoking, alcohol intake, habitual exercise, blood pressure, waist circumference.	Self-administered questionnaires, anthropometric measurements and biological samples.	Not detailed	Daytime from 8 to 17, 2-shifts started at 6,30 or 15 h. 3-shifts started at 6,30, 14,30 and 22,30 h.	8 hours per shift.	Logistic regression	Uric acid and morning/evening shift work contributed to the development of metabolic syndrome. After regression as well.	Self-administered questionnaires, lack of data on shift work (no direction of rotation, years in shifts, changes between shifts) No direct uric acid/ shift relationship.
Uetani et al. (2011)**	Japan	Prospective cohort study between 1991 and 2005***	6886, 4079 daytime workers, 2807 shift workers	Steel company	Not detailed	Not detailed	Weight, Height, BMI, age, total cholesterol, creatinine, glycosylated hemoglobin A1c, AST, GGT, uric acid. Smoking and drinking habits, habitual exercise.	Self-questionnaires verified in personal interview during health check-ups, anthropometric measurements and biological samples	Not detailed	Daytime work/ Shift work. Irregular shift work such as 24 h and fixed night work were excluded.	Clockwise rotation. 5 day shifts, 2 rest days, 5 evening shifts, 1 rest day, 5 night shifts, 2 rest days. Every shift started at 7, 15 and 23 h.	Pooled logistic regression	At the start of the study, those who were overweight on day shifts had more uric acid than those on rotating shifts (no regression study).	Exercise measured as regular or non-exercise. No variables related to living, working or dietary intake or socioeconomic situation. There were no further conclusions between shift work and uric acid using logistic regression.

Author and year	Country	Study design	No of workers	Worksite	Ages	Minimum time in the workplace	Variables (socio-demographic, life factors and anthropometric measurements)	Data collection procedure	Definition of hyperuricemia	Shift description	Shift characteristics (type of rotation, rotation speed, working hours per shift, number of days per month)	Main type of statistical analysis	Main findings or conclusions	Limitations
Dochi et al. (2009)**	Japan	Prospective cohort study between 1991 and 2005***	8886, 4079 daytime workers, 2807 shift workers	Steel company	Not detailed.	Not detailed.	Weight, Height, BMI, age, total cholesterol, creatinine, glycosylated hemoglobin A1c, AST, GGT, uric acid. Smoking and drinking habits, habitual exercise.	Self-questionnaires verified in personal interview during health check-ups, anthropometric measurements and biological samples	Not detailed.	Daytime work/ Shift work	Clockwise rotation. 5 day shifts, 2 rest days, 5 evening shifts, 1 rest day, 5 night shifts, 2 rest days. Every shift started at 7, 15 and 23 h.	Pooled logistic regression	At the beginning of the study, uric acid levels were higher in day workers than in shift workers (no regression study).	Exercise measured as regular or non-exercise. No variables related to living, working, dietary intake or socio-economic situation (although the latter were considered equal between shifts and non-shifts). They did not evaluate the history of shift change. There are no further conclusions between shift work and uric acid with logistic regression.
Suwazono et al. (2009)**	Japan	Prospective cohort study between 1991 and 2005***	7104, 4219 daytime workers, 2885 shift workers	Steel Company. No women in shift work.	Not detailed.	Four groups of 0 years (control), 1-3 years, 4-10 years and over 11 years.	Weight, Height, BMI, age, total cholesterol, creatinine, glycosylated hemoglobin A1c, AST, GGT, uric acid. Smoking and drinking habits, habitual exercise.	Self-questionnaires verified in personal interview during health check-ups, anthropometric measurements and biological samples	Not detailed.	Daytime work/ Shift work	Clockwise rotation. 5 day shifts, 2 rest days, 5 evening shifts, 1 rest day, 5 night shifts, 2 rest days. Every shift started at 7, 15 and 23 h.	Pooled logistic regression	At the beginning of the study, uric acid levels were higher in day workers than in shift workers (no regression study). Shift workers were older, drank daily, smoked and did not exercise regularly, compared to day workers. An inverse relationship was found between uric acid and glycosylated hemoglobin (HbA1c).	Exercise measured as regular or non-exercise. No variables related to living, working, dietary intake or socio-economic situation (although the latter were considered equal between shifts and non-shifts). They did not evaluate the history of shift change. There are no further conclusions between shift work and uric acid with logistic regression.

(*): direct relationship, (**): indirect relationship, (***) : different studies from the same cohort

Data collection was carried out using questionnaires and self-administered questionnaires. In three of them, (all from the same cohort) the data collected was later verified in a personal interview. Analytical data was collected in all studies.

Only three studies detailed the values that define hyperuricemia. The study by Oh et al. set the value at ≥ 7 mg/dL for an exclusively male population; the study by Shen et al., defined hyperuricemia in men at ≥ 416 $\mu\text{mol/L}$ (7 mg/dL) and 357 $\mu\text{mol/L}$ (6 mg/dL) in women and the study by Hulsegge et al., defined it at >7.0 mg/dL in men and >6 mg/dL in women.

The shift definitions and their characteristics were very heterogeneous. One study described the shift as alternating between daytime and shift work without providing any other characteristics¹⁵. The studies addressing the same cohort described it as daytime; shift work excluding 24 hours; and the fixed night shift, with the hourly rotation being distributed over five mornings, two rest days, five afternoons, one rest day, five nights, two rest days²⁵⁻²⁷. The study by Hulsegge et al.¹⁰ described the type of shift (afternoon, evening, night but able to sleep and rotating shifts) and collected the total number of years and months of shifts and their frequency (shifts without nights, one to four nights per month and five or more nights per month). Kawada et al. [27] describe daytime shifts as 8 a.m. to 5 p.m. and rotating shifts starting at 6.30 a.m., 2.30 p.m. and 10.30

p.m. Rauchenzauner et al.²⁸ only differentiate between being on-call for 24 hours and not being on-call (8 a.m. to 4.30 p.m.). They mention a frequency of four 24-hour shifts per month.

The main type of statistical analysis used was logistic regression. One study analysed its data using a linear mixed model and another using the Wilcoxon test and the Spearman correlation coefficient.

Of the eight articles reviewed, four studied the relationship between shift work and uric acid as the main objective and four did so indirectly. In the first four, different conclusions were obtained. Shen et al.¹⁵ found a higher prevalence of hyperuricemia in men, but after controlling for confounding factors they found shift work to be a protective factor. Oh et al.¹⁶ also found a relationship, whereas Hulsegge et al.¹⁰. Rauchenzauner et al.²⁸ found that uric acid decreased during 24-hour shifts and then increased, compared to non-shift workers.

One study relates shift work and uric acid to metabolic syndrome, Kawada et al.²⁷. Three studies using the same cohort reported higher uric acid levels in daytime workers at the start of the study than shift workers. (Dochi et al. 2009; Suwazono et al. 2009; Uetani et al. 2011)²⁵⁻²⁷. The main limitations were the lack of data linked to food intake and exercise, pharmacological treatments, the measurement of renal function, and, in particular, the lack of information around the shift work characteristics.

Finally, the quality of the studies included in the qualitative synthesis was analyzed according to the STROBE and CONSORT statements. In the STROBE assessment, study quality ranged from 14 to 20 (maximum 22). The lowest scores corresponded to the studies carried out by Kawada et al.²⁷ and Oh et al.¹⁶ and the highest scores corresponded to Uetani et al.²⁶ and Shen et al.¹⁵. The studies' biggest weakness was related to

sections 7 (clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.); 13c (Consider the use of a flow diagram); 14b (Indicate the number of participants with missing data for each variable of interest); and 16a (Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision). (Table III).

Table III: Assessment of the quality of studies included in the systematic review (STROBE Statement).

	Title/ Abstract		Background/ rationale	Objectives	Study design	Setting	Participants		Variables	Data sources/ measurement	Bias	Study size	Quantitative variables	Statistical methods				
	1						2	3						4	5	6	7	8
	a	b					a	b						a	b	c	d	e
Shen et al. (2019)*	1	1	1	1	1	1	1	na	1	1	1	1	1	1	1	na	na	1
Hulsegge et al. (2019)*	0	1	1	1	1	1	1	na	1	1	0	1	1	1	1	1	na	1
Oh et al. (2014)*	0	1	1	1	0	1	1	na	1	1	0	1	1	1	1	na	na	1
Uetani et al. (2011)**	1	1	1	1	1	1	1	na	0	1	1	1	1	1	1	1	na	1
Dochi et al. (2009)**	1	1	1	1	1	1	1	na	0	1	0	1	1	1	1	1	1	1
Suwazono et al. (2009)**	1	1	1	0	1	1	1	na	0	1	1	1	1	1	1	1	1	1
Kawada and Otsuka. (2014)**	1	1	1	0	0	1	1	na	0	1	1	1	1	1	1	0	1	1

(Continued)

	Participants			Descriptive data			Outcome data	Main results			Other analyses	Key results	Limitations	Interpretation	Generalizability	Funding	Total
	13			14				15	16								
	a	b	c	a	b	c		a	b	c							
Shen et al. (2019)*	1	0	0	0	0	na	1	0	1	na	1	1	1	1	1	0	18
Hulsegge et al. (2019)*	1	1	0	1	0	1	1	0	na	na	0	1	1	1	0	1	15
Oh et al. (2014)*	1	1	0	0	1	na	1	0	1	na	na	1	1	1	1	0	14
Uetani et al. (2011)**	1	1	0	1	1	1	1	0	na	na	1	1	1	1	1	1	19
Dochi et al. (2009)**	1	1	0	1	0	1	1	0	na	na	1	1	1	1	1	1	17
Suwazono et al.(2009)**	1	1	0	1	0	1	1	0	1	na	1	1	1	1	1	1	17
Kawada and Otsuka. (2014)**	1	0	0	1	0	1	1	0	na	na	1	1	1	1	1	1	14

1= recommendation included in the study, 0=recommendation not included, na= not applicable. In the items with sub-sections, not complying with it is considered if any of them does not include the recommendation; (*): direct relationship, (**): indirect relationship.

With regard to the CONSORT evaluation, the study by Rauchenzauner et al. [28] was the only one evaluated and it obtained a score of 14 out of a maximum of 25 given by the scale. (Table IV).

Quantitative synthesis

Of the eight studies included in the qualitative synthesis, three were excluded for meta-analysis: the studies by Suwazono et al.²⁵ and Uetani et al.²⁶ because they used the same worker cohort and sample base as Dochi et al.²⁴; and the study by Oh et al.¹⁶, because the outcome variable is qualitative (hyperuricemia >7 mg/dL). Therefore, five studies were finally included in the quantitative synthesis analysis, including a total of 4420 and 9193 shift and non-shift workers respectively. Of these five studies, only Hulsegge et al.¹⁰ showed higher mean hyperuricemia in shift workers,

5.2 mg/dL (SD=1.1), while for the group of non-shift workers, the mean uricemia was 5.0 mg/dL (SD=1.2). The meta-analysis showed an overall mean difference of -0.04 95% CI (-0.11, 0.04) p=0.32 (Figure 2). The heterogeneity of the analysis was low (I²= 40%) p=0.15.

The risk of bias assessment was carried out through the Cochrane RevMan tool (Figure 3). The presence of associated biases due to the lack of randomisation in the recruitment of participants has been detected in two studies, Kawada et al.²⁷ and Shen et al.¹⁵. On the other hand, four of the five meta-analysed studies are observational: three present a prospective longitudinal analytical design (cohorts) and Shen et al. a cross-sectional design, while Rauchenzauner et al. carried out a randomised clinical trial.

Table IV: Assessment of the quality of studies included in the systematic review (CONSORT Statement).

	Title	Abstract	Background	Objectives	Trial design	Change from protocol	Participants	Settings and location	Interventions	Outcomes	Changes to outcomes	Sample size	Inter analyses and stopping guidelines	Sequence generation (method)	Sequence generation (type)	Allocation concealment mechanism	Implementation	Blinding	Similarity of interventions
	1		2		3		4		5	6		7		8		9	10	11	
	a	b	a	b	a	b	a	b		a	b	a	b	a	b			a	b
	1	0	1	1	0	1	1	1	1	1	1	1	na	1	1	0	1	na	na

(Continued)

Statistical methods	Additional analyses	Participant flow	Losses and exclusions	Recruitment	Trial end	Baseline data	Numbers analysed	Outcomes and estimation	Binary outcomes	Ancillary analyses	Harmst	Limitations	Generalizability	Interpretation	Registration	Protocol	Funding	Total
12		13		14		15	16	17		18	19	20	21	22	23	24	25	14
a	b	a	b	a	b			a	b									
1	na	1	0	0	1	1	1	1	na	na	na	1	0	1	0	0	1	

1= recommendation included in the study, 0=recommendation not included, na= not applicable. In the items with sub-sections, not complying with it is considered if any of them does not include the recommendation.

Figure 2: Meta-analysis forest plot.

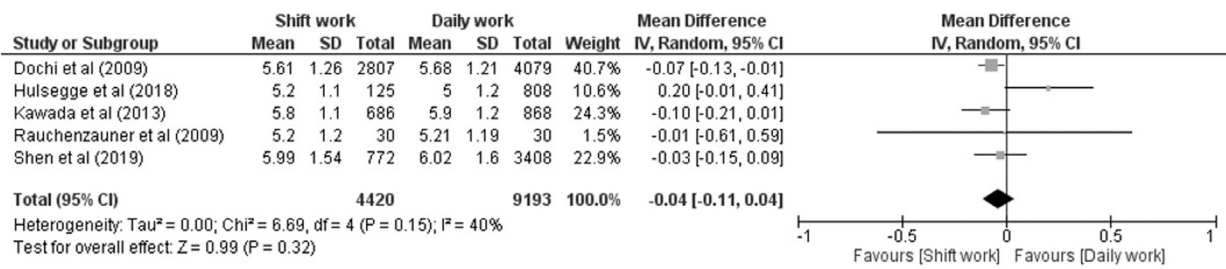
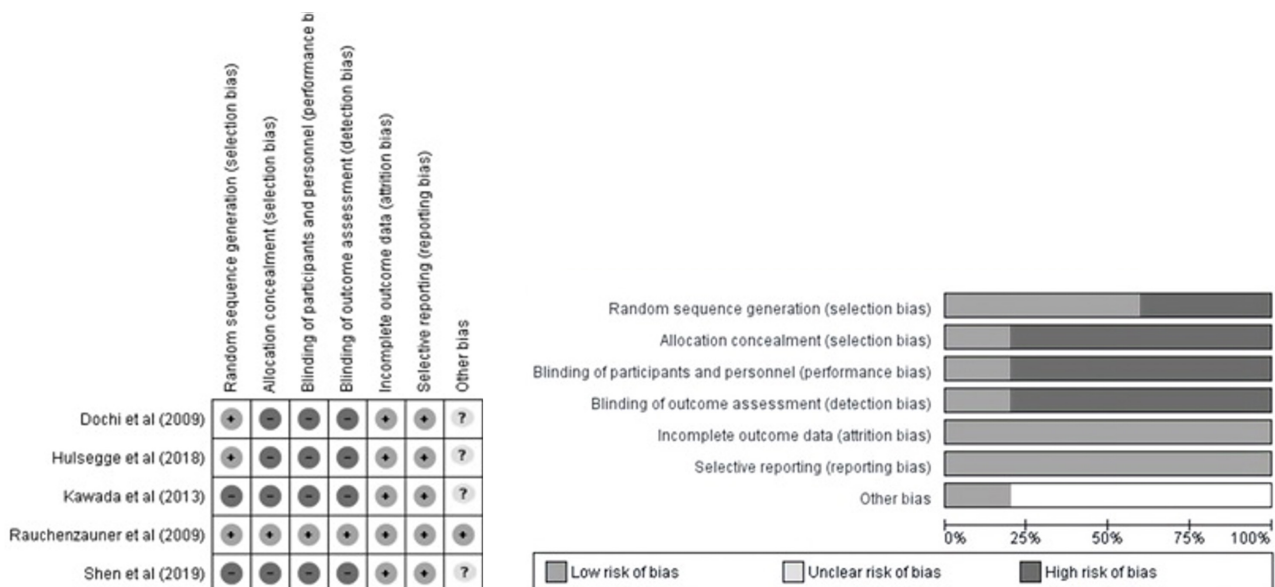


Figure 3: Overall risk of bias (Revman).



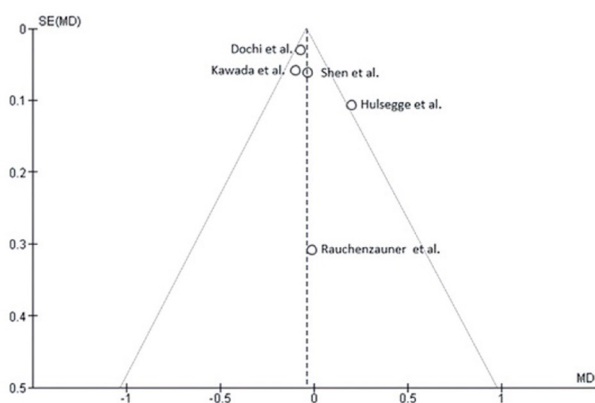
In the latter, there is concealment in the results evaluation but in the others there is only concealment in the allocation and blinding for participants and staff. The evaluation of the degree of evidence and a summary of findings table was produced with the Grade Pro tool, and the overall evidence score is low (Table V).

Finally, publication bias was analysed for the five studies included in the meta-analysis through the funnel plot, highlighting their low standard error and their symmetry, which is interpreted as low risk for publication bias. (Figure 4).

Table V: Evidence profile (Grade Pro).

Question: Do shift workers have more hyperuricemia than non-shift workers?										
No of studies	Design	Certainty assessment					No of patients		Effect	Certainty of evidence (GRADE)
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Shift Work	Daily Work	Mean Differences (95% CI)	
Average uric acid value (mg/dL) in shift workers and non-shift workers										
5	Observational studies (Cohort study n=3) Observational studies (Cross-sectional study n=1) Experimental study (Randomized clinical trial n=1)	No serious	No serious	No serious	No serious	All possible residual confounding factors could reduce the demonstrated effect	4.420	9.193	-0.04 (-0.11, 0.04)	⊕⊕○○ LOW

Figure 4: Publication bias (Funnel plot).



Discussion

This systematic review and meta-analysis has aimed to evaluate studies that relate to shift work and hyperuricemia in order to answer the question: do shift workers have higher uric acid levels than non-shift workers? The available evidence demonstrates independence between shift work and hyperuricemia.

The different kinds of shift work and their superficial descriptions are a usual problem²⁹. Only four studies differentiated between day and shift work, and of these, only two (from the same cohort) specified the type of rotation, frequency and hours per shift. Of the remaining four, the descriptions were also incomplete as Chastin et al.³⁰ have also pointed out. To the lack of unanimity in their definition must be added the absence of assessment of aspects that influence shift work, such as the type of shift, the direction and frequency of rotation or the absence

of data on intensity measured by years of exposure and number of shifts per month. Factors associated with shift work disorder, defined by the International Classification of Sleep Disorders (ICSD) as the presence of insomnia and/or excessive sleepiness temporarily due to a work schedule that overlaps with usual sleep time (Sateia, 2014), should also be assessed, since the relationship between shift work, night work, and sleep-related problems is well documented³¹.

Other factors, directly related to uric acid, such as the lack of assessment of dietary aspects, which are in turn influenced by cultural, demographic and social aspects; pharmacological and even herbal dietary treatments or renal function, should be included in research as their influence on uric acid metabolism has been clearly substantiated and the need to address them in a systematic way is essential if generalisable results are to be achieved. Even in values such as the reference value for considering hyperuricemia, a small but important difference in valuation was detected since some considered the initial value to be high if it was ≥ 7 mg/dL and others if it was >7 mg/dL, which makes reviewing the intervals and biological reference criteria necessary in order to adequately evaluate the results³².

Uric acid is a value that is increasingly being recognised as a cardiovascular risk factor^{33,34} and is usually included in serological marker assessments associated with this risk. However, the associations between these and shift work are inconclusive [35,36]. This is more evident, as we have shown in this review, if we focus exclusively on uric acid.

Study limitations

Several limitations are the result of the high level of heterogeneity in the analysed studies' conclusions and

quality. This is in line with the problems outlined and the results seen in this review. First, the low representation of studies outside Asia makes multi-ethnic comparisons between workers difficult. Second, the scarcity of studies detected limits comparison and discussion between studies, making it difficult to analyse publication bias due to the small sample size. Third, as we have shown, the definitions of shift work were very heterogeneous and the confounding factors and statistical analyses also varied between studies. Fourth, the inclusion of studies with an observational design in the meta-analysis led to the existence of biases derived from non-randomisation in recruitment and non-blinding for participants and researchers, which subtracted evidence from the quantitative analysis. Finally, limiting searches to the last ten years as well as only English and Spanish publications should also be taken into account.

In conclusion, the evidence provided in this review shows independence between shift work and hyperuricemia. Studies related either directly or indirectly to shift work and hyperuricemia in the last ten years have been identified and this has revealed a deficit of updated studies in different populations and work situations. In addition to the shift type and its characteristics (total years of shift work, type of rotation, frequency, hours of work per shift and number of days per shift and month), it would be of particular interest to collect data on dietary, pharmacological and physical activity patterns, the chronotype, sleep time and renal function, among others, as the limitations of the analysed studies have revealed.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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ORIGINAL

Behavioral studies of mice with breast cancer after treatment with new anticancer agent, Rh2-containing arginine-graphene

Estudios de comportamiento de ratones con cáncer de mama después del tratamiento con un nuevo agente anticancerígeno, arginina-grafeno que contiene Rh2

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Abstract

Objectives: Ginsenoside Rh2-containing arginine-reduced graphene (Gr-Arg-Rh2) is a new designed anticancer nondrug for treatment of cancer. In this study, behavior of mice with breast cancer was evaluated after treatment with Gr-Arg-Rh2.

Methods: Thirty-two cancerous mice were divided into 4 groups and treated every three days for a duration of 32 days: Group 1, PBS: 60 µl (6 mg/kg), Group 2, Rh2: 60 µl (6 mg/kg), Group 3, Gr-Arg: 70 µl (3 mg/kg), and Group 4, Gr-Arg-Rh2: 70 µl (3 mg/kg). Behavioral demonstrations were assessed following the treatment.

Results: Results showed that the mice treated with the Gr-Arg and Gr-Arg-Rh2 appeared to be more energetic than Rh2 and control groups.

Conclusions: Based on the results, Gr-Arg-Rh2 can reduce cancer-related fatigue and low energy in cancerous patients.

Key words: Ginsenoside Rh2-containing arginine- highly porous graphene, Ginsenoside Rh2, Breast Cancer, Energy, Fatigue.

Resumen

Objetivos: El grafeno reducido con arginina que contiene ginsenosido Rh2 (Gr-Arg-Rh2) es un nuevo fármaco anticanceroso diseñado para el tratamiento del cáncer. En este estudio, se evaluó el comportamiento de ratones con cáncer de mama tras el tratamiento con Gr-Arg-Rh2.

Métodos: Treinta y dos ratones con cáncer fueron divididos en 4 grupos y tratados cada tres días durante 32 días: Grupo 1, PBS: 60 µl (6 mg/kg), Grupo 2, Rh2: 60 µl (6 mg/kg), Grupo 3, Gr-Arg: 70 µl (3 mg/kg), y Grupo 4, Gr-Arg-Rh2: 70 µl (3 mg/kg). Se evaluaron las manifestaciones conductuales tras el tratamiento.

Resultados: Los resultados mostraron que los ratones tratados con el Gr-Arg y el Gr-Arg-Rh2 parecían tener más energía que los grupos Rh2 y control.

Conclusiones: Según los resultados, el Gr-Arg-Rh2 puede reducir la fatiga y la baja energía relacionadas con el cáncer en los pacientes cancerosos.

Palabras clave: Grafeno altamente poroso con arginina, Ginsenosido Rh2, Cáncer de mama, Energía, Fatiga.

Introduction

Cancer-related fatigue and low energy are very common in various cancers¹. Approximately 80-100% of cancerous patients have these complications². This type of fatigue is different from the fatigue of daily life³. Most cancer patients complain of weakness, lethargy, fatigue and low energy⁴. Fatigue in movement, eating, walking, showering, etc. are common in these patients⁵. Patients with breast cancer are no exception. The fifth leading cause of cancer-related death in women is breast cancer⁶. Various strategies can be used for reduction of cancer-related fatigue and low energy such as exercise, yoga, massage therapy, counseling, nutritional counseling^{7,8}. Plant-derived compounds can have multiple biological effects⁹. Ginseng and active ingredients derived from it, is one of these plants with effective biological substances¹⁰. In our previous study, we showed that Ginsenoside Rh2-containing arginine-reduced graphene, nanostructures with the most important agent derived from Ginseng, have potent anticancer activity against various cancers¹¹. On the other hand, it's proven that both American and Asian ginseng, is a promising treatment for fatigue¹². Given that these researchers, in this article, we evaluated the effect of Gr-Arg-Rh2 on reduction of cancer-related fatigue and low energy in mice with breast cancer.

Methods

Thirty three mice with breast cancer were included in this study. All experimental protocols were approved by the Ethical Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran (Project code: IR.SSU.fm.REC.1397.42). The conditions of keeping the mice were suitable, and they were provided with the right food and water. These mice were divided to four groups:

Group 1) PBS as placebo controls (N=8), group 2) Rh2 (N=8), group 3) Gr-Arg (arginine-treated highly porous graphene) (N=8), and group 4) Gr-Arg-Rh2 (Rh2 -treated Gr-Arg) (N=8). The mice were given intravenous injections of the drug or a placebo every three days and 10 times during 32 days. Mobility and vibrancy are considered as factors associated with life quality in cancerous patients. We evaluated the distances traveled and velocities of the animals' movements as a mobility and vibrancy assessment method. For this evaluation, the entire animal mobility was recorded by a video camera 24 hours a day. The dimensions of all cages were the same. We also evaluated the animal's ability to hang from its tail. For each group, the mean of tail hangings for all the mice was evaluated. The mean distance traveled by the mice along the area of the cage was also calculated for each group. These two acquired sets of data were comprised among the examined groups.

Results

During the treatment period, the mice treated by Gr-Arg-Rh2, indicated a significant increase in the distance moved and velocity compared with other groups. In those mice treated by Gr-Arg-Rh2, the mean of tail hanging rates was significantly higher than other examined groups. This group was more likely to escape when hung from the tail. They seemed to have more energy and looked healthier. In addition, the mice treated by the Gr-Arg appeared to be more energetic than Rh2 and control groups.

Discussion

The distance traveled and velocity of the animals' movements were considered as an assessment of mobility and vibrancy. In breast cancer treatment, different disorders such as fatigue, mood swings, anxiety, as well as cognitive impairments were reported in most of the survivors. These disorders lead to an impairment in the quality of life during and after chemotherapy. Similar behaviors were seen in the animal model, especially in rodent models. Santos et al. revealed that tumors or tumor resection can affected the behavior of the mice in a nyctohemeral (day/night)-dependent manner¹³. Chemotherapy can also change the patients' behavior by directly affecting their brain with oxidative stress, inflammation, and neurovascular damage. This disorder is called chemotherapy-induced behavioral deficit¹⁴. Loman et al. showed that increased fatigue and decreased cognitive performance in paclitaxel-treated mice were related to an increase of circulating chemokine and pro-inflammatory cytokine/chemokine in the brain¹⁵. As mentioned above, in our study, the mice in Gr-Arg-Rh2 and Gr-Arg groups had more energy and were healthier than other groups. The improvement of the healing process and the reduction of cancer-induced- inflammation can be the main reason behind the increased levels of energy and mobility in the mice of these two groups.

Conclusion

Results showed that Gr-Arg-Rh2 can reduce cancer-related fatigue and low energy in cancerous patients.

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Competing interests

The authors declare no competing interests.

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The role of anxiety, fear and resilience in preventive behaviors against COVID-19: a cross-sectional study with nursing students

El papel de la ansiedad, el miedo y la resiliencia en las conductas preventivas frente al COVID-19: un estudio transversal con estudiantes de enfermería

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Abstract

Objectives: This study aims to explore the relationships between resilience, fear of COVID-19, anxiety and use of preventive behaviors related to COVID-19 among nursing students.

Methods: A cross-sectional study was conducted with 220 first-year nursing students during 2020.

Results: A significant relationship emerged between resilience ($p < .05$), fear of COVID-19 ($p = .01$), anxiety ($p < .01$) and use of preventive behaviors. Overall, the independent predictors were fear of COVID-19 ($p = .003$) and male sex ($p = .016$).

Conclusions: It is essential to develop resilience among students further to increase their preventive behaviors against COVID-19.

Key words: Anxiety, COVID-19, Fear; Nursing Students, Psychological Resilience, Preventive Behaviors.

Resumen

Objetivos: Este estudio tiene como objetivo explorar las relaciones entre la resiliencia, el miedo al COVID-19, la ansiedad y el uso de comportamientos preventivos relacionados con el COVID-19 entre estudiantes de enfermería.

Metodología: Se realizó un estudio transversal con 220 estudiantes de primer año de enfermería durante el año 2020.

Resultados: Surgió una relación significativa entre resiliencia ($p < .05$), miedo al COVID-19 ($p = .01$), ansiedad ($p < .01$) y uso de conductas preventivas. En general, los predictores independientes fueron el miedo a la COVID-19 ($p = 0,003$) y el sexo masculino ($p = 0,016$).

Conclusiones: Es esencial desarrollar aún más la resiliencia entre los estudiantes para aumentar sus comportamientos preventivos contra el COVID-19.

Palabras clave: Ansiedad, COVID-19, Miedo; Estudiantes de Enfermería, Resiliencia Psicológica, Comportamientos Preventivos.

Introduction

The pandemic's severity and the associated uncertainty become stressors affecting people's mental health¹⁻³. The virus does not spread by itself, but through people's social behaviour which remains the only vehicle for transmission of the virus despite the recommendations and restrictions issued by the health authorities⁴.

Psychological models, such as the common-sense model of illness self-regulation, explain how individuals acquire and maintain health-related behaviours⁵. But what are the psychological factors behind compliance with the established preventive measures against COVID-19? One of them may be resilience, which is understood as a measure of the ability to cope with stress and which results from the combination of different individual characteristics. Keener et al. (2021) recommend resilience training to improve life quality and maintain clinical performance among healthcare professionals during the COVID-19 pandemic⁶. High resilience scores are also associated with enhanced self-care in samples of patients requiring long-term care (like in the case of diabetes mellitus), as reported by Boell et al. (2020)⁷. For Zager et al. (2021), resilience seems to be an essential protective factor for people to manage stressful situations such as the coronavirus pandemic and associated lockdowns⁸.

In addition, other factors such as fear and anxiety can generate more lavish use of self-protection measures from individuals against COVID-19 and those who trivialise its consequences. For instance, during the first months of the pandemic in Wuhan (China), Liu et al. (2020) reported that younger people experienced higher psychological stress than older people did, and most survey respondents adhered to specific measures stipulated by health authorities⁹. However, Leung et al. (2005) make some differentiation from these results in their study during the SARS epidemic in Hong Kong: where subjects, who perceived a higher likelihood of contracting SARS and dying, scored higher on anxiety and presented a better adoption of personal protective measures¹⁰.

There are multiple literature reviews and studies on the psychological repercussions of this health crisis¹¹⁻¹³, and the psychological factors that influence compliance with COVID-19 preventive measures⁹, but a small number of studies have focused on the behavioural factors that make health sciences students comply with health measures in the current crisis¹⁴. Considering that nursing students must face situations of risk of contagion both in their clinical practices and in their social environment, the present study aims to explore the association of resilience, fear and anxiety caused by COVID-19 with the level of compliance with preventive behaviours against COVID-19 within nursing students.

Methods

Participants

A cross-sectional study was conducted with first-year nursing students (2020) in a public university in Madrid (Spain). All first-year students were invited to participate in the study (n = 230). A total of 220 students agreed to participate. The study objectives and methodology were explained to them, and they signed an informed consent form prior to their participation. Students, who did not accept the conditions of the study, did not sign the informed consent form, and those who stated personal health reasons for not participating were excluded.

Instruments

Each participant was given a survey based on several questionnaires collecting data on sociodemographic characteristics, resilience status, preventive behavioral habits, anxiety levels, and fear of COVID 19. In addition, the participants were asked if they had been in contact with patients with mild, moderate or severe symptoms of COVID-19. The sociodemographic data collected to control analyses were age, gender, marital status, and employment status. The following validated self-report questionnaires, among others, were used to assess participants' habits concerning COVID-19:

- **Resilience:** The Spanish adaptation of the Connor-Davidson Resilience Scale (CDRS) was used to measure resilience status¹⁵. It contains 25 items grouped into 5 dimensions: persistence-tenacity-self-efficacy, control under pressure, adaptability and support networks, control and purpose, and spirituality. Each item is rated on a 5-point Likert scale ranging from 0 (not at all) to 4 (almost always). The total score constitutes the total Resilience value, whose cut-off points are ≤ 70 (low), 70-87 (intermediate), and ≥ 88 (high). The Spanish version obtained a high level of internal consistency as measured with Cronbach's α ($=.86$)¹⁶.

- **Anxiety:** The Coronavirus Anxiety Scale (CAS) was used to assess anxiety levels among students¹⁷. The tool consists of 5 items rated on a scale of 0 to 4 according to the frequency of symptoms, with 0 being "never" and 4 being "nearly every day". The following manifestations of coronavirus anxiety were covered: cognitive (repetitive thinking; worry), behavioral (dysfunctional activities; avoidance; compulsive behaviors), emotional (fear and anxiety), and physiological (sleep disturbances). The Spanish version has a high level of internal consistency ($\omega=0.89$; ordinal $\alpha=0.89$)¹⁸.

- **Preventive behaviors:** The Use of Preventive Behaviors scale (UPB) was employed to analyze preventive behaviors. This scale was developed by the researchers of this study to assess behaviors to prevent the spread of the coronavirus as prescribed by the CDC¹⁹. It includes 8 behaviors "wear a face mask", "wear gloves", "keep

a safe distance with other people”, “wash or sanitize hands”, “clean objects and surface with hand sanitizer, bleach, alcohol, etc.”, “take precautions when coming home from the supermarket by washing food, sanitizing the mobile phone or keys, etc.”, “protect oneself when touching potentially infectious areas such as doorknobs, lifts, credit card readers, etc.” and “avoid enclosed spaces or make sure they are properly ventilated”. A true or false response is required for each statement. Each behavior was scored as 10, -10, 7, 5, -5, 4, -4, 2, -2 according to the consensus reached by the researchers regarding importance given to these behaviors to prevent the dissemination of the disease and the level of self-protection. An example of the weights of each behavior is shown in **table I**.

• **The Coronavirus Fear Scale (CFS)**, designed to assess the fears and concerns experienced by individuals during the COVID-19 pandemic, was used to analyse levels of fear among students^{20,21}. The questionnaire contains four factors: (F1) fear of contagion, disease, and death; (F2) fear of shortages of basic consumer goods; (F3) fear of social isolation; and (F4) work and income-related fears. The CFS is made up of 18 items rated on a 5-point Likert scale ranging from 1 (“Not at all or very little”) to 5 (“Very much or extremely”). Internal consistency as measured using α was =.89²².

Procedure

Data collection took place between October and December 2020, and the survey was conducted anonymously online (prior to the survey they had had to sign an electronic informed consent form to participate). Participants' personal data were anonymized for confidentiality using a numerical code. The survey data were transcribed into a database using the anonymous identifier codes for each participant. The principles enshrined in the Helsinki Declaration on Biomedical Research Involving Human Subjects were always observed. The faculty's Research Committee approved the research protocol.

Data analysis

A descriptive analysis was performed using proportions and numbers of events for variables sex, employment

status, marital status and close contact with a person with COVID-19. In addition, performed age in years with means and standard deviations. Potential relationships between the different dimensions (resilience, anxiety and fears with preventative behaviors) were identified using univariate and multivariate linear regression, with a significance level of 5%. All analysis were performed using SPSS program version 25.

Results

Sample characteristics

Of the total number of students participating, 84.3% were female, 50% were over 18 years old (mean (standard deviation) = 19.9(5.6)), approximately 80% were single, and 88.6% were unemployed. 53% of those who were employed worked in the healthcare sector. Since the start of the pandemic, 26% of participants had been in close contact with a person with severe COVID-19 symptoms, 39.8% had been in close contact with a person with mild COVID-19 symptoms, and 34.2% had not been in close contact with anyone with COVID-19 (**Table II**).

Correlations with use of preventive behaviours

A moderate positive relationship was found between the UPB score and the scores obtained from the CAS. Also, there was a moderate relationship between the score obtained from the UPB and the scores obtained from the overall CFS. There was a moderate relationship between the “fear of contagion, disease, and death activity (F1)” factor score of the CFS and a low relationship the score obtained from the “fear of shortages of basic consumer goods (F2)” of the CFS. There was not a statistical relationship between the score obtained from the CDRS and the UPB. No significant relationships were found between “fear of social isolation (F3)” and “work and income-related fears” factors of the CFS with the UPB scale (**Table III**).

Relationships among anxiety, fear of COVID-19, resilience and preventive behaviours

When analyzing the relationships of the study variables, as a result of univariate analyses regarding the prediction of the use of preventive behaviours by nursing students,

Table I: Weighting was awarded to the UPB questionnaire responses according to expert consensus.

Item	Yes (Weighting)	No (Weighting)
1. Do you always or almost always wear a face mask when you leave your home?	10	- 10
2. Do you always or almost always wear gloves when you leave your home?	-5	5
3. Do you always or almost always keep a safe distance from other people outside your home (at least 2 meters)?	10	- 10
4. Do you think you wash or sanitize your hands too often?	7	-4
5. Do you regularly clean objects and surfaces with hand sanitizer, bleach, alcohol, etc.?	4	-2
6. Do you regularly take precautions when coming home from the supermarket by washing your food, sanitizing your mobile phone or keys, etc.?	4	-2
7. Do you usually protect yourself when touching potentially infectious areas such as doorknobs, lifts, credit card readers, etc.?	4	-2
8. Do you avoid enclosed spaces or make sure they are properly ventilated?	10	-10

Table II: General characteristics of the sample.

		N=220	response %
Sex	Female	172	84.3
	Male	32	15.7
	No response	16	
Employment status	Unemployed	178	88.6
	In the healthcare sector	13	6.5
	In another sector	10	5.0
	No response	19	
Marital status	Single	173	85.6
	Not single	29	14.4
	No response	18	
Close contact with a person with COVID-19	No contact	67	34.2
	Mild symptoms	78	39.8
	Severe symptoms	51	26.0
	No response	24	
Age in years	19.9 (mean)	5.6 (standard deviation)	

Table III: Correlations of levels of resilience, anxiety and fear of COVID-19 with use of preventive behaviours.

	Use of preventive behaviours (UPB)
Anxiety (CAS)	$r = .185^{**}$ $p = .006$
Resilience (CDRS)	$r = .076$ $p = .267$
Total fear (CFS)	$r = .191^{**}$ $p = .005$
“Fear of contagion, disease, and death” (F1)	$r = .274^{**}$ $p = .000$
“Fear of shortages of basic consumer goods” (F2)	$r = .159^{*}$ $p = .019$
“Fear of social isolation” (F3)	$r = .020$ $p = .768$
“Work and income-related fears” (F4)	$r = .075$ $p = .271$

Abbreviations: UPB, use of preventive behaviours scale, CAS, coronavirus anxiety scale; CDRS, Connor-Davidson Resilience Scale; CFS, coronavirus fear scale.
*low level correlational relationship.
**moderate correlational relationship

Table IV: Univariate linear regression between fear of COVID-19 (CFS), types of fears (F1 and F2) anxiety (CAS) and use of preventive behaviours (UPB).

Dependent Variable: UPB					
	Coeff	Std.Error	p-value	Lower-CI95%	Upper-CI95%
CFS	0.30	-0.11	.01	0.09	0.51
CFS-F1	0.86	0.21	.00	0.45	1.27
CFS-F2	0.96	0.40	.02	0.16	1.75
CAS	1.21	0.44	.01	0.35	2.07

Abbreviations: UPB, use of preventive behaviours scale, CAS, coronavirus anxiety scale; CFS, coronavirus fear scale.

which was assessed with the linear regression analysis, a statistically significant difference was determined between the use of preventive behaviors (UPB) and the Resilience scale ($p=.032$). Therefore, individuals with a low or moderate resilience obtained similar mean values on the UPB. Conversely, individuals with a high resilience status got higher mean values on the UPB than the other two groups (**Figure 1**).

An analysis of the relationships between preventive behaviors, anxiety levels, and fear levels also showed a significant positive relationship between the CFS scale and UPB scale ($p<.05$) (**Table IV**).

Figure 1: Resilience and Use of Preventive Behaviours (UPB).

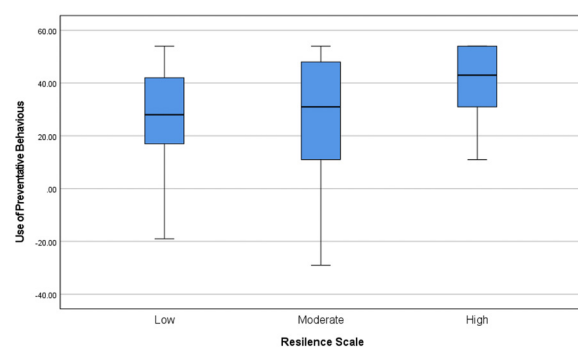


Table V: Stepwise multiple linear regression model: relationships between fear of COVID-19 and sex with UPB scale.

Model	R	R ²	Adjusted R ²	Standard error of estimate	Change statistic		Sig. of change in F
					Change in R ²	Change in F	
1	.243 ^a	.059	.054	18.29037	.059	11.396	.001
2	.299 ^b	.089	.079	18.04579	.030	5.940	.016

Model		Unstandardized coefficients		Standardized coefficients	t	Sig.
		B	Standard Error	Beta		
1	CFS	.377	.112	.243	3.376	.001
2	CFS	.332	.112	.214	2.971	.003
	Male Sex	-8.789	3.606	-.176	-2.437	.016

Abbreviations: UPB, use of preventive behaviours scale, CFS, coronavirus fear scale.

Table VI: Stepwise multiple linear regression model: relationships between types of fear of the CFS scale and sex with UPB scale.

Model	R	R ²	Adjusted R ²	Standard error of estimate	Change statistic		Sig. of change in F
					Change in R ²	Change in F	
1	.325a	.105	.100	17.83684	.105	21.304	.000
2	.365b	.133	.124	17.60296	.028	5.842	.017

Model		Unstandardized coefficients		Standardized coefficients	t	Sig.
		B	Standard Error	Beta		
1	F1	.997	.216	.325	4.616	.000
2	F1	.924	.215	.301	4.295	.000
	Male Sex	-8.467	3.503	-.169	-2.417	.017

Abbreviations: UPB, use of preventive behaviours scale, CFS, coronavirus fear scale.

This means that higher scores on the CFS will result in higher scores on UPB. Of the four factors or dimensions on the CFS scale, only F1 ("fear of contagion, disease, and death") and F2 ("fear of short-ages of basic consumer goods") ($p < .05$ for F1 and F2) influence scores on the UPB scale, with the result that higher scores on F1(F2) result in higher scores on the UPB. (Table IV). It also follows that higher CAS scores indicate higher UPB scores ($p < .05$) (Table IV).

Finally, the experience of close contact with a person with COVID-19 since the start of the pandemic was not associated with the UPB scale ($p = .58$).

When the scales of the study were introduced in a stepwise multiple linear regression model, with sociodemographic variables, a statistically significant difference was determined between the UPB scale based on the CFS scores ($p = .003$) and male sex ($p = .016$). The most significant models are presented in table V. When the four factors of the CFS scale were introduced in the model only F1 predicted scores on the UPB scale ($p < .001$) together with male sex ($p = .017$) (Table VI).

Discussion

Individuals with high resilience score higher on use of preventive behaviors than individuals with low/moderate

resilience, with no differences observed between these two groups. These results are consistent with the conclusions of Keener et al. (2021) focused on health professionals⁶ and those obtained with patient samples according to Boell et al. (2020)⁷.

The difference between the results of this study and those mentioned above is that preventive behaviors in response to COVID-19 are only observed among subjects with very high resilience scores. In contrast, no preventive behaviors are observed among people with moderate and low resilience scores. This indicates that subjects with very high resilience scores cope better with preventive behaviors than people with moderate and low resilience in environments where self-care measures vary significantly (use of face masks, social distancing, ventilation of enclosed spaces, limited family gatherings). According to Zager et al. (2021), resilience may be an essential protective factor for individuals to adapt to stressful situations such as the coronavirus pandemic and associated lockdowns⁸. This can also be since the sample is of students of recent incorporation, and only the very resilient can reconcile self-care with the development of their lives.

In addition, a significant relationship was observed in the study: higher CFS scores indicate higher use of preventive behaviors (UPB). During the initial months of the pandemic in Wuhan, China, Liu et al. (2020) reported that younger

people experienced more tremendous psychological stress than older people. Most respondents adhered to the specific behaviors stipulated by the health authorities⁹. However, it is also true that these measures are not as flexible as in Spain.

Examining the four factors or dimensions of the CFS, it was observed that only “fear of contagion, disease, and death” and “fear of shortages of basic consumer goods” affect the UPB score, with “fear of contagion, disease, and death” being the most influential, as seen in the multivariate regression model. This echoes the findings of Leung et al. (2005) during the SARS epidemic in Hong Kong: subjects who perceived a greater likelihood of contracting SARS and dying scored higher on anxiety, and higher anxiety levels indicated greater adoption of personal protective measures. However, the results of this study also revealed that male respondents, highly young people, significantly older people, and people with lower levels of education were less likely to engage in preventive behaviors (10). According to our study, in the multivariate linear analysis, male sex is related to lower use of preventive behaviors consistent with other studies²³.

Further studies should be carried out to further explain the lack of association between close contact with a person with severe COVID-19 and use of preventive behaviors. This absence may be due to the effect of some variable such as fear as reported in Sandin et al. (2020) who found that a close contact with a person with severe COVID-19 and the fear of COVID-19 were closely related²⁴.

Limitations

The limitations of this study include the lack of data from students in other health science disciplines. Future studies should include larger samples from different academic years to ascertain whether maturity level or patient exposure influences compliance with protective measures and resilience scores.

Given that only subjects with very high resilience scores were correlated with adherence to preventive behaviors, it is essential to develop resilience among students further to increase their mean scores.

This and other similar studies could help identify the most suitable nurses for COVID-19 wards and hospitals to avoid the unintentional scattering of these professionals.

The data also showed that students who were more compliant with preventive behaviors feared death and contagion and were females. This may inform prevention strategies based on self-preservation and economic recovery as motivating factors for compliance.

The lack of instruments to evaluate the use of preventive behaviors has led us to develop our own instrument. Despite not having carried out a validation study, due to the nature of the questions, it has allowed us to identify

the use that students make of preventive behaviors and relate them to validated scales. Future studies could be proposed to validate this instrument.

Finally, we believe that these findings may be used to develop programs targeting different student psychological profiles to enhance resilience and improve students' ability to fulfil their professional roles and set a daily example on compliance with personal preventive behaviors, which will become an essential skill for future professionals in the pandemic era.

Conclusions

Taking the results mentioned above into consideration can draw the following implications regarding the relationship between resilience, fear, and anxiety in complying with preventive behaviors in response to COVID 19:

- Only individuals with high resilience score higher on the use of preventive behaviors.
- Higher anxiety level indicates higher use of preventive behaviors.
- “Fear of contagion, disease, and death” and “fear of shortages of basic consumer goods” affect the use of preventive behaviors, with “fear of contagion, disease, and death” being the most influential.
- Students who had been in close contact with a person with severe COVID-19 did not score higher on prevention behaviors.
- Fear of coronavirus, especially “fear of contagion, disease and death”, and female sex independently predict use of preventive behaviors.

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Disclosures

The authors report no actual or potential conflicts of interest.

Author contribution

AMM and LIMS designed the study and collected the data. GM and PRGD analysed the data. All authors aided in interpreting the results and have made a significant contribution to the final manuscript.




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ORIGINAL

Exploring the awareness and potential HIV/AIDS transmission mode among women in Mbaise Imo state, Nigeria: A cross-sectional study

Exploración del conocimiento y del modo de transmisión potencial del VIH/SIDA entre las mujeres del estado de Imo Mbaise, Nigeria: un estudio transversal

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Abstract

Background: Globally HIV/AIDS is the leading cause of infectious disease mortality; surpassing tuberculosis and malaria. Understanding the perceived risk and knowledge of infection is imperative and needed particularly among women in rural communities. This study was carried out to explore the awareness and potential HIV/AIDS transmission mode among women in Mbaise Imo State, Nigeria.

Methods: A descriptive cross-sectional research design was adopted for the study. A structured questionnaire was used to obtain the information for this study. Potential participants were approached and interviewed at three local governments areas in Mbaise Imo State, Nigeria. The participants for this study were recruited through convenience sampling method as there was known to be no complete sampling frame. A sample of 240 participants was recruited and Statistical Package for Social Sciences (SPSS) version 23.0 was used in the analysis of the study.

Results: Respondents within the age bracket 25-29 had the highest 60 (25%) respondents while the least 20 (8.3%) respondents were 15-19 years age bracket. About 100 (41.7%) of the women heard about HIV/AIDs through mass media and majority 230 (95.8%) agreed that HIV/AIDs can be contacted through unprotected. Those who disagreed that kissing can lead to HIV/AIDs were 120 (50%) while 68 (28.3%) agreed. 154 (64.2%) of the respondents disagreed that living/working with a person who has AIDs can lead to transmission of AIDs while 42 (17.5%) agreed.

Conclusion: The study identified that women in Mbaise had Media as their potential source of information about HIV/AIDs. Sensitization through Media is an essential tool to make information available on the risk factors of HIV and how to reduce its spread.

Key words: Knowledge, perception, attitudes, perceived risk, HIV/AIDs.

Resumen

Antecedentes: A nivel mundial, el VIH/SIDA es la principal causa de mortalidad por enfermedades infecciosas, superando a la tuberculosis y la malaria. Es imperativo y necesario comprender el riesgo percibido y el conocimiento de la infección, especialmente entre las mujeres de las comunidades rurales. Este estudio se llevó a cabo para explorar el conocimiento y el modo de transmisión potencial del VIH/SIDA entre las mujeres del estado de Mbaise Imo, Nigeria.

Métodos: Se adoptó un diseño de investigación transversal descriptivo para el estudio. Se utilizó un cuestionario estructurado para obtener la información para este estudio. Se contactó con los participantes potenciales y se les entrevistó en tres áreas de gobierno local del Estado de Mbaise Imo, Nigeria. Los participantes de este estudio fueron reclutados mediante el método de muestreo de conveniencia, ya que se sabía que no había un marco de muestreo completo. Se reclutó una muestra de 240 participantes y en el análisis del estudio se utilizó el Paquete Estadístico para las Ciencias Sociales (SPSS) versión 23.0.

Resultados: El mayor número de encuestados en la franja de edad de 25 a 29 años fue de 60 (25%), mientras que el menor número fue de 20 (8,3%) encuestados en la franja de edad de 15 a 19 años. Alrededor de 100 (41,7%) de las mujeres habían oído hablar del VIH/SIDA a través de los medios de comunicación y la mayoría, 230 (95,8%), estaban de acuerdo en que el VIH/SIDA se puede contraer sin protección. 120 (50%) estaban en desacuerdo con que los besos puedan provocar el VIH/SIDA, mientras que 68 (28,3%) estaban de acuerdo. 154 (64,2%) de los encuestados estaban en desacuerdo con que vivir/trabajar con una persona que tiene el sida puede conducir a la transmisión del sida, mientras que 42 (17,5%) estaban de acuerdo.

Conclusión: El estudio identificó que las mujeres de Mbaise tenían a los medios de comunicación como fuente potencial de información sobre el VIH/SIDA. La sensibilización a través de los medios de comunicación es una herramienta esencial para dar a conocer los factores de riesgo del VIH y cómo reducir su propagación.

Palabras clave: Conocimiento, percepción, actitudes, riesgo percibido, VIH/SIDA.

Introduction

HIV/AIDS is the most common cause of infectious illness death worldwide, surpassing tuberculosis and malaria¹. In 2015, 18.6 million girls and women worldwide were living with HIV, with approximately one million girls and women becoming infected for the first time². Women are always considered a vulnerable category to HIV/AIDS infection because of their innate susceptibility, decreased sexual autonomy, and men's sexual authority and privilege³. A vulnerability paradigm model supports this assumption, explaining the etiology and progression of women becoming the most vulnerable victims of the HIV epidemic⁴. The paradigm's central pillar emphasizes gender-based social disparities, such as women's lack of authority to defend themselves against HIV/AIDS, and men are more likely than women to infect their partners due to hazardous sexual and drug use habits. To put it another way, guys are active HIV transmitters but not HIV preventers⁴.

According to research, because they are exposed to infected fluids for longer periods of time during sexual intercourse, women are more vulnerable to HIV/AIDS infection via vaginal intercourse than men^{4,5}. The vagina has a larger risk of tissue injury during sexual intercourse, allowing the virus to enter the vagina more easily. Younger girls are especially vulnerable because their immature mucosal surfaces are more easily ripped during sexual contact⁵. AIDS-related deaths decreased from 2.3 million (2.1 million–2.5 million) in 2005 to an estimated 1.7 million (1.6 million–2.0 million) in 2011. AIDS-related mortality increased from 14 000 (8600–28 000) in 2001 to 25 000 [17 000–35 000] in 2011 in the Middle East and North Africa^{4,6}.

In Latin America, antiretroviral medication has helped reduce the annual number of people dying from AIDS-related causes to 57 000 (35 000–86 000) in 2011, down from 63 000 (35 000–105 000) ten years earlier⁷. In the Caribbean, an estimated 10,000 (8000–12000) people died from AIDS-related causes in 2011, nearly half as many as in 2001. In Western and Central Europe, as well as North America, antiretroviral medication has significantly reduced AIDS-related mortality, particularly in countries with the most severe epidemics. Over the last decade, the number of people dying from AIDS-related causes in these areas has remained largely stable, with an estimated 29 000 (26 000–36 000) in 2011⁷. However, the findings show that HIV continues to disproportionately afflict sex workers, men who have sex with men, and those who inject drugs. HIV prevention and treatment initiatives frequently overlook these critical demographics⁸. In terms of AIDS-related deaths, Asia, which has the highest number of deaths outside of Sub-Saharan Africa (about 330 000 (260 000–420 000) persons in 2011), has remained stable. In Eastern Europe and Central Asia, AIDS-related mortality continues to rise. A total of 90 000 (74 000–110 000) people died of AIDS-related causes

in 2011, up from 15 000 (11 000–26 000) in 2001. The number of persons newly diagnosed in the Russian Federation grew from 39 207 in 2005 to 62 581 in 2010⁷.

Newly reported HIV cases have been rising in Central Asia's smaller outbreaks since 2005. (Kyrgyzstan, Tajikistan and Uzbekistan). In this location, the use of contaminated injecting equipment is still the predominant mode of transmission. HIV-related tuberculosis (TB) continues to be a severe problem, as TB is still the top cause of death among HIV-positive people. Sub-Saharan Africa is home to more than 80% of HIV and tuberculosis patients⁷. Antiretroviral therapy is increasingly being recommended for the prevention of HIV transmission, according to scientific data. HIV transmission occurs solely between people who have HIV, and the viral load is the most important risk factor for transmission⁹. Lowering the viral load reduces the risk of transmission. Antiretroviral therapy reduces viral load substantially, and multiple observational studies have shown that it can prevent HIV transmission⁹. Antiretroviral therapy started early reduced HIV-1 sexual transmission and clinical occurrences, demonstrating that it has both personal and public health benefits¹⁰.

The prevention of HIV transmission from mother to child adds to the body of evidence that antiretroviral therapy works. Perinatal AIDS cases have virtually disappeared in the United States and Europe, owing to the implementation of guidelines for universal counselling, voluntary HIV testing, and ARVs for pregnant women and new-born infants¹⁰. In 2008, the majority of the 430 000 new paediatric HIV infections were in sub-Saharan Africa, where there is recent evidence that ARVs can be used to decrease transmission to 1 percent¹¹. They may also develop negative attitude towards HIV positive people due to over emphasis of the dreadfulness of HIV infection. It may produce irrational behaviour in women toward those with HIV/AIDS. Hence, this study was carried out to assess the awareness and potential HIV/AIDS transmission mode among women in Mbaise Imo State, Nigeria.

Methods

Study Design and Sample Selection

A cross-sectional survey based on a questionnaire interview was used to obtain the information for this study. Potential participants were approached and interviewed at three local governments areas in Mbaise Imo State, Nigeria. The participants for this study were obtained using a convenience sampling method as there was known to be no complete sampling frame. A sample of 240 participants was recruited.

Data/Statistical Analysis

Data was cleaned, entered and analysed using statistical packages for social sciences version 25.0. Frequency

and contingency table was used to show the distribution of data. Quantitative data was summarized using mean and proportion and percentages.

Ethical Consideration

The study protocol and study tools were reviewed and approved by the Ethics committee of Abia State University. Before starting the data collection, approval and permission were gained from the Transitional Chairman of the three local government areas. Verbal consent was obtained from all the potential participants before the start of the interview. Participants were informed about the purpose and the benefits of carrying out the study and were also advised that participation was voluntarily, and the questionnaire was anonymous.

Results

Demographic Characteristics of Respondents

From **table I** the respondents within the age bracket 25-29 had the highest 60 (25%) respondents, followed by those within the age bracket 35-39 with 42 (17.5%). Those within 40 years and above had 36 (15%) respondents; 20-24 had 24 (10%) while the least respondents were 15-19 years age bracket with 20 (8.3%). Majority 228 (95%) of the respondents were Christians while 8 (3.3%) and 4 (1.7%) were traditionalists and Muslims respectively. A lot 124 (51.7%) had secondary certificates followed by 68 (28.3%) who were university graduates. The least 48 (20%) had primary certificates while 0 (0%) were illiterates. The urban 172 (71.7%) dwellers dominated while a few 68 (28.3%) were rural dwellers. According to the monthly income of the respondents, 106 (44.2%) earn 30,000-50,000 per month, followed by 92 (38.3%) who earn above 50,000 a month while few 42 (17.5%) earn less than 30,000 per month.

Sources of HIV/AIDS Information

Table II showed that 100 (41.7%) of the respondents heard about HIV/AIDS through mass media such as television, radio and newspapers followed by those who got it from books 61 (25.4%). 55 (22.9%) heard about HIV/AIDS through health worker, those relatives taught on HIV/AIDS were 14 (5.8%) while 10 (4.2%) heard it from their friends.

The Response of Modes of HIV/AIDS Transmission

Table III showed that majority 230 (95.8%) agreed that HIV/AIDS can be contacted through unprotected sex, 6 (2.5%) disagreed while 4 (1.7%) were neutral. Those who disagreed that kissing can lead to HIV/AIDS were 120 (50%) followed by 68 (28.3%) who agreed that it can lead to HIV/AIDS while 52 (21.7%) were neutral. Also 130 (54.2%) disagreed that HIV/AIDS can be transmitted through cough/sneeze, followed by 60 (25%) who were neutral while 50 (20.8%) agreed. 118 (49.2%) disagreed that HIV/AIDS can be transmitted through bites of flies/mosquitoes/other insects followed by 70 (29.2%) who agreed while 52 (21.7%) were neutral. A lot 152 (63.3%) of the respondents disagreed that HIV/AIDS can be

Table I: Demographic Characteristics of Respondents.

Variables	Frequency (n=240)	Percentage
15-19	20	8.3%
20-24	24	10%
25-29	60	25%
30-34	58	24.2%
35-39	42	17.5%
40 and above	36	15%
Religion		
Christianity	228	95%
Muslim	4	1.7%
Traditionalist	8	3.3%
Educational qualification		
Illiterate	0	0%
Primary	48	20%
Secondary	124	51.7%
Tertiary	68	28.3%
Resident		
Rural	68	28.3
Urban	172	71.7
Monthly Income		
>30,000	42	17.5
30,000 – 50,000	106	44.2
<50,000	92	38.3

Table II: Sources of HIV/AIDS Information.

Variables	Frequency (n=240)	Percentage
Mass media (TV, Radio, etc.)	100	41.7%
Relatives	14	5.8%
Books	61	25.4%
Health worker	55	22.9%
Friend	10	4.2%
Total	240	100%

Table III: The Response of Modes of HIV/AIDS Transmission.

Way of Transmission	Frequency (n=240)		
	Disagree	Agree	Neutral
Sex contact without proper protection (heterosexual or homosexual)	6 (2.5%)	230 (95.8%)	4 (1.7%)
Kissing	120 (50%)	68 (28.3%)	52 (21.7%)
Cough/sneeze	130 (54.2%)	50 (20.8%)	60 (25%)
Bites of flies/mosquitoes/other insects	118 (49.2%)	70 (29.2%)	52 (21.7%)
Sharing foods or drinks	152 (63.3%)	48 (20%)	40 (16.7%)
Sharing clothing	168 (70%)	22 (9.2%)	50 (20.8%)
Sharing utensils (e.g., spoon, cup, fork, etc.)	148 (61.7%)	42 (17.5%)	50 (20.8%)
Pregnancy	32 (13.3%)	166 (69.2%)	42 (17.5%)
Living/working with a person who has AIDS	154 (64.2%)	42 (17.5%)	44 (18.3%)
Skin contact (hug or shake hands)	204 (85%)	16 (6.7%)	20 (8.3%)

gotten through sharing food or drinks, followed by 48 (20%) who agreed while 40 (16.7%) were neutral. More so, 168 (70%) of the respondents disagreed that sharing of clothing can lead to transmission of HIV/AIDs while 22 (9.2%) and 50 (20.8%) agreed and disagreed respectively. More 148 (61.7%) of the respondents also disagreed that sharing utensils such as spoons, cup and fork can lead to transmission of HIV/AIDs, 50 (20.8%) were neutral while 42 (17.5%) agreed. Majority 166 (69.2%) believed that HIV/AIDs can be transmitted through pregnancy, 42 (17.5%) were neutral while 32 (13.3%) disagreed. Furthermore, 154 (64.2%) of the respondents disagreed that living/working with a person who has AIDs can lead to transmission of AIDs, 44 (18.3%) were neutral while 42 (17.5%) agreed. Nevertheless, 204 (85%) disagreed that HIV/AIDs can be transmitted through skin contact like hug or hand shake, 20 (8.3%) were neutral while 16 (6.7%) agreed.

Discussion

This study aimed to determine the knowledge, perceptions, attitudes and personal perceived risk of HIV/AIDS among women in Mbaise Imo State, Nigeria. The finding discovered that women in Mbaise Imo State, Nigeria are adequately knowledgeable about the modes of HIV/AIDS transmission. This finding is similar to a study, which they found that females were more knowledgeable than males about general HIV/AIDS knowledge¹². However, some misconceptions exist, wherein some surveyed respondents still believe that HIV/AIDS can be transmitted through mosquito bites, sharing utensils, foods or drinks and clothing. The significant increased awareness and knowledge about HIV/AIDS among women have given credit and supported efforts done by various parties such as the government, NGOs and the media in which they have successfully reached their target messages out to this population.

Previous research have shown that stigma and discrimination related to HIV/AIDS have had profound effect on the lives of people living with HIV/AIDS, and acted as an obstacle to effective HIV prevention and treatment among these people¹³. The present study found that moderate, rather than clear-cut positive perceptions and a discriminatory attitude towards PLHIV exist within women respondents who are reasonably knowledgeable about the modes of HIV/AIDS transmission. Essentially, women respondents think that people living with HIV/AIDS should be blamed for bringing the disease into the community. As a result of this blame-the-victim stigma, many refuse to come forward for treatments.

This study found that majority of the respondents does not think that they are at risk of HIV/AIDS infection. According to the Health Belief Model of behaviour change, individuals must perceive themselves to be at risk of the health threat, before they take actions to reduce risky behaviours or to

engage in healthy alternative behaviour. Hence, a study suggested that adolescents who report high perceived risk for HIV/AIDS practise safer sexual behaviours, whereas those who perceive low risk for contracting HIV/AIDS report practising unsafe sexual behaviours¹⁴. This study, therefore, provides base information and insight into outlining strategic communication plans to tackle this group who thinks they are not vulnerable to HIV/AIDS infection. While publicly promoting condom use in HIV/AIDS prevention is seemed to be contentious in Mbaise the finding shows that high proportion of the surveyed respondents want to use condoms to protect themselves or their partners from contracting HIV/AIDS infection. This study found that majority (51.7%) had secondary school certificate followed by University graduates (28.3%). Those with primary school certificates were 20% while none of the respondent is an illiterate. Here also the urban dwellers (71.7%) were more knowledgeable than the rural dwellers (28.3%). This study also confirmed that majority of the participants earn a reasonable amount on monthly basis. The findings showed that the overall score of HIV/AIDS and socioeconomic factors indicate that the HIV/AIDS-related knowledge and attitudes was significantly higher in respondents with higher educational levels, higher wealth indices, identified as Christian and who were exposed to communication media (radio, TV) one or more times a week. Findings also indicate that while rural dwelling women scored lower than their urban counterparts in knowledge and attitude scores. A study in Congo as well had the same findings among rural-urban dwellers¹⁵.

Studies in a SSA context reported similar responses and attributed the observed rural-urban differences to illiteracy and the inaccessibility of HIV/AIDS interventions such as condom use and counselling in rural areas¹⁶. Beyond the African context, studies examining urban-rural differences in HIV knowledge in India and Canada reported similar observations¹⁷. Furthermore, accurate knowledge on HIV transmission was significantly higher in respondents with post-secondary education. Similar observations have been reported in Botswana¹⁸. Girl's school attendance was shown to increase their knowledge of HIV and consequently reduce their risk of infection by 11.6%. Christian women had significantly higher scores in knowledge of and attitudes towards HIV/AIDS than women of Islamic or other religion. Contrasting studies in Tanzania report a positive association between Christianity and HIV stigma towards people living with HIV/AIDS¹⁹. In this study, wealth index was a strong predictor of HIV knowledge and attitudes among women. Consistent results were reported in Ghana and Ethiopia¹⁹. Studies also indicate that women of high socioeconomic status in Nigeria and DRC had positive attitudes towards people living with HIV/AIDS compared with women in low economic brackets²⁰. Furthermore, results indicate a relationship between the frequency of media use and respondents' HIV/AIDS-related knowledge and attitudes. This is consistent with cross-sectional data pooled from

SSA countries. Media use across 13 SSA countries was shown to moderate safe sex behaviour, and the effects of mass media campaigns against HIV transmission was shown to be effective^{18,19}. It is noteworthy that the study highlights a positive association of media use with wealth index and suggests that media use benefits individuals of higher SES than those of lower SES across SSA.

Furthermore, mass media was shown to minimize HIV related stigma, indicating that interventions made on HIV knowledge has the potential to positively improve attitudes towards HIV as well. The relatively lower contribution of education to the variance in knowledge and attitude scores, on the other hand, imply the occurrence of factors that are more likely to be rooted to the belief system and perception of the problematic⁴. This indicated the necessity for strategic interventions aimed at identifying and addressing the structural issues influencing women's knowledge and attitude towards this epidemic. Findings of this study have important research and policy implications. Hence, these findings contribute to the understanding of the factors that may affect or improve women's awareness regarding HIV transmission, including mother-to-child transmission.

Conclusion

The study identified women's gaps in HIV knowledge and their attitudes towards individuals with HIV/AIDS. This study also discovered some factors such as education, age, religion, high social status coupled with media use were significantly associated with women's HIV/AIDS-related knowledge and attitudes towards infected individuals.

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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ORIGINAL

Evaluation of the failure rate of fixed orthodontic retainers: A systematic review and meta-analysis

*Evaluación de la tasa de fracaso de los retenedores de ortodoncia fija:
revisión sistemática y metanálisis*

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Abstract

Objectives: After completing and stopping orthodontic treatment, orthodontic retention is very important because optimal aesthetic positions must be maintained, and the function of the teeth must not change. The present study aimed to evaluate the failure rate of fixed orthodontic retainers.

Methods: All articles published in international databases such as PubMed, Scopus, Science Direct, ISI Web of knowledge, and Embase between 2012 to May 2022 are included. The Cochrane Collaboration's tool and Newcastle-Ottawa Scale were used for risk assessment. 95% confidence interval on risk ratio were done with random effect model and Mantel-Haenszel method. Meta-analysis of data collected from selected studies was performed using STATA.V16 software.

Results: In the initial review, duplicate studies were eliminated, abstracts of 518 studies were reviewed, two authors reviewed the full text of 70 studies, and finally, twelve studies were selected. Risk ratio of failure rates between fibers reinforced composite and the 0.0175" stainless steel wire was -0.09 (RR, 95% CI -0.34, 0.15; p=0.45) (I²=67.29%; P=0.03; moderate heterogeneity).

Conclusions: Based on the findings of the present meta-analysis, No difference was observed between fibers reinforced composite and the 0.0175" stainless steel wire in terms of failure rate, and the highest failure rate is observed in the upper jaw.

Key words: Orthodontic appliances, orthodontic retainers, meta-analysis.

Resumen

Objetivos: Después de completar y detener el tratamiento de ortodoncia, la retención de ortodoncia es muy importante porque se deben mantener posiciones estéticas óptimas y la función de los dientes no debe cambiar. El presente estudio tuvo como objetivo evaluar la tasa de fracaso de los retenedores de ortodoncia fijos.

Métodos: Se incluyen todos los artículos publicados en bases de datos internacionales como PubMed, Scopus, Science Direct, ISI Web of Knowledge y Embase entre 2012 y mayo de 2022. Para la evaluación del riesgo se utilizó la herramienta de la Colaboración Cochrane y la Escala de Newcastle-Ottawa. El intervalo de confianza del 95% en la razón de riesgos se realizó con el modelo de efectos aleatorios y el método de Mantel-Haenszel. El metanálisis de los datos recopilados de los estudios seleccionados se realizó con el software STATA.V16.

Resultados: En la revisión inicial se eliminaron los estudios duplicados, se revisaron los resúmenes de 518 estudios, dos autores revisaron el texto completo de 70 estudios y finalmente se seleccionaron doce estudios. La relación de riesgo de las tasas de falla entre el compuesto reforzado con fibras y el alambre de acero inoxidable de 0,0175" fue de -0,09 (RR, IC del 95%: -0,34; 0,15; p=0,45) (I²=67,29%; P=0,03; heterogeneidad moderada).

Conclusiones: Con base a los hallazgos del presente metanálisis, no se observaron diferencias entre el compuesto reforzado con fibras y el alambre de acero inoxidable de 0,0175" en cuanto a la tasa de fallas, y la tasa de fallas más alta se observó en el maxilar superior.

Palabras clave: Aparatos de ortodoncia, retenedores de ortodoncia, metanálisis.

Introduction

After completing and stopping orthodontic treatment, orthodontic retention is very important because optimal aesthetic positions must be maintained, and the function of the teeth must not change. Therefore, orthodontic retention is a stage that is not separate from orthodontic treatment^{1,2}. Specialists perform two methods for retention: 1- fixed (the device is averaged on the lingual tooth surfaces)³; 2- removable (in the form of transparent thermoform splints or acrylic plates)⁴. Based on the available evidence, several factors are effective in the stability of orthodontic treatment, including the individual characteristics of the patient (age, gender) and clinical characteristics (type of primary malocclusion, pathology of the surrounding soft tissues)⁵. Recurrence may occur after orthodontic treatment, which can be caused by various causes, such as muscle imbalance, stable reconstruction of periodontal tissues, or aging and growth-related changes⁶. Age is considered a very important factor in the movement of teeth, which generally occurs in all people with age, whether with or without orthodontic history⁷.

On the other hand, individual characteristics cannot be changed, and other influencing factors must be well investigated; therefore, the retention phase protocol must be adjusted best. The demand for orthodontic cosmetic treatment has recently expanded significantly due to tooth beauty and smile design⁸⁻¹⁰. Therefore, the stability of treatment results is very important, and patients emphasize this point because recurrence may cause dissatisfaction with the treatment and bring physical and emotional problems for the patient¹¹. Therefore, the patient should be examined several times over a year regarding the treatment process. The use of removable retainers is very challenging for the patient because, on the one hand, it is the patient's responsibility to maintain them, and on the other hand, it is the patient's responsibility to maintain oral and dental hygiene¹². Using a fixed retainer makes retention less dependent on patient compliance¹³. One of the most discussed and challenging issues is the best stability of the treatment, which compares two methods of using wire or fiber splint; also, the materials used are very important for the best stability of the treatment. There are also many disagreements on the fixed bonding method; therefore, the present study aimed to evaluate the failures rate of fixed orthodontic retainers.

Method

Search strategy

Based on PRISMA guidelines¹⁴, the present study conducts a systematic review and meta-analysis of all articles published between January 2012 and May 2022 in international databases, including PubMed, Scopus, Science Direct, Embase, and ISI Web of Knowledge. The Google Scholar search engine employed the PICO strategy to answer the research questions (Table I).

Table I: PICO strategy.

PICO strategy	Description
P	Population: People with completion of orthodontic treatment
I	Intervention: fiber reinforced composite
C	Comparison: stainless steel wire
O	Outcome: failure rate

The following keywords were used to search:

(((((“Orthodontic Retainers”[Mesh]) OR (“Orthodontic Retainers/adverse effects”[Mesh] OR “Orthodontic Retainers/classification”[Mesh] OR “Orthodontic Retainers/statistics and numerical data”[Mesh])) OR (“Orthodontic Appliances, Fixed”[Mesh] OR “Orthodontic Appliances, Removable”[Mesh])) AND “Bone Wires”[Mesh]) OR “Orthodontic Wires”[Mesh]) AND “Restolux SP 4” [Supplementary Concept].

Eligibility criteria

Inclusion criteria:

1. Randomized controlled trials, cohort studies, cross-sectional studies, and retrospective studies.
2. The article's full text was accessible and included information about the follow-up period.
3. Only English-language articles with published studies were selected.
4. Comparison of the intervention group with the control group.
5. Fixed retention failure defined.
6. Human samples.

Exclusion criteria:

1. in-vitro and in-vivo studies, Review studies, case reports, and letters to the editor.
2. No reporting fixed retention failure.

Selection process and Data collection process

Two reviewers blindly and independently extracted data from the included papers' full texts and abstracts for Data extraction. Kappa statistics were used to check the amount of agreement between the reviewers before the screening. The values of kappa were higher than 0.80. Studies data were reported by the first author's name, years, study design, several patients, and outcome.

Risk of bias assessment

The randomized control trial studies' quality was assessed using the Cochrane Collaboration's tool¹⁵. Low risk received a scale score of 1, while high and unclear risk received a score of 0. The scale scores have a range of 0 to 6. High quality means a higher score.

The non-randomized control trial studies' quality was assessed using The Newcastle-Ottawa Scale (NOS) [16], which measures three dimensions (selection, comparability of cohorts, and outcome) with a total of nine items, was

used to evaluate the quality of the cohort studies and case-control studies. Studies classified as low, medium, or high quality, had NOS scores of 1-3, 4-6, and 7-9.

Data analysis

Effect measures and Synthesis methods

STATA.V16 software was used to analyze the data to examine the failure rate used a risk ratio (95% confidence interval) with a fixed effect model and the Mantel-Haenszel method.

The level of heterogeneity was assessed using the I2 index test (I2 50% = low levels, 50-I2 75% = moderate, and I2>75% = high levels).

Results

After the initial search for them in databases, five hundred eighteen articles were identified. Duplicate articles were deleted (n=59) after importing all articles into the EndNote. X8 software. One hundred thirty-seven articles were entered and examined in the second stage. At this stage, 389 unrelated articles were excluded from the study while reviewing the titles and abstract articles. The full texts of 70 articles were reviewed in the third step. Twelve articles that met the inclusion criteria and were published between January 2012 and May 2022 eventually entered the analysis. (Figure 1).

Characteristics

Ten randomized controlled trial studies and two Retrospective studies have been included in the present article. The total number of patients was 1261 (male: 552; female: 709). The mean follow-up period was 21.42 months (Table II).

Bias assessment

According to Bias assessment tools, all studies had a moderate risk of bias (moderate quality).

Failure rates

The Risk ratio of failure rates between fibers reinforced composite and the stainless steel wire was -0.09 (RR, 95% CI -0.34, 0.15; p=0.45) (I²=67.29%; P=0.03; moderate heterogeneity). In terms of Failure rates, no statistically significant difference was observed between the two groups. These findings show that the two groups are almost identical in terms of Failures (Figure 2).

According to a subgroup meta-analysis examining the subgroups in terms of the follow-up period, it was observed that the follow-up period is non-effective in the effectiveness and survival rate (Figure 3).

Figure 1: PRISMA flowcharts.

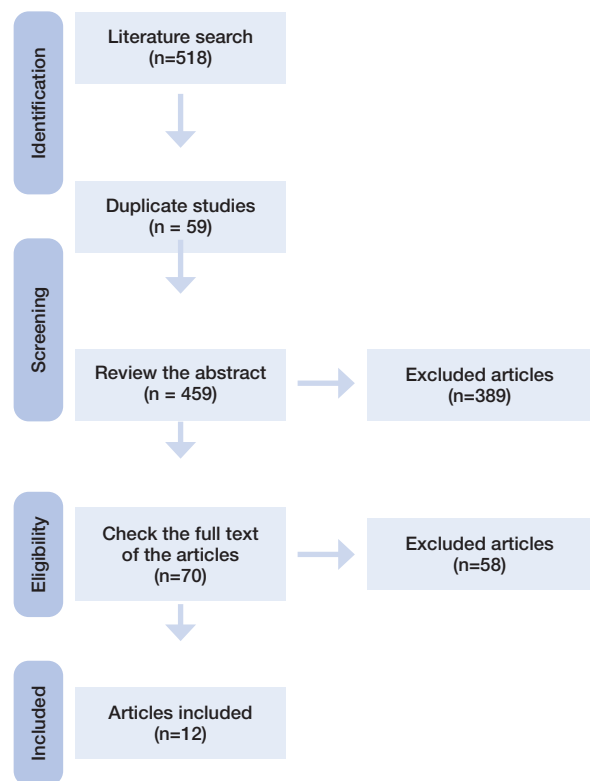


Table II: Summary of the findings reported in selected studies.

Study. Years	Study design	Number of patients		Follow-up (years)
		Male	Female	
Scribante et al., 2020 ¹⁷	Randomized controlled trial	50	50	>1
Kartal et al., 2020 ¹⁸	Randomized controlled trial	20	32	>1
Gelin et al. 2020 ¹⁹	Randomized controlled trial	18	43	>1
Arash et al., 2020 ²⁰	Randomized controlled trial	99	161	>1
Nagani et al., 2020 ²¹	Randomized controlled trial	44	8	6
Kocher et al., 2019 ²²	Retrospective cohort study	44	44	>1
Gunay et al., 2016 ²³	Randomized controlled trial	37	83	>1
Sobouti et al., 2016 ²⁴	Randomized controlled trial	60	68	2
Sfondrini et al., 2014 ²⁵	Randomized controlled trial	35	52	1
Farronato et al., 2014 ²⁶	Retrospective cohort study	60	59	>1
Bazargani et al., 2012 ²⁷	Randomized controlled trial	26	26	>1
Salehi et al., 2013 ²⁸	Randomized controlled trial	59	83	1.5

Figure 2: The Forest plot showed failure rates.

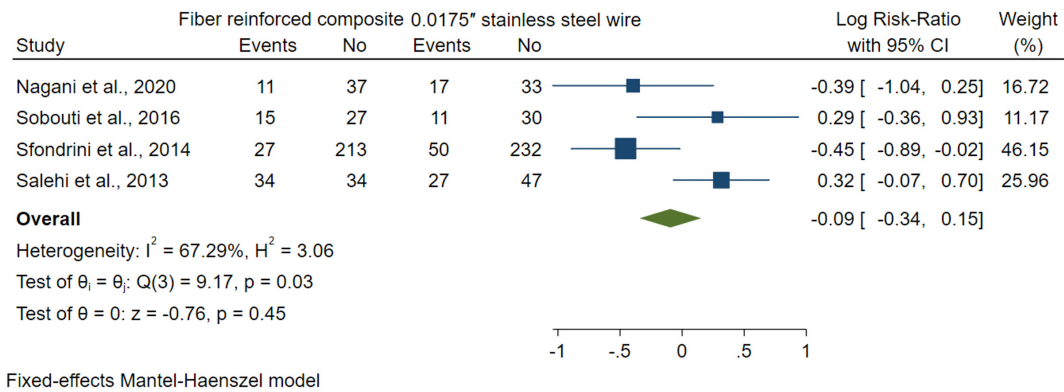
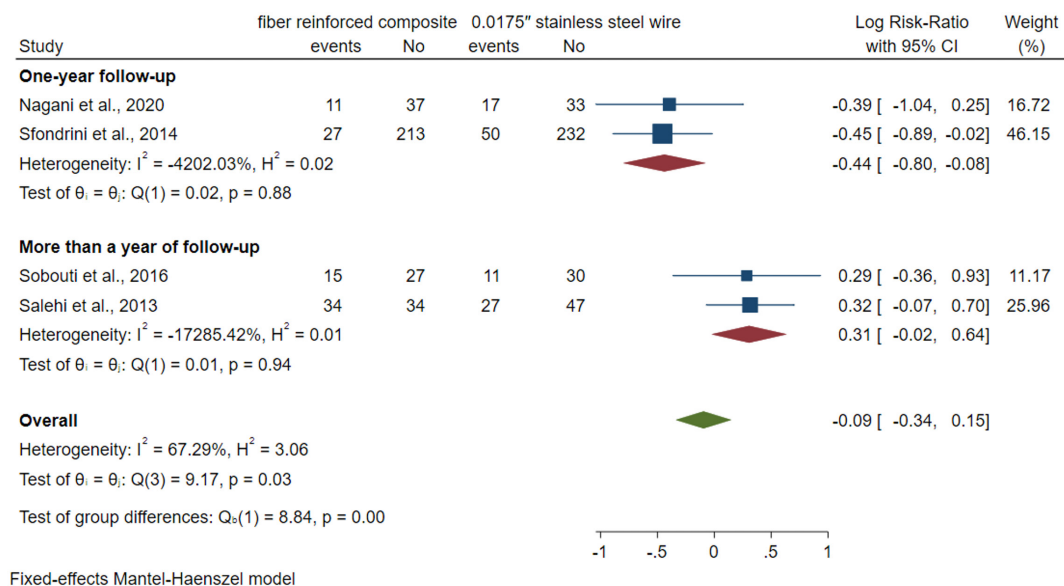


Figure 3: The Forest plot showed a subgroup meta-analysis of the different follow-up periods.



Discussion

The present Systematic Review and Meta-analysis study aims to evaluate the failure rate of fibers reinforced composite orthodontic retainers. The aim of orthodontic retention, the last stage of treatment, is to maintain the teeth in their corrected positions after orthodontic treatment²⁹. A study reported that failures occur more often after two years of retainer placement³⁰. Evidence shows that the clean enamel surface to be bonded, avoiding occlusal interference and dry field can be important factors in bonding considered successful maintainers³¹. In the current study, among the selected and eligible studies, only four studies were eligible for meta-analysis, none of which mentioned wire untwisting.

Also, another very important factor affecting failure is the interface between composite and enamel, which should be well investigated. The evidence shows that the bonding agent can improve the bonding efficiency. The meta-analysis of the present study showed that the risk ratio of failure rates between fibers reinforced composite and the stainless steel wire was -0.09, and no difference was observed between the two groups.

In Jazer's study, no difference was observed between the two investigated groups (fibers reinforced composite and the 0.0175" stainless steel wire) in terms of failures; one of the factors affecting failures is wire fracture.

The studies found no correlation between the patient's periodontal condition and the wire used^{19,32}. Research has shown that the placement of retainer is non-effective in the occurrence of symptoms of periodontal tissues³³. According to the findings of a study, one of the most important factors affecting failures is the presence of plaque, plaque or inflammation and the patient's lack of oral and dental hygiene³³. The studies have not investigated the final effect of etching times, which varies between 15 and 60 seconds based on available evidence, on debonding rates.

Limitations and future suggestions

providing information about this is very important, and it is suggested that future studies focus on etching or rinsing time to increase knowledge in this field. The present study had limitations that can be pointed to the difference in bonding factors, differences in different studies, and children the growing age. Since studies have shown that growth in children and adolescents can affect retention stability^{20,25,28}, it is also observed that with age, tooth movement occurs in all general populations. In terms of heterogeneity between studies, it was medium to high due to the type of study design, the use of different types of wire, measurement time, and the type of study. The

follow-up period in the studies was very variable; One of the most important factors affecting stability in the retention phase is the growth variable. In this study, failure and fractures were considered together due to the small number of studies, but from a scientific point of view, the fracture is observed due to the material's stiffness.

Conclusion

According to the findings of the present study, follow-up periods of one year or more than one year are not effective on the failure rate. The failure rate in the one-year follow-up periods was 44%, and in the higher follow-up periods, it was 31%. No difference was observed between fibers reinforced composite and stainless steel wire in terms of failure rate.

Conflict of Interest

The authors declared that there is no conflict of interest.

Acknowledgments

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Evaluation of the effect of silver nanoparticles in root canal treatment: A systematic review and meta-analysis

Evaluación del efecto de las nanopartículas de plata en el tratamiento del conducto radicular: revisión sistemática y metanálisis

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Abstract

Objective: The present study was conducted to evaluate the effect of silver nanoparticles in root canal treatment.

Methods: All articles published in international databases such as PubMed, Scopus, Science Direct, ISI Web of knowledge, and Embase until July 2022 included. A 95% confidence interval (CI) for effect size with a fixed effect modal was calculated. Data analysis was performed using Stata/MP.V17 software.

Results: In the initial review, the abstracts of 141 studies were reviewed, two authors reviewed the full text of 30 studies, and finally, eight studies were selected. The effectiveness of silver nanoparticles compared to the control group was 86% (ES: 95% CI, 0.39 to 1.33; $p < 0.001$).

Conclusions: Based on the findings of the present meta-analysis, AgNPs have a high antimicrobial effect in preventing the persistence of microorganisms in the root canal.

Key words: Nanoparticles, Root Canal Irrigants, Root Canal Therapy.

Resumen

Objetivos: El presente estudio se realizó para evaluar el efecto de las nanopartículas de plata en el tratamiento de conductos radiculares.

Métodos: Se incluyen todos los artículos publicados en bases de datos internacionales como PubMed, Scopus, Science Direct, ISI Web of Knowledge y Embase hasta julio de 2022. Se calculó un intervalo de confianza (IC) del 95% para el tamaño del efecto con un modal de efectos fijos. El análisis de datos se realizó utilizando el software Stata/MP.V17.

Resultados: En la revisión inicial se revisaron los resúmenes de 141 estudios, dos autores revisaron el texto completo de 30 estudios y finalmente se seleccionaron ocho estudios. La eficacia de las nanopartículas de plata en comparación con el grupo control fue del 86 % (ES: 95 % IC, 0,39 a 1,33; $p < 0,001$).

Conclusiones: Según los hallazgos del presente metanálisis, las AgNP tienen un alto efecto antimicrobiano en la prevención de la persistencia de microorganismos en el conducto radicular.

Palabras clave: Nanopartículas, Irrigantes del conducto radicular, Terapia del conducto radicular.

Introduction

One of the reasons that can cause the root canal treatment to fail is the presence of microorganisms in the root canal, which must be done with methods such as mechanical cleaning and irrigation using antimicrobial solutions to reduce the persistence of microorganisms^{1,2}. However, disinfection requires patients to visit again, or people are busy nowadays, so saving time is very important³. The evidence indicates that despite the disinfection of the root canal, the persistence of microorganisms in the root canal is evident⁴. Generally, an antimicrobial agent that can be effective on Gram-positive, aerobic, or Gram-negative bacteria is used for disinfection, which is an inappropriate choice and is effective only on one type of microbe^{5,6}. The most common disinfectants are sodium hypochlorite and chlorhexidine. Sodium hypochlorite can dissolve tissue residues and has high antibacterial effectiveness. However, one of its advantages is that organic materials can affect its efficiency; Studies have shown that sodium hypochlorite is used in different concentrations from 0.5% to 6%. The effectiveness of chlorhexidine on antimicrobial activity is very high. However, one of its disadvantages is that it is not able to dissolve tissue residues in the canal^{7,8}.

As a result, there is a need for an optimal root canal cleaner to be available that has both high safety and proven effectiveness. Studies using photodynamic therapy have reported nanoparticles to have a high antimicrobial effect, which can be used to disinfect root canals^{9,10}. Recent studies have suggested using nanoparticles due to their size and their effectiveness on microbes at lower levels¹¹⁻¹⁴. One of the most popular proposed nanowires is Silver nanoparticles (AgNPs), whose action mechanism is controversial and has many challenges¹¹. AgNPs can cause cell membrane perforation by affecting bacteria; Evidence has shown that cell DNA denaturation can also be affected by AgNPs¹⁵. There is no evidence that the size or concentration of AgNPs affects the mechanism of action. However, dentists use it because of its effective properties on antimicrobial activity. Studies have shown the positive effect of using nanoparticles on antimicrobial activity in the root canal¹⁶⁻¹⁹. Therefore, the present study was conducted to evaluate the effect of silver nanoparticles in root canal treatment.

Methods

The present study is a systematic review and meta-analysis that was conducted based on PRISMA guidelines²⁰. In this study, international databases such as PubMed, Scopus, Science Direct, ISI, Web of Knowledge, and Embase were reviewed to select articles related to the purpose of this study until July 2022. Mesh keywords were used for searching in PubMed, and similar keywords were searched in other databases. In the current study, **table I** shows the response to PICO;

the Google Scholar search engine was also used. MeSH terms keywords:

((("Nanoparticles"[Mesh]) OR ("Nanoparticles/ administration and dosage"[Mesh] OR "Nanoparticles/ adverse effects"[Mesh] OR "Nanoparticles/ classification"[Mesh] OR "Nanoparticles/ standards"[Mesh] OR "Nanoparticles/statistics and numerical data"[Mesh] OR "Nanoparticles/ toxicity"[Mesh])) AND "Silver"[Mesh]) AND ("Dental Pulp Cavity"[Mesh] OR "Root Canal Preparation"[Mesh] OR "Root Canal Therapy"[Mesh] OR "Root Canal Obturation"[Mesh] OR "Root Canal Irrigants"[Mesh])) OR ("Root Canal Irrigants/administration and dosage"[Mesh] OR "Root Canal Irrigants/ adverse effects"[Mesh] OR "Root Canal Irrigants/ classification"[Mesh] OR "Root Canal Irrigants/ standards"[Mesh]).

Table I: PICO strategy.

PICO strategy	Description
P	Population: tooth roots with root canals infected with any microbial organism
I	Intervention: silver nanoparticles
C	Comparison: conventional irrigants or did not have an irrigant
O	Outcome: Effectiveness

Inclusion and exclusion criteria

In-vitro studies, articles published in English included. Studies other than In-vitro studies, conflicting data with objective, and studies without full text were excluded from the study.

Reporting and extracting study data

It used a checklist that included the author's name, year of publication, type of study, Specimens, Bacterial Inoculation, groups, and Detection; the data of the studies were extracted and reported in **table II**.

Evaluating the quality of studies

The quality of the studies was evaluated based on the risk of bias assessment of the previous Systematic Review and Meta-analysis of In Vitro Studies^{21,22}. The way of scoring the studies is such that if a study did not report one to three cases, it is of high quality (low risk of bias); Failure to report four to six cases indicates moderate quality (moderate risk of bias) and more than six cases indicates that the quality of the studies is very low (high risk of bias).

Data analysis

STATA.V17 software was used for data analysis. Effect size with 95% confidence interval (CI) with fixed effect modal and inverse-variance method were done. The level of heterogeneity was evaluated using the I² index test (I² < 50% = low levels, 50 < I² < 75% = moderate and I² > 75% = high levels).

Table II: Data extracted from studies selected.

No.	Study. Years	Study design	Sample size		Bacterial Inoculation
			Experimental Group	Control group	
1	Gholami et al., 2022 ²³	In-vitro	AgNP solution (1.0 mL, particle size 27.43 nm and 29.66 nm) for 20 min	Alcoholic solution of CHX (2 mg/mL)	Enterococcus faecalis
2	Farahat et al., 2022 ²⁴	In-vitro	AgNP solution, 200ppm	SNPs Gel	Enterococcus faecalis
3	Razumova et al., 2022 ²⁵	In-vitro	AgNP solution	CHX	Enterococcus faecalis
4	Abdelfatah et al., 2020 ²⁶	In-vitro	AgNPs solution	CHX and sterile saline	Enterococcus faecalis
5	Kushwaha et al., 2018 ²⁷	In-vitro	AgNP suspension (20 nm, 3 min)	CHX (2 %)	Enterococcus faecalis
6	De Almeida et al., 2018 ²⁸	In-vitro	AgNP solution (5- 20 nm, 1 min)	Saline ultrasonically activated (1 min, 0.85%)	Enterococcus faecalis
7	Afkhami et al., 2017 ²⁹	In-vitro	AgNP suspension (30 nm, 5 min)	NaOCl (2.5%, 5 min)	Enterococcus faecalis
8	Wu et al., 2014 ³⁰	In-vitro	AgNP solution (2 min)	NaOCl (2%)	Enterococcus faecalis

Table III: Data extracted from studies selected.

No.	Study. Years	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Risk of Bias
1	Gholami et al., 2022 ²³	Yes	NR	Yes	Yes	Yes	Yes	Yes	NR	None	Low
2	Farahat et al., 2022 ²⁴	Yes	NR	Yes	Yes	Yes	Yes	Yes	NR	None	Low
3	Razumova et al., 2022 ²⁵	Yes	NR	Yes	Yes	Yes	Yes	Yes	NR	None	Low
4	Abdelfatah et al., 2020 ²⁶	Yes	NR	Yes	Yes	Yes	Yes	Yes	NR	None	Low
5	Kushwaha et al., 2018 ²⁷	Yes	NR	No	Yes	Yes	Yes	Yes	NR	NR	Medium
6	De Almeida et al., 2018 ²⁸	Yes	NR	Yes	Yes	Yes	Yes	Yes	NR	None	Low
7	Afkhami et al., 2017 ²⁹	Yes	NR	Yes	Yes	Yes	Yes	Yes	NR	None	Low
8	Wu et al., 2014 ³⁰	Yes	NR	Yes	NM	Yes	NR	Yes	NR	None	Medium

Results

The search was conducted based on the mentioned keywords, and 141 studies were found in the introduced databases; After entering the studies into the EndNote.x8 software, duplicate studies were removed, and finally, the abstract of 110 studies were reviewed, and the studies that met the inclusion criteria were left out for the full-text review; at this stage, 80 studies were removed. The full text of 30 studies was carefully reviewed, and studies that had incomplete data, very low quality, or did not include the inclusion criteria and matched the exclusion criteria were excluded from the study (22 articles); finally, eight articles were selected, and their data were extracted for meta-analysis (Figure 1).

Characteristics

Eight in-vitro studies have been included in the present article; a summary of the data of the selected studies is reported in table II.

Risk assessment

According to table III, out of the eight selected studies, two studies were of medium quality and six studies were of high quality; the answers to 9 questions are summarized in table III; all studies did not report Sample Size Statistically Calculated and Observer/Evaluator Blind to the Groups.

Assessment of Antibacterial Activity

The significantly highest reduction in bacteria count was followed by silver nanoparticles groups (p=0.00); the effectiveness of silver nanoparticles compared to the control group was 86% (ES: 95% CI, 0.39 to 1.33; p<0.001). (I²<0%; P=1.00; low heterogeneity) (Figure 2). Galbraith plot for heterogeneity analysis showed no inconsistency across studies (Figure 3).

- Q1: Were Human Teeth Used as Specimens?
- Q2: Was the Sample Size Statistically Calculated?
- Q3: Was Bacterial Inoculation Verified?
- Q4: Was Particle Size Mentioned?
- Q5: Was a Control Group Present?
- Q6: Were the Teeth Cleaned and Shaped before Irrigation?
- Q7: Was the Irrigation Time the Same for Experimental and Control Groups?
- Q8: Was the Observer/Evaluator Blind to the Groups?
- Q9: Was There Any Conflict of Interest?
- NR: not reported; NM: Not mentioned

Figure 1: PRISMA flowcharts.

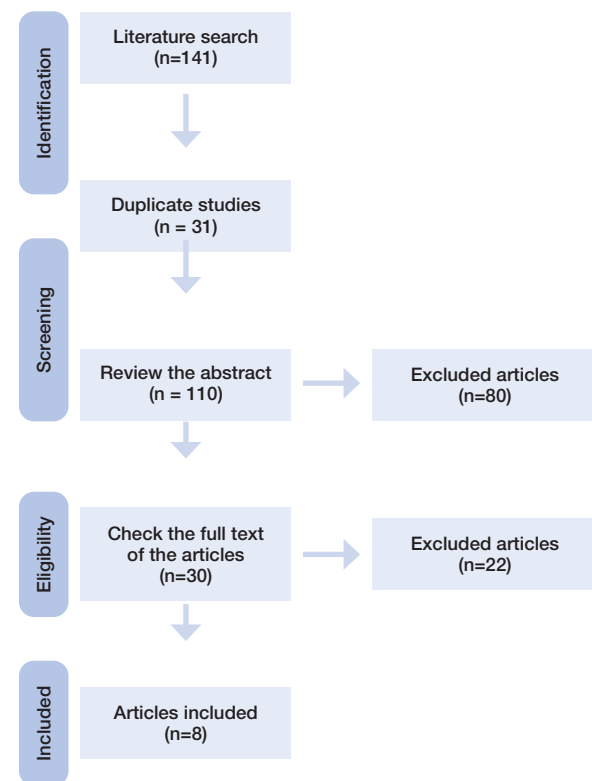


Figure 2: The Forest plot showed the effectiveness of silver nanoparticles on Antibacterial Activity.

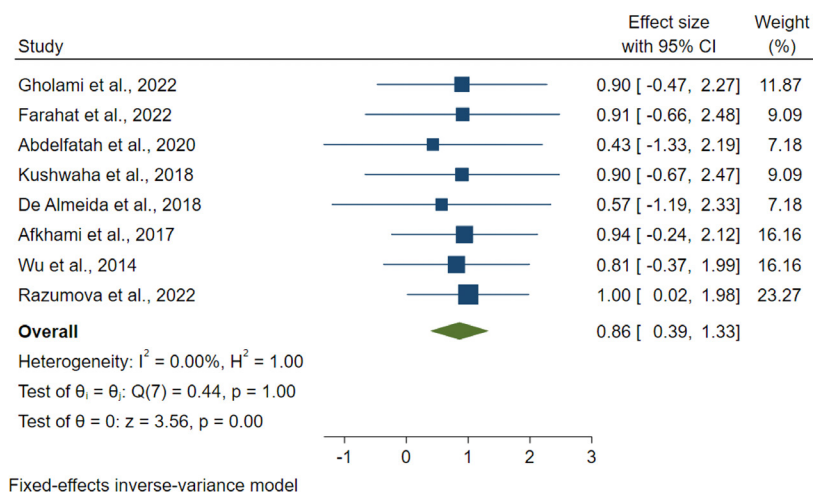
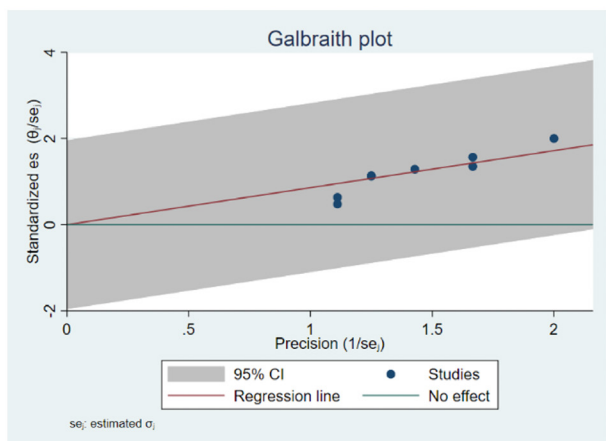


Figure 3: Galbraith plot for assessing heterogeneity.



Discussion

In recent years, the use of nanotechnology in medicine and dentistry has received much attention. In dentistry, to achieve ideal oral and dental health, nano dentistry has been proposed, which is the use of biotechnology, nanomaterials, and dental nanorobotics^{31,32}. In the past years, nanotechnology has been used in orthodontic treatments, periodontal diseases, dental implants, the development of nanocomposites, drug delivery systems, and the making of disinfectant solutions³³. Due to their small size, nanoparticles can be used in a very small volume, so they have better antimicrobial performance. As reported, several mechanisms of AgNPs make bacteria less resistant to them. As studies have shown, the main challenge in root canal treatment is treatment failure, which is caused by repeated infections and antimicrobial agents

that have become resistant to the use of antibiotics^{19,34-37}. Today, the effort is to introduce an ideal antiseptic so that the treatment failure can be practically reduced and root canals free from germs can be obtained for the general public. Studies have shown that *Enterococcus faecalis* was isolated from many examined samples³⁸⁻⁴⁰. Also, some studies have reported *Fusobacteria* and *Pseudomonas* with a high prevalence ratio^{41,42}. The literature shows that nanoparticles can have antimicrobial effects⁴³⁻⁴⁵. Silver is one of the oldest nanoparticles used as antimicrobial agents^{46,47}. However, the mechanism of action of AgNPs is not precisely known, and several methods have been proposed. Based on the findings of the present study, the use of AgNPs can have an antimicrobial effect; the experimental group had a significant improvement compared to the control group. Nanoparticles have increased antimicrobial activity by decreasing size due to increased surface area, which allows for greater interaction between ions and the microbial organism. The properties of nanoparticles are different from their corresponding bulk materials, resulting from a high surface-to-volume ratio⁴⁸. It can be stated that nanoparticles perform a better antimicrobial function by increasing the surface-to-volume ratio. It affects their biocompatibility and cytotoxicity much less than conventional compounds⁴⁹⁻⁵¹.

One of the limitations of the present study was that most of the existing studies had used AgNPs as an additive for a detergent and were not considered due to possible confounders excluded from the study. The standard or non-standard of the tested conditions can also affect the study results, which tried to use the criteria to determine the strength of the study protocol. In the studies, the concentration of the used solution and the size of the particles were different, which can be considered a confounding factor, and the findings of the present study

should be interpreted with caution. Also, one of the other limitations of the study was the time of disinfection in the studies, which was different from each other and could affect the results of the study; In the future, it is better to conduct studies with a similar method (particle size, concentration of silver nanoparticles and disinfection time) to provide better results with stronger evidence. One of the similarities of the informants was the use of syringes for AgNP; however, the needle size of the syringes was not the same. In the studies, the contact times of AgNP compared to other detergents differed from 1 to 20 minutes, which should be used with caution. More studies are needed, taking into account the size of the particles, the concentration of silver nanoparticles, the time of disinfection, similar to other studies, and taking into account the changes in the properties that affect the antimicrobial activity of silver nanoparticles to confirm the current evidence and provide more accurate and comprehensive results.

Conclusions

Based on the findings of the present study, AgNPs have a high antimicrobial effect in preventing the persistence of microorganisms in the root canal and root canal treatment failure, and AgNPs with different formulations can have an antimicrobial effect. However, the present study had limitations that should be considered when interpreting the results; Also, the size of the particles, the concentration of silver nanoparticles, and the time of disinfection can affect the antimicrobial properties of AgNPs, which requires more studies in this field.

Conflict of Interest

The authors declared that there is no conflict of interest.

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Screen Addiction among nursing students during confinement in Morocco

Adicción a las pantallas entre los estudiantes de enfermería durante el confinamiento en Marruecos

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Abstract

Aim: The objective of this study is to evaluate the psychological experience during confinement by psychological scales of student nurses and health technicians.

Material and Methods: To explore this topic, we used an anonymous questionnaire based on, in addition to status and individual conditions, scales assessing depression (Beck) and internet addiction (IAT).

Results: We were able to collect after a rigorous sorting 98 answers, of which 87.8% are women with an average age of 20 years. Beck, 18.36% according to the IAT scale are problematic Internet users with possible life consequences. The function of the mother, the place of residence and the domain of internet use such as social networks, TV and electronic entertainment are the variables that show a statistically significant difference with a $P < 0.05$, and the use of social networks is a risk factor for problematic internet use ($OR=2.21e+10$, and $p < 0.001$).

Discussion: The exploration of depression and the problematic use of the Internet has concluded that there is an undeniable impact of confinement on young students.

Key words: Depression, problematic internet use, confinement, covid-19, young student, Morocco.

Resumen

Objetivo: El objetivo de este estudio es evaluar la experiencia psicológica durante el encierro mediante escalas psicológicas a estudiantes de enfermería y técnicos sanitarios.

Material y métodos: Para explorar este tema, se utilizó un cuestionario anónimo basado, además de en el estado y las condiciones individuales, en escalas que evalúan la depresión (Beck) y la adicción a Internet (IAT).

Resultados: Pudimos recoger tras una rigurosa clasificación 98 respuestas, de las cuales el 87,8% son mujeres con una edad media de 20 años. Beck, el 18,36% según la escala IAT son usuarios problemáticos de Internet con posibles consecuencias en la vida. La función de la madre, el lugar de residencia y el dominio de uso de Internet como las redes sociales, la televisión y el entretenimiento electrónico son las variables que muestran una diferencia estadísticamente significativa con una $P < 0,05$, y el uso de las redes sociales es un factor de riesgo para el uso problemático de Internet ($OR=2,21e+10$, y $p < 0,001$).

Discusión: La exploración de la depresión y el uso problemático de Internet ha concluido que existe un innegable impacto del encierro en los jóvenes estudiantes.

Palabras clave: Depresión, uso problemático de Internet, encierro, covid-19, joven estudiante, Marruecos.

Introduction

The advent of the global COVID-19 pandemic and the need to mitigate the spread and transmission of the coronavirus, many countries, including Morocco, had to issue lockdown advisories and impose lockdown restrictions and social distancing protocols^{1,2}. Consequently the pandemic has disrupted lives, societies and economies around the world^{3,4}.

A large number of studies show varying degrees of psychological distress and neuropsychiatric problems in individuals as adverse consequences of these events. However, certain groups of individuals experienced lower levels of stress and reported a greater sense of well-being⁵.

These results could be attributed to a variety of factors such as greater control over life, flexible working arrangements, time spent with family, social support and above all resilience. For many others, stress and maladjustment during the pandemic have led to various health risk behaviors (poor diet, sedentary behaviors, alcohol use, drug use, sleep problems, use excessive media and technology, etc.)⁶.

Technology and the internet have been implicated in many maladaptive patterns or unhealthy responses to stressors. Prolonged school closures have prompted educational institutions to adopt online teaching-learning models for students which has increased the use of varied screens⁷.

Multiple investigators have explored internet overuse, online gaming, virtual gambling, social media addiction, electronic device use disorders, and excessive screen time during the COVID pandemic -19⁷⁻¹⁰, these studies, mainly conducted in Asia and Europe, show that these behaviors were linked to poor physical or mental health. Other studies have highlighted the emergence of these new psychological disorders, according to Griffiths, excessive use should not be equated with problematic use. However, there are several theories associated with the research context^{11,12}. Intends to make sense of internet use and assumes that individuals spend a lot of time on the internet in order to alleviate life stress and negative feelings and Social cognitive theory states that human behavior can be explained by the triad of personal, behavioral and environmental factors, and their mutual causation. Individual factors, the individual's behavior and the environment mutually affect each person's current and future behavior¹³.

In the present study, the objective is to begin an evaluation of the psychological experience during confinement by evaluating depression and Internet addiction among students of the Higher Institute of Nursing Professions and health techniques

of Rabat (ISPITS) Morocco, in order to verify if there are variables that can determine the probability of these disorders.

Materials and methods

Type of study

A cross-sectional, descriptive and analytical study was conducted between May 1, 2021 and June 1, 2021, using an anonymous questionnaire, which explores the three main axes of this work, firstly the socio-demographic conditions, including age, sex, level of education, marital status, second religious, economic data and data related to schooling and third the evaluation of the psychological experience during confinement by psychological scales; the BECK to assess depression, and IAT to assess Internet addiction.

Evaluation scales of psychological experience

BECK scale is a 13-item scale rated from 0-3 with a maximum score of 39. This instrument can be useful for evaluating depressive symptoms, or screening for major depressive disorders in target populations, its interpretation in favor of depression is 'it is greater than three, with an identification of 3 intensities of depression, mild for a score of 4 to 7, moderate for a score of 8 to 15 and severe if the score is greater than 16'¹⁴.

Scale AIT is a scale with 20 items noted from 0-5 with a maximum score of 100, the total score with the questionnaire is obtained by the sum of the points with the various items. Score from 20 to 49; no excessive use of the internet, Score from 50 to 79; problematic internet use with possible consequences on your life, Score from 80 to 100; problematic internet use with severe repercussions on your life¹⁵.

Data management and statistical analysis

The qualitative variables were presented in the form of frequencies and percentages, the quantitative variables were presented in mean standard deviation (SD) or median (interquartile range, IQR). The Chi-square (χ^2) test or Fisher's exact test were carried out according to their specific application conditions, to identify the differences in the proportions of categorical variables between three groups (group 1: normal score less than 20, group 2: score between 20 and 49 which does not present excessive use of the Internet and group 3: score between 50 to 79 which presents a problematic use of the Internet with possible consequences on life). In addition, multivariate logistic regression analyzes are used to identify risk factors for problematic screen use. All independent variables presenting a statistically significant value with $P < 0.05$ between the three groups were taken into account in the multivariate logistic regression. Data management and statistical analysis were performed using JAMOVI software for Windows.

Results

Participant characteristics

A total of 98 participants meeting the study criteria were included. The predominant sex was female (87.8%), with an average age of 20 years. More than half (60.2%) live with the family and of which 69.4% have mothers without professions. 55% of the participants were scholarship students. The most used educational platform for distance learning courses was google Meets (48%). Compared to Internet use on schooling, the results revealed that 66.7%

report a decrease in academic performance, 92% mainly use social networks, 38.7% pay 200 Drh per month for the Internet (Table I).

BECK and AIT characteristics

The majority of students with no medical and surgical history, 59.2% present depression (mild 28.6%, medium 26.5%, severe 4.1%) according to the Beck scale.

Table I: Participants characteristics.

Variable	N (%) (N=98)	Normal	No excessive internet use	Problematic internet use with possible consequences on your life	P
Age (M ± SD)	20 (1.04)	20+ /-0.805	20+/-1.09	20.2+/-1.04	0.739
Gender					0.630
Women	86 (87.8 %)	19 (22.4%)	49 (57.6%)	17 (20%)	
Man	12 (12.2 %)	2 (16.7%)	9 (75%)	1 (8.3%)	
Place of residence					0.043
With the family	59 (60.2 %)	10 (17.2%)	40 (69%)	8 (13.8%)	
With the friends	30 (30.6 %)	7 (23.3%)	116 (53.3%)	7 (23.3%)	
Boarding school	9 (9.2 %)	2 (28.6%)	2 (28.6%)	3 (42.9%)	
Father's function					0.317
Employee	18 (18.4%)	3 (17.6%)	13 (76.5%)	1 (5.9%)	
Official	23 (23.5%)	6 (26.1%)	9 (39.1%)	8 (34.8%)	
Free profession	27 (27.6%)	7 (25.9%)	15 (55.6%)	5 (18.5%)	
Retirement	24 (24.5%)	4 (16.7%)	16 (66.7%)	4 (16.7%)	
No occupation	6 (6.1)	1 (16.7%)	5 (83.3%)	0 (0%)	
Mother's role					0.005
Employee	9 (9.2%)	1 (11.1%)	7 (77.8%)	1 (11%)	
Official	10 (10.2%)	2 (20%)	1 (10%)	7 (70%)	
Free profession	7 (7.1%)	1 (14.3%)	4 (57.1%)	2 (28.6%)	
Retirement	4 (4.1%)	1 (25%)	3 (75%)	0 (0%)	
No occupation	68 (69.4)	16 (23.9%)	43 (64.2%)	8 (11.9%)	
School year					0.443
First year	15 (16.3 %)	3 (20%)	9 (60%)	3 (20%)	
Second year	42 (42.9 %)	12 (28.6%)	25 (59.5%)	5 (11.9%)	
Third year	40 (40.8 %)	6 (15%)	24 (60%)	10 (25%)	
Repeating					1.000
Yes	4 (4.1 %)	1 (25%)	3 (75%)	0 (0%)	
No	94 (95.9 %)	20 (21.5%)	55 (59.1%)	18 (19.4%)	
The Scholarship					0.222
Yes	55 (56.1 %)	15 (27.3%)	32 (58.2%)	8 (14.5%)	
No	43 (43.9 %)	6 (14.3%)	26 (61.9%)	10 (23.8%)	
Use of platform to study remotely					0.160
CLASSROOM	6 (8. %)	3 (50%)	2 (33.3%)	1 (16.7%)	
MEETS	35 (48%)	5 (14.3%)	26 (74.3%)	4 (11.4%)	
ZOOM	33 (44%)	10 (30.3%)	18 (54.5%)	5 (15.2%)	
Internet and Academic Performance					0.157
Yield increase	25 (33.3 %)	6 (24%)	13 (52%)	6 (24%)	
Decreased yield	50 (66.7%)	12 (24.5%)	33 (67.3%)	4 (8.2%)	
Average number of study hours spent in the institute per week	18 (10 ;28)	16 (10 ;25)	18 (10.5; 28.8)	17 (10 ;24.8)	0.612
Use of the Internet					0.004
Social Networks	69 (92 %)	18 (26.5%)	44 (64.7%)	6 (8.8%)	
TV and Entertainment	6 (8 %)	0 (0%)	2 (33.3%)	4 (66.7%)	
Login Mode					0.158
4G	27 (36 %)	4 (14.8%)	17 (63%)	6 (22.2%)	
WIRELESS	48 (64 %)	14 (29.8%)	29 (61.7%)	4 (8.5%)	
Amount paid for internet					0.566
50DH	7 (9.3 %)	2 (28.6%)	5 (71.4%)	0 (0%)	
100DH	23 (32 %)	3 (13%)	15 (65.2%)	5 (21.7%)	
200DH	29 (38.7 %)	10 (34.5%)	16 (55.2%)	3 (10.3%)	
>200DH	15 (20 %)	3 (20%)	10 (66.7%)	2 (13.3%)	

According to the interpretation of the AIT scale, we were able to classify the participants into 3 groups, group 1 (normal 21.6%), group 2 (no excessive use 59.8%), group 3 (problematic use with possible consequences on life 18.36%). By comparing the 3 groups and using the Chi-square (χ^2) test or Fisher's exact test, we find that there is a statistically significant difference with a $P < 0.05$ of the function of the mother, the place of residence and the domain of internet use such as social networks, television and electronic entertainment. (Table II).

Regarding the results of the multivariate logistic regression and adjusting for confounding factors, we find that the use of social networks is a risk factor for problematic Internet use (OR=2.21e+10, CI [6.91e+ 9–7.08e+10], and $p < 0.001$) (Table III).

Discussion

According to the results of this study, the participants were mainly women, single with an average age of 20, more than half lived with the family and whose mothers were without professions, the majority had no history, 59.2% present depression according to the Beck scale, 18.36% are problematic Internet users with possible consequences on life according to the IAT scale, therefore depression and problematic use with possible consequences on life are negative consequences of the covid 19 pandemic on ISPIST students.

The function of the mother, the place of residence and the domain of internet use such as social networks, TV and electronic entertainment are variables that present a

Table II: Medico-surgical-psychiatric characteristics of the participants.

Variable	N (%) (N=98)	Normal	No excessive internet use	Problematic internet use with possible consequences on your life	P
Taking Medication					
No	83 (84.7%)	17 (20.5%)	51 (61.4%)	15 (18.1%)	0.660
Yes	15 (15.3%)	4 (28.6%)	7 (50%)	3 (21%)	
Medical-Surgical-Psychiatric history					
Medical	14 (14.3%)	4 (30.8%)	6 (46.2%)	3 (23.1%)	0.255
Psychiatric	4 (4.1%)	2 (50%)	1 (25%)	1 (25%)	
RAS	80 (81.6%)	15 (18.8%)	51 (63.7%)	14 (17.5%)	
Family history of problematic substance use					
Yes	80 (81.6%)	18 (22.8%)	45 (57%)	16 (20.3%)	0.582
No	18 (18.4%)	3 (16.7%)	13 (72.2%)	2 (11.1%)	
Beck scale					
No depression	40 (40.8%)	9 (22.5%)	26 (65%)	5 (12.5%)	0.294
Mild depression	28 (28.6%)	8 (29.6%)	14 (51.9%)	5 (18.5%)	
Average depression	26 (26.5%)	3 (11.5%)	17 (65.4%)	6 (23.1%)	
Severe depression	4 (4.1%)	1 (25%)	1 (25%)	2 (50%)	
Internet Addiction Scale (IAT)					
Normal	21 (21.6 %)				—
No excessive internet uses	58 (59.8 %)	—	—	—	
Problematic internet use with possible consequences on your life.	18 (18.36 %)				

Table III: Multivariate Analysis.

	Model 1 Multivariate Analysis			Model 2 Multivariate Analysis		
	OR	CI 95%	p	OR	CI 95%	p
Mother's role						
Employee	*					
Official	0.98	[0.09–10.05]	0.989	2.10 ⁰⁻⁶	[0.00–inf]	0.993
Free profession	0.17	[0.01–2.32]	0.185	8.64	[0.85–87.95]	0.068
Retirement	1.91	[0.05–64.22]	0.717	3.34	[0.079–140.98]	0.527
No occupation	1.59 ⁰⁺⁷	[0.00–inf]	0.971	2.15 ⁰⁻⁵	[0.00–inf]	0.986
Place of residence						
With the family	*					
With the friends	0.5	[0.13– 1.88]	0.3	1.08	[0.12–9.52]	0.940
Boarding school	1.92 ^{e-14}	[0.0000–inf]	0.94	0.614	[0.03–12.58]	0.752
Use of the Internet						
Social Networks	*					
TV and Entertainment	1.66 ⁰⁺⁹	[5.20 ^{e+8} – 5.32 ^{e+9}]	<0.001	2.21 ^{e+10}	[6.91 ^{e+9} –7.08 ^{e+10}]	<0.001

statistically significant difference with a $P < 0.05$ between the 3 groups and the use of social networks is a risk factor for problematic screen and internet use ($OR=2.21e+10$, $IC[6.91e+9-7.08e+10]$, $p < 0.001$).

Parallel to these results, Wheaton examined the relationship between media use, susceptibility to emotional contagion, and emotional responses to the COVID-19 outbreak among 603 university students with an average age of 22.92; the results revealed that media consumption during the pandemic significantly predicted the degree of anxiety related to COVID-19¹⁶.

Moreover, another large-scale Chinese cross-sectional study, conducted on a sample of 512 college students with an average age of 22, found that social media use was significantly associated with depressive symptoms and mental illness symptoms. anxiety, this finding suggests that COVID-19-related stress explains the relationship between social media use and depression¹⁷.

Similar conclusions were drawn by Li and colleagues indicating that social media was associated with negative mental health consequences. Investigators analyzed data from 68,685 university students at two stages of the pandemic; shortly after the start of the pandemic (T1) and 1 month later (T2). Comparing T1 and T2, social media usage was significantly higher at the start of the pandemic. Heavy social media use (>3 h/day) at T1 was found to be a significant predictor of acute stress and anxiety symptoms, but not depressive symptoms. The authors concluded that the use of social media can exert a negative influence on mental health in the short and long term¹⁸. Moreover, the results obtained from an online survey and published by Shoa and his colleagues point in the same direction. The authors assessed individuals' emotional state, regulation and coping strategies during the COVID-19 outbreak among 528 Chinese citizens with an average age of 35 years. They reported that coping strategies (based on social media), such as disclosing and sharing negative emotions, generate stressful effects. Additionally, stress and anxiety can cause digital emotions to contagion¹⁹.

In a population-based study carried out in Hong Kong, a telephone survey was administered to 1070 adults (658 social media users and 412 non-users) between May and June 2020. The results showed that the relationship between social media use and mental health may be influenced by age. In fact, the young participants got a lot of information from social media that could easily trigger stress²⁰.

Additionally, time spent on social media has been associated with symptoms of depression during the COVID-19 pandemic, possibly because spending more time on social media involves greater exposure to

information about COVID-19. 19 and a greater likelihood of experiencing infodemic and emotional contagion²¹. These data are substantially consistent with those of a study conducted on 185 young adults with an average age of 21 years, from several countries[28] showing that an increase in the use by young people of social media sites and services streaming during the pandemic period resulted in increased internet use and gaming addiction that significantly predicted high scores for depression, loneliness, escape, poor sleep quality, and related anxiety to the pandemic¹³.

Moreover, according to several surveys, the increased use of Internet games is linked to poor psychological adjustment. In fact, gambling has been used by adolescents and young adults as a coping mechanism to deal with the psychological distress of the pandemic²²⁻²⁵. Other studies have reported contrasting results. As the survey conducted by David and Roberts suggests, the use of smartphones can mitigate the negative impact of confinement on social connection and well-being. The authors tested 400 undergraduate students from a major American university, 52% of the participants were women with an average age of 20, and they reported that confinement is associated with social connection and well-being, subjectively lower and at higher levels of stress and depression. They also found that smartphone use improves social relationships, as more smartphone use improves social connection and is associated with better psychological well-being²⁶. This appears to be consistent with a study carried out in Italy to explore the relationships between anxiety, perceived vulnerability to illness, and smartphone use during the COVID-19 pandemic. For the 194 university students surveyed with an average age of 21, the use of smartphones seems to mitigate the negative impact of the covid 19 pandemic on social relations²⁷. Another study to verify the effect of social media on mental health during COVID-19 was carried out among 248 international university students in the Netherlands²⁸. The authors found that social media use had a positive impact on mental health outcomes during the COVID-19 pandemic in terms of improvement in depressive symptoms. Another study to verify the effect of social media on mental health during COVID-19 was carried out among 248 international university students in the Netherlands²⁸. The authors found that social media use had a positive impact on mental health outcomes during the COVID-19 pandemic in terms of improvement in depressive symptoms²⁸. These results were confirmed by Sewall et al. who conducted a four-wave panel study of 384 young American adults with a mean age of 24.5 years to examine the association between mental health, objective use of digital technology, and stressors related to the pandemic. They reported that the use of digital technology did not contribute to increases in depression, anxiety, or suicidal ideation²⁹.

Conclusion

Technology in the context of the covid 19 pandemic has played two opposing roles: on the one hand, it is a tool for communication, sharing, education and remote care, thus helping young people to preserve their mental health during the period of confinement, on the other hand it is responsible for a disorder of problematic use of the internet screen and social networks, this problematic use can have the negative consequence on life of poor academic performance, and a psychological distress, so attention must be paid by professionals, psychologists and psychiatrists to detect the suffering and loss of young people during the pandemic.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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Molecular study in breast Paget's disease and its relationship with the prognosis: A retrospective-analytical study

Estudio molecular en la enfermedad de Paget de la mama y su relación con el pronóstico: Un estudio retrospectivo-analítico

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Abstract

Introduction: Paget's disease of the breast is a rare disease with an incidence of 0.5 to 5%. The role of molecular markers is not well understood in this type of cancer. Therefore, we decided to study the relationship between the status of molecular markers and the patient's prognosis and survival rates.

Materials and methods: This cross-sectional survival study was done by census sampling method. After collection, the data were entered into SPSS software version 18, and survival was assessed using Kaplan-Meier curves and Log-Rank test. P-value less than 0.05 was considered statistically significant.

Results: A total of 52 patients with a mean age of 48.89 ± 12.51 was obtained. 57.7% of patients had right breast involvement. 44 patients (84.6%) had infiltrating ductal carcinoma (IDC) and 3 patients (5.8%) had ductal carcinoma in-situ (DCIS). Thirty-five patient (67.3%) had a positive estrogen receptor, 29 patient (55.8%) had positive progesterone receptor and 32 patients (61.5%) were HER2neu positive. 14 patients (26.9%) have died. The mean survival time was 98.08 months and the one, two, three, four, and five-years survival rate were 92%, 85%, 80%, 73%, and 69%, respectively. There was a statistically significant difference between the mean survival rate and HER2neu status. So that the mean survival in HER2neu positive patients was significantly higher than HER2neu negative patients ($p < 0.002$).

Conclusion: Based on the findings of the study, it can be concluded that patients with Paget's disease have a long-life expectancy and HER2neu status is an effective factor in survival.

Key words: Breast cancer, Paget's disease, hormone receptors.

Resumen

Introducción: La enfermedad de Paget de la mama es una enfermedad rara con una incidencia del 0,5 al 5%. El papel de los marcadores moleculares no se conoce bien en este tipo de cáncer. Por ello, decidimos estudiar la relación entre el estado de los marcadores moleculares y el pronóstico y la supervivencia de las pacientes.

Materiales y métodos: Este estudio transversal de supervivencia se realizó mediante el método de muestreo censal. Tras la recogida, los datos se introdujeron en el programa informático SPSS versión 18, y la supervivencia se evaluó mediante curvas de Kaplan-Meier y la prueba de Log-Rank. El valor p menor de 0,05 se consideró estadísticamente significativo.

Resultados: Se obtuvo un total de 52 pacientes con una edad media de $48,89 \pm 12,51$ años. El 57,7% de las pacientes tenían afectación de la mama derecha. 44 pacientes (84,6%) tenían carcinoma ductal infiltrante (CDI) y 3 pacientes (5,8%) tenían carcinoma ductal in situ (CDIS). Treinta y cinco pacientes (67,3%) tenían un receptor de estrógeno positivo, 29 pacientes (55,8%) tenían un receptor de progesterona positivo y 32 pacientes (61,5%) eran HER2neu positivos. 14 pacientes (26,9%) fallecieron. El tiempo medio de supervivencia fue de 98,08 meses y la tasa de supervivencia a uno, dos, tres, cuatro y cinco años fue del 92%, 85%, 80%, 73% y 69%, respectivamente. Hubo una diferencia estadísticamente significativa entre la tasa de supervivencia media y el estado de HER2neu. Así, la supervivencia media de las pacientes HER2neu positivas fue significativamente mayor que la de las pacientes HER2neu negativas ($p < 0,002$).

Conclusiones: En base a los resultados del estudio, se puede concluir que los pacientes con enfermedad de Paget tienen una larga esperanza de vida y el estado de HER2neu es un factor efectivo de supervivencia.

Palabras clave: Cáncer de mama, enfermedad de Paget, receptores hormonales.

Introduction

Paget's disease of the breast is a type of breast neoplasm that affects the skin of the nipple. This disease, or rather breast cancer, in many cases was associated with a non-invasive ductal carcinoma of the mammary gland tissue, although it can also be associated with invasive cancer¹⁻⁵. The results of a study conducted in Turkey on patients with Paget's breast showed that in 63% of patients there is a palpable mass on examination, in 33% eczema, erythema, and nipple ulcer, and in 10% there is discharge from the breast⁶. Histologically, a multifocal or multicentric tumor was observed in 21% of patients⁷⁻⁹. The results of another study conducted in Thailand on 27 patients with Paget's disease showed that 11 patients with clinical symptoms of Paget's disease, of which 7 had palpable breast mass¹⁰. Results of Arafah M et al, showed that most of the patients with breast Paget's disease were positive for HER2neu receptor¹¹. Other studies conducted on Paget's disease showed that ER, PR, receptor expression in Paget's disease were lower than other types of breast carcinoma and survival of patients with Paget's disease alone was better than patients with underlying of invasive carcinoma¹²⁻¹⁴. Because Paget's disease of the breast is one of the diseases in which the role of molecular markers is not well understood; Our study aimed to investigate the molecular status of Paget's disease and its relationship with the patient's survival time and prognosis.

Materials and Method

This descriptive cross-sectional survival study was done on patients with Paget's disease of the breast during the years 2006 to 2018. After the approval of the dissertation in the ethics committee of the university (IR.SSU.MEDICINE.REC.1399.172) with a pre-prepared checklist that includes the variables under study such as age, side involvement, type of accompanying pathology, molecular status including; estrogen receptor, progesterone receptor, and HER2neu status, overall survival rate (the patient's life condition from the time of diagnosis until the end of the study). The necessary variables were extracted from patients' hospital folders and pathology reports and then the collected data were entered into the preparation checklist. Sampling was by census method and all patients with Paget's breast disease referred to the hospitals in Yazd were included in the study during the mentioned period. Patients whose files were incomplete and could not be accessed were excluded from the study. In case of incomplete files, the necessary information was requested by telephone.

Statistical Analysis:

All registered data were analyzed using SPSS software version 18 for Windows (SPSS, Chicago, IL) and analyzed using appropriate descriptive indicators (frequency

distribution, mean and median), ANOVA and Chi-square statistical tests. The survival rate was assessed by using Kaplan-Meier curves and Log-rank test. P value less than 0.05 was considered statistically significant.

Ethical Considerations:

This study was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran and registered with the protocol number "IR.SSU.MEDICINE.REC.1399.172". Participants were provided written informed consent and were included in the study after they were provided information on treatment methods.

Results

In this study, 52 patients with a mean age of 48.89 ±12.51 years with a minimum age of 26 and maximum age of 78 years were obtained. Fourteen patients (26.9%) were in the age group under 40 years, 27 (51.9%) in the age group of 40 to 59 years, 11 (21.2%) in the age group equal or older than 60 years old. The frequency distribution of the involvement side in the studied patients showed that in 30 patients (57.7%) the tumor was on the right side and in 22 patients (42.3%) it was on the left side. The results of the study on the prevalence of comorbid cancer showed that 44 patients (84.6%) had infiltrated ductal carcinoma (IDC) and 3 patients (5.8%) had DCIS.

The results of the study on the frequency distribution of the type of receptor in the studied patients showed that 35 patients (67.3%) had estrogen receptors, 29 patients (55.8%) had progesterone receptors and 32 patients (61.5%) had HER2neu positive status. The results of the study on the frequency distribution of patient's mortality rate showed that at the end of the study, 38 patients (73.1%) were alive and 14 patients (26.9%) have died. The mean survival time of patients using the Kaplan-Meier curve with a 95% confidence interval (CI = 95%) was 98.08 months (8.06 years) with a minimum duration of 21 days and a maximum duration of 145 months (**Figure 1**). According to the **figure 1**, it can be seen that the survival of patients was equal to 118.87 months (or 9.77 years). Also, the survival rates of one, two, three, four, and five-years were 92%, 85%, 80%, 73%, and 69%, respectively. The results of the study on the mean survival time of patients in terms of age showed that the lowest survival rate was in the age group over 60 years (52.91 months). (**Figure 2**) Other information is given in **table I**. By using the Log Rank test, there is no statistically significant difference between the mean survival of patients according to age ($P > 0.05$). The mean survival time of the patients in terms of side involvement showed that the mean survival in patients with right and left involved sides was 97.92 and 58.42 months, respectively. Other information is given in **table I**.

Figure 1: Mean survival time in the studied patients.

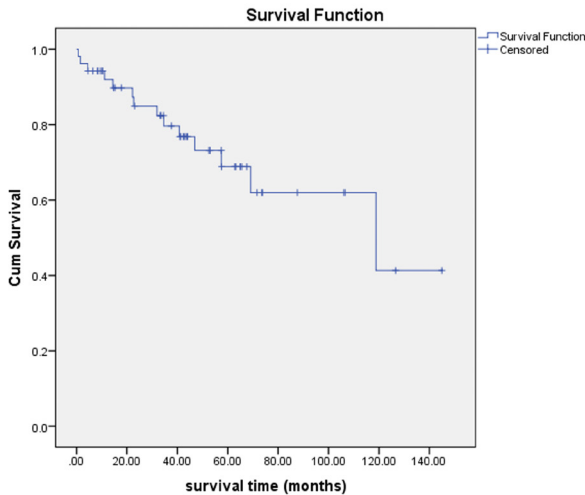


Figure 2: Mean survival time based on patient's age.

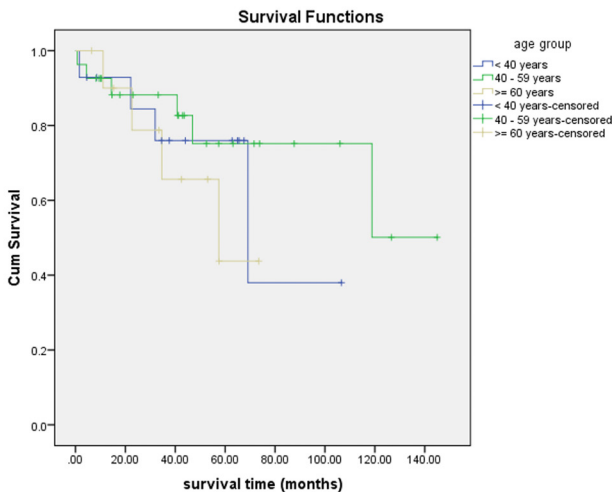


Figure 3: survival time based on Her2 neu status.

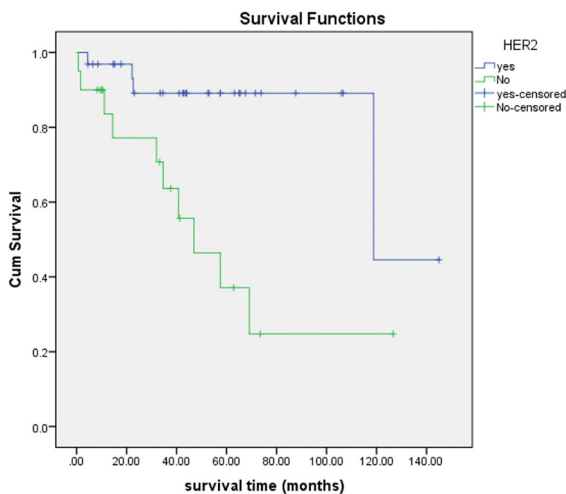


Table I: Molecular status in studied patients and correlation with survival time.

	number	Died (N)	Mean survival time (month)	P value
Estrogen receptor				
Positive	35	12	79.53	0.065
Negative	17	2	129.64	
Total	52	14	98.07	
Progesterone receptor				
Positive	29	8	87.39	0.715
Negative	23	6	108.74	
Total	52	14	98.07	
Her 2neu status				
Positive	32	4	119.44	0.002
Negative	20	16	59.78	
Total	52	20	98.07	

The mean survival time of the patients in terms of the estrogen receptor status, was 79.53 months for positive group and 129.65 months, for negative groups, respectively. Other information is given in **table I**. By using the Log Rank test, it showed that there was no statistically significant difference between the mean survival of patients in terms of estrogen receptor status ($P>0.05$). The results of the study on the mean survival time of patients in terms of progesterone receptor status showed that the mean survival in the group that had positive and negative progesterone receptors were 87.39 and 108.74 months, respectively. Other information is given in **table I**. There was no statistically significant difference between the mean survival rate of patients according to the status of progesterone receptor ($P>0.05$) (Log-rank test).

There was a statistically significant difference between the mean survival rate of patients according to HER2neu status ($P<0.05$); The mean survival in HER2neu positive patients (119.45) was significantly higher than HER2neu negative patients. **Figure 3**

Discussion

Paget's disease of the breast is a rare disease that first described by James Paget in 1874¹⁴. The most clinical manifestation of Paget's disease is a skin lesion in the nipple area. In most cases, this disease is associated with an in situ ductal carcinoma²⁻⁹. Different results have been reported in terms of progesterone and estrogen receptors¹⁵. HER2neu status can also affect patients' prognosis. The results of our study showed that the mean age of the patients was 48.89 ± 12.51 years and 51.9% of the patients were in the age group of 40 to 59 years. In the study conducted by Wang, the mean age of the patients was 51.8 years¹³. The results of another study conducted in Thailand showed that the mean age of patients was 50.31 and the age range of patients was 36-68 years¹². The results of both studies were in line with the results of our study. Paget's disease of the breast seems to occur more in the fifth and sixth decades of life. Previous studies

have reported a prevalence of cancer associated with Paget's disease from 67 to 100 percent; In most studies, more than 90% are reported. A study by Muttarrak on 27 patients with Paget's breast found that the prevalence of Paget's disease was 1.14% among patients with breast carcinoma¹². The results of our study on the prevalence of comorbid cancer showed that 44 patients (84.6%) had IDC and 3 patients (5.8%) had DCIS. The results of Wang's study showed that out of 137 patients, 7 had Paget's disease without any underlying cancer and 130 others had underlying cancer or DCIS¹³. The results of a study conducted in the Greece showed that 68.5% of patients with Paget's disease of the breast were simultaneous with DCIS or IDC¹⁴. As reported in previous studies, a high percentage of cases of Paget's disease is associated with underlying malignancy, and the most common malignancy associated with this disease was ductal carcinoma of the breast¹⁵⁻¹⁸. The results of the present study on the frequency distribution of receptor type in the studied patients showed that 35 patients (67.3%) had estrogen receptors, 29 patients (55.8%) had progesterone receptors and 32 patients (61.5%) were positive for HER2neu. The results of a study conducted in China showed that the positive rates of ER, PR, and HER2 neu were 29.2%, 38%, and 78.1%, respectively¹⁹. HER2neu seems to be the most common marker used in patients with Paget's disease of the breast. In a study conducted by Salvadori B et al. in 1976 on 91 patients with Paget's disease, it was found that the outcome of surgical treatment on the 5 and 10-year survival rates was 59% and 44%, respectively, as well as the average survival. Also, the average survival of patients was 9 years²⁰. The 5 and 10-year survival rates were 38% and 22% in patients with a palpable breast mass and 92% and 82% in patients without palpable mass, respectively²¹. Regarding the survival rate and prognosis of patients and the role of hormone receptors and other factors affecting the prognosis of the disease, the results of our study showed that 14 (26.9%) of patients died. The mean survival time in the studied patients was 98.08 months and the survival rates of one, two, three, four, and five-years were 92%, 85%, 80%, 73%, and 69%, respectively. There was a statistically significant difference between the mean survival of patients according to HER2neu status. The mean survival in HER2neu positive patients (119.45) was significantly higher than in HER2neu negative patients. In a study conducted by Ling H et al. in 2013 in China on 52 patients with Paget's breast and invasive breast carcinoma, it was found that 24 patients (46.2%) did not have clinical symptoms of Paget and the results showed that the presence of underlying carcinoma increased the risk of lymph node involvement, decreased expression of hormone receptors, increased expression of HER2neu and reduced the 5-year survival rate of patients⁹. The results of Wang study showed that the 2-year and 5-year survival rates were 99% and 96%, respectively¹³. There was a statistical relationship between the duration of the disease, HER2neu positivity, tumor stage and lymph node involvement, and metastasis with survival, which is

consistent with the present study. The results of another study showed that 92.9% of Paget cells were positive for the marker C-erbB-2, 100% for Cyclin D1, 85.7% for Ki-67, and 14.3% for Bcl-2. The results of this study also showed that the positive molecular markers of HER2neu, Cyclin D1, and Ki-67 in patients with Paget's disease were associated with greater invasiveness, worse prognosis, and lower survival rate¹⁹. Five- and ten-years survival rates in patients with palpable breast mass were 38% and 22%, respectively, and in patients without palpable mass were 92% and 82%, respectively. The results of the Ling H study showed that the presence of underlying carcinoma increased the risk of lymph node involvement, decreased expression of hormone receptors, increased expression of HER2neu, and decreased 5-year survival⁹.

Conclusion

According to the results of the study and the high average survival and 5-year survival rate of patients, it can be concluded that in general, Paget's disease of the breast has a good prognosis and the survival rate is high in these patients. Also, according to the results, it can be said that none of the variables of age, breast side involved, the status of hormone receptors (estrogen and progesterone) effects on the survival rate of patients with Paget disease, and the only effective factor on the survival rate is HER2neu status, so patients who are HER2neu positive have higher survival time.

Conflict of Interest

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

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Characterisation of HLA-DR antigen in patients type 1 diabetes mellitus in patient attending a tertiary hospital in Enugu, south-east Nigeria

Caracterización del antígeno HLA-DR en pacientes con diabetes mellitus de tipo 1 que acuden a un hospital terciario de Enugu, en el sureste de Nigeria

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Abstract

Background: The association between HLA-DR antigen and diabetes mellitus was studied in know diabetic patient on medication at University of Nigeria Teaching Hospital Enugu. The study was done to characterize the HLA-DR antigen in patients with type 1 diabetes mellitus attending University of Nigeria Teaching Hospital, Enugu.

Materials and methods: Ethical clearance was obtained from the Hospital Research Ethics Committee, while informed consent was obtained from each member of the studied group. Whole blood was collected from each subject using standard venipuncture into an EDTA anticoagulant bottle and fluoride tube. The fasting glucose level was determined by enzymatic oxidase-peroxidase method and glycated hemoglobin (HbA1c) spectrophotometrically. The HLA-DR antigen alleles were studied using sequence specific primer polymerase chain reaction (SSP-PCR) techniques.

Results: The mean results of glucose and HbA1c levels were normal and showed no significant difference when they were compared according to their alleles. The correlation using Kruskal-Wallis test and Dunn's Multiple comparison test showed no significant difference in all the group; HbA1cvs HLA-DR antigens and glucose levels vs HLA-DR antigens $P = 0.7325$ and $P = 0.6081$. However, the alleles HLA- DRB4*01 (17.5%), DRB1* 03 (29.2%) and DRB1*15 (35%) showed higher frequencies in the group studied.

Conclusion: This infers that these alleles may be predictive of diabetes in Enugu.

Key words: HLA-DR antigen, genetic risks, diabetes mellitus, patients.

Resumen

Antecedentes: Se estudió la asociación entre el antígeno HLA-DR y la diabetes mellitus en pacientes diabéticos conocidos que reciben medicación en el University of Nigeria Teaching Hospital de Enugu. El estudio se realizó para caracterizar el antígeno HLA-DR en pacientes con diabetes mellitus de tipo 1 que acuden al University of Nigeria Teaching Hospital de Enugu.

Materiales y métodos: Se obtuvo la autorización del Comité Ético de Investigación del Hospital, y el consentimiento informado de cada miembro del grupo estudiado. Se extrajo sangre total de cada sujeto mediante una venopunción estándar en un frasco anticoagulante con EDTA y un tubo de fluoruro. El nivel de glucosa en ayunas se determinó por el método enzimático de la oxidasa-peroxidasa y la hemoglobina glucosilada (HbA1c) por espectrofotometría. Los alelos del antígeno HLA-DR se estudiaron mediante técnicas de reacción en cadena de la polimerasa con cebadores específicos de secuencia (SSP-PCR).

Resultados: Los valores medios de glucosa y HbA1c fueron normales y no mostraron diferencias significativas cuando se compararon según sus alelos. La correlación mediante la prueba de Kruskal-Wallis y la prueba de comparación múltiple de Dunn no mostró diferencias significativas en todo el grupo; niveles de HbA1c frente a antígenos HLA-DR y niveles de glucosa frente a antígenos HLA-DR $P = 0,7325$ y $P = 0,6081$. Sin embargo, los alelos HLA- DRB4*01 (17,5%), DRB1* 03 (29,2%) y DRB1*15 (35%) mostraron mayores frecuencias en el grupo estudiado.

Conclusiones: Esto infiere que estos alelos pueden ser predictivos de la diabetes en Enugu.

Palabras clave: Antígeno HLA-DR, riesgos genéticos, diabetes mellitus, pacientes.

Introduction

According to their distinct roles in the immune system, HLA molecules are typically divided into three classes: HLA-I, HLA-II, and HLA-III¹. Subclasses are further separated into the major classes: There are six types of HLA-I molecules: HLA-A, HLA-B, HLA-C, HLA-E, HLA-F, and HLA-G. There are also eight types of HLA-II molecules: HLA-DMA, HLA-DMB, HLA-DOA, HLA-DOB, HLA-DPAI, HLA-DPBI, HLA-DQA1, HLA-DQBI, HLA-DRA, HLA-2. The complement system's components are encoded by HLA-III molecules. Class I and class II molecules have different functions and structural characteristics: Class I molecules are found in almost all nucleated cells and are made up of a single a chain that is non-covalently attached to a short polypeptide (32-microglobulin) and delivers intracellular peptides from the virus to CD8+ cytotoxic T lymphocytes, which causes the lysis of the infected cells. Immune system cells with particular functions, such as dendritic cells, macrophages, and B cells, express class II molecules³.

The main objective of HLA-DR is to introduce peptide antigens to the immune system that may be of foreign origin in order to stimulate or inhibit T-(helper)-cell responses that ultimately result in the generation of antibodies against the same peptide antigen. DR are commonly found in antigen-presenting cells, such as macrophages, B-cells, and dendritic cells. Since the DR "antigen" on the cell surface is frequently produced in response to stimulation, DR is also a sign of immunological stimulation⁴.

A strong association of certain HLA class II (DR and DQ) subtypes with T1D has been very consistently demonstrated across all population groups studied, though specific risk alleles (and especially their frequencies) vary across ethnic groups and/or geographical regions. The major genetic risk factors for type 1 diabetes mellitus (T1D) map to the major histocompatibility complex region on chromosome 6p21.3⁵.

In NIDDM patients, clusters of HLA-DR positive macrophages have been seen to surround islet amyloid deposits. HLA class II has been strongly related to Type 1 Diabetes, although there is limited research connecting HLA class II to NIDDM. HLA DRB1*04 and DRB1*07 have been found as several HLA alleles linked to NIDDM, while DR3, DR4, DR7, DR11, and DR13 6–9 have also been linked to the condition⁶⁻⁹.

Material and methods

Sample size

Blood sample was collected from 120 participants, all of which are individuals with type 1 diabetes mellitus. Approximately 5 ml of blood was collected using standard venipuncture techniques. 2 mL was placed in

sodium fluoride tubes for fasting blood glucose and 3 mL was placed in EDTA tubes for hemoglobin ale (HbA1c) and HLA-DR assays. Fluoride tube samples were tested at room temperature within 6 hours of collection. EDTA samples were stored in a refrigerator at a temperature of -4 °C before being assayed within 48 hours.

Eligibility criteria

Written consent was obtained from the subjects after reviewing the Participant Information Sheet. The subjects of this study were diabetic subjects from the University Teaching Hospital of Nigeria, Enugu and were of Nigerian descent. Subjects (n = 120) consisted of women and men of various ages.

Ethical clearance

The study was approved by the Institutional Review Board of the University of Nigeria Teaching Hospital Enugu and the subjects received a written informed outlet to initiate the study approved by the Institutional Review Board of the hospital. The study complies with the Declaration of Helsinki.

Methodology

All reagents used are commercially prepared and analytically tested

Measurement of glucose level

A. Spectrum Reagent (Ref 250)

Enzymatic glucose oxidase - peroxidase method was used for the estimation of glucose.

Procedure:

Three test tubes labeled blank, standard and sample were placed and 1 ml of reagent was added to each. 10 µl plasma was added to standard tubes and 10 µl plasma was added to appropriately labeled sample tubes. Nothing was added to tubes marked blank, except glucose reagent they were then mixed and incubated at 37°C. for 10 minutes. The absorbance of the samples and standards against the reagent blank was measured at 420 nm within 30 minutes.

B. Determination of Glycated Haemoglobin (HBALC) by tecodiagnosics, U S.A (Teco Diagnostics Reagent)

Procedure:

a. Hemolysate Preparation:

Into tubes (13 x 100 mm) labeled: Standard, Control, Sample 1, etc 500ul Lysing Reagent was dispensed and 100ul of the well-mixed blood sample, standard or control was placed unto the appropriately labeled tube and mixed well. They were allowed to stand for 5 minutes.

b. Glycohemoglobin Preparation

Into 13 x 100 mm glass tubes labeled: Standard, Control, Sample 1, etc, 3.0ml of GlycohemoglobinCation-

exchange Resin was dispensed to each. Before use, the resin was mixed by inverting at least 10 times. The bottle was swirled after addition to each 5 tubes. From Step a3, 100ul of the hemolysate was added. The Filter Separators was positioned in the tubes so that the rubber sleeve is approximately 1 cm above the liquid level. The tubes were placed on the rocker and mixed continuously for 5 minutes. The tubes were then removed from the rocker. The Filter Separator was pushed into the tubes until the resin is firmly packed. The supernatant was poured into a cuvette for absorbance measurement. The instrument was adjusted to zero absorbance at 415 nm with deionized water as the blank. The absorbance values for Standard, Control, Sample 1, etc were read and recorded.

Total Hemoglobin Fraction:

Into test tubes labeled Standard, Control, Sample 1, etc, 5.0 ml deionized water was dispensed. From Step a3, 20ul of the hemolysate was placed into the appropriately labeled tubes and mixed. The instrument was adjusted to zero absorbance at 415 nm with deionized water as the blank. The absorbance values for standard, control and sample were read and recorded. These readings are for total hemoglobin.

Calculations

The result was determined in the following step:

$$\% \text{Glyco.} = \frac{R(\text{unknown})}{(R \text{ standard})} \times \text{standard cone}$$

Where R:

$$R \text{ unknown} = \text{Ratio (unknown)} = \frac{\text{Abs.of Glyco (unknown)}}{\text{Abs.of Total Hb (unknown)}}$$

$$R \text{ (standard)} = \text{Ratio (standard)} = \frac{\text{Abs.of Glyco (standard)}}{\text{Abs.of Total Hb (standard)}}$$

C. Processing of whole blood to guanidium isothiocyanate (GITC) lysate

Procedure:

Whole blood sample was transferred into a 15ml tube that was labeled serially. Cold Ix RCLB buffer (10 ml) was added to each sample and the tube was properly mixed by inversion. The 15 ml tube (sample tube) was placed on ice for 10 minutes. The tubes were wiped carefully and centrifuged at 4000 rpm for 7 minutes. The supernatant was carefully decanted into the waste bucket while making sure the-cell pellet was not lost. Cold Ix RCLB buffer (10 ml) was added to the cell pellet, mixed by vortexing and steps 3-5 were repeated. Sterile PBS (10 ml) was added to the cell pellet, mixed by vortexing and centrifuged at 4000 rpm for 7 minutes. The supernatant was decanted;

5ml of sterile PBS was then added into each tube, mixed by vortexing and centrifuged at 4000 rpm for 5 minutes. The supernatant was decanted into the waste bucket (care was taken not to discard the pellet), and the 15 ml tubes were drained on a clean towel. While draining, the GITC buffer was prepared by adding 10ul BME to the 1ml of GITC. Activated GITC (1ml) containing BME was added to the white cell pellets in the tube. The GITC lysate was homogenized using blunt end 18G needle and 5ml syringe 18-times. The GITC lysate was transferred into 2ml cryovial using sterile Pasteur pipettes. And labeled accordingly for immediate nucleic acid extraction or storage at minus 20°C. For quality control Purpose, 1ml of GITC buffer containing (3ME was transferred into a cryovial, labeled as control and was treated as a sample during nucleic acid extraction. All GITC lysate sample were stored at the minus 20°C freezer.

D. Blood genomic DNA (gDNA) purification/ extraction using GeneJETgDNA purification kit by Thermo Scientific, Lithuania.

Procedure:

For each sample, 200 µl GITC lysate was transferred to a 2 ml Eppendorf tube, 400 µl lysate, 20 µl proteinase K was added. Mix well by vortexing. Samples were then incubated at 56°C for 10 minutes with occasional vortexing. Add 200 µl absolute ethanol (100%) and mix by vortexing. The prepared lysate was transferred to the GeneJETgDN extraction column placed in a collection tube. Centrifuge the column at 6000 rpm for 1 minute. Collection tubes containing flow-through solution were discarded. Place the GeneJETgDNA extraction column into a new 2 mL collection tube. Wash buffer I, 500 µl was added. It was then centrifuged at 8000 rpm for 1 minute. The flow-through was discarded and the extraction column was returned to the collection tube. 500 µl of wash buffer II (with ethanol added) was added to the GeneJET gDNA extraction column. Centrifuged at 12,000 rpm for 3 minutes. The flow-through collection tube was discarded and the GeneJET gDNA extraction column was transferred to a sterile 1.5 mL microcentrifuge tube. Add 200 µl of Elution Buffer to the center of the membrane of the GeneJET gDNA Extraction Column to elute the gDNA. Then incubate at room temperature for 2 minutes and centrifuge at 8000 rpm for 1 minute. 8. The extraction column was discarded and the purified DNA was stored at -20°C.

E. Sequence specific primers polymerase chain reaction (SSP-PCR) by Olerupssp AB, Sweden.

Human leukocyte antigen (HLA) was previously determined using a lymphotoxicity test. However, this test has been superseded by polymerase chain reaction (PCR)-based DNA typing techniques due to error rates and lack of resolution at the allelic level. In most PCR-based techniques, the PCR process is only required as an amplification step for the desired target

DNA and as a post-amplification step to distinguish between different alleles. In contrast, in the SSP-PCR methodology (sequence-specific primers – SSP), discrimination between different alleles is made during the PCR process. This shortens and simplifies the post-amplification step to a simple gel electrophoresis detection step. The results of the SSP test can be either positive or negative, so there is no need to interpret the results complicatedly. Moreover, the typing resolution of SSP-PCR is higher than other PCR-based typing techniques. This is because each primer pair defines two sequence motifs encoded in cis. H. on the same chromosome. Additionally, the synthetic properties of the SSP reagents resulted in improved stability and reduced lot-to-lot variability.

Procedure:

For each sample, the following reaction mixture were carried out. 4µ of DR primer mixes + 5µ PCR master mix + 2µ of gDNA using a well labeled microplate. Caped carefully and minifuged for 30 sec. It was then transferred to thermal cycler (PCR machine) and run using the program um exp00l; at the following thermal profile. 95°C for 5 min.

- I. 95°C for 30 sec.
- II. 64°C for 50 sec.
- III. 72°C for 50 sec.
- IV. 72°C for 5 min.
- V. Step ii-iv for 35 cycles

The reaction mixture was then removed after completion of the run. Ready for gel electrophoresis.

F. Agarose gel electrophoresis.

2% Agarose gel preparation

4 g of agarose powder was dissolved in 200 mL of Tris base, acetic acid, and EDTA (TAE) buffer in a 250 mL Scholtduran bottle. The mixture was well stirred and microwaved at medium temperature for 8 minutes.

It was cooled to about 36°C. and 10 µL of ethidium bromide solution was added. Then shake to obtain a homogeneous mixture. Inserted the electrophoresis comb into the gel mold. The comb creates wells in which samples are placed. Warm agar was then poured into the mold, allowed to gel, and chilled for 20 minutes. The cold gel was placed on a dark surface to facilitate sample placement in the wells. Each sample was mixed with a small amount of dye using a micropipette. Samples were then loaded into the wells. Place the sample-loaded gel in the electrophoresis chamber. The sample side must face the black or negative terminal. TAE buffer was injected into both sides of the chamber so that the buffer level covered the top of the gel. The electrophoresis lid was placed in the chamber and the power was turned on. Make sure the voltage is 100V and it works for 30 minutes. The power was turned off and the electrophoresis lid was removed. Then the gel was taken out and placed in a transilluminator. A transilluminator is a UV lightbox. An image of the gel was taken and ethidium bromide fluoresced and various allelic bands were seen.

Results

The study group included 120 participants (61 women and 59 men). The average age of participants at the time of the study was 48.8 ± 32.0 years. Group mean, median, standard deviation, minimum, maximum, 25% percentile, 75% percentile, lower limit of 95% confidence interval for mean, upper limit for 95% confidence interval for mean, and standard error for fasting plasma glucose levels Decided. Depending on the HLA-DR type, as shown in **table I**.

The mean, median standard deviation, minimum value, maximum value, 25% percentile, 75% percentile, lower 95% confidence interval of mean, upper 95% confidence interval of mean and standard error of glycated hemoglobin value were group according to their HLA-DR type as shown in **table II**.

Table I: Summary Sugar and HLA DR Type.

	DRB 1* 03:01	DRB 1* 03:02	DRB 1* 04:01	DRB 1* 07:01	DRB 1* 15:01	DRB 1* 15:02	DRB 3* 01:01	DRB 1* 16:01	DRB 4* 01:01
Number of Values	19	16	6	6	28	17	4	6	21
Minimum 25% Percentile	3.800	3.800	4.100	3.200	3.000	3.400	4.100	3.500	3.300
Median 75% Percentile	4.125	4.000	4.100	3.200	3.800	4.500	4.100	3.500	3.750
Maxim Mean	14.10	18.80	5.300	5.100	20.90	6.800	42.00	7.900	5.100
Std. Deviation	6.300	8.214	4.533	3.933	6.91	5.929	23.05	5.633	4.522
Std. Error	3.553	5.809	0.6658	1.021	5.169	2.444	26.80	2.203	1.188
Lower 95% CI of mean	1.256	2.196	0.3844	0.5897	1.558	0.9237	18.95	1.272	0.3961
Upper 95% CI of mean	3.329	2.842	2.879	1.396	3.219	3.668	-2.17.7	0.1607	3.603
Sum	9.271	13.59	6.187	6.471	10.16	8.189	263.8	11.11	5.436
	50.40	57.50	13.60	11.80	73.60	41.50	46.10	16.90	40.70

Table II: Summation for AIC and HLA DR type.

	DRB 1* 03:01	DRB 1* 03:02	DRB 1* 04:01	DRB 1* 07:01	DRB 1* 15:01	DRB 1* 15:02	DRB 3* 01:01	DRB 1* 16:01	DRB 4* 01:01
Number of Values	19	16	6	6	28	17	4	6	21
Minimum 25%	4.600	3.000	3.10	8.100	4.300	4.700	3.400	4.200	2.400
Percentile	4.850	3.600	3.100	8.100	4.900	5.100	3.400	4.200	2.650
Median 75%	8.450	4.500	6.000	8.700	5.600	5.900	6.050	6.700	5.500
Percentile	12.03	8.000	8.900	8.800	7.700	6.400	8.700	11.90	12.20
Maxim	15.10	10.40	8.900	8.800	12.60	9.400	8.700	11.90	12.40
Mean	8.563	5.800	6.000	8.533	6.591	6.129	6.050	8.600	6.800
Std. Deviation	3.883	2.681	2.900	0.3786	2.435	1.561	3.748	3.966	4.318
Std. Error	1.373	1.013	1.674	0.2186	0.7342	0.5899	2.650	2.290	1.439
Lower 95% CI of mean	5.316	3.320	-1.204	7.593	4.955	4.685	-27.62	-1.252	3.481
Upper 95% CI of mean	11.81	8.280	13.20	9.474	8.227	7.572	39.72	18.45	10.12
Sum	68.50	40.60	18.00	25.60	72.50	42.90	12.10	25.80	61.20

Table III: Frequency distribution of HLA-DRB1, DRB3, and DRB4 in participant.

S/N	Allele	F	%
1	HLA-DRB1 03	35	29.2
2	04	6	5
3	07	6	5
4	15	42	35
5	16	6	5
6	HLA-DRB3 01	4	3.3
7	HLA-DRB4 01	21	17.5

The distribution of HLA-DRB1, HLA-DRB3, HLA-DRB4 alleles is summarized in **table III**. A total of 5 different HLA-DRB1 alleles, a HLA- DRB3 and HLA-DRB4 were detected. With HLA-DRB4*01 HLA- DRB1*03 and DRB1*15 were presents in highly frequencies of 21 (17.5%), 35 (29.2%) and 42(35%) respectively.

Table IV

Table Analyzed		A1c Vs HLA DR type		
Kruskal-Wallis test				
P value		0.7323		
Exact or approximate P value?		Gaussian Approximation		
P value summary		ns		
Do the medians vary signif. (P < 0.05)		No		
Number of groups		9		
Kruskal-Wallis statistic		5.234		
Dunn's Multiple Comparison Test	Difference in rank sum	Significant? P<0.05?	Summary	
DRB1*03-01 vs DRB1*03;02	13.13	No	ns	
DRB1*03-01 vs DRB1*04:01	9.458	No	ns	
DRB1*03-01 vs DRB1*07:01	-3.875	No	ns	
DRB1*03-01 vs DRB1*15:01	7.307	No	ns	
DRB1*03-01 vs DRB1*15:02	8.054	No	ns	
DRB1*03-01 vs DRB3*01:01	11.88	No	ns	
DRB1*03-01 vs DRB1*16:01	0.2917	No	ns	
DRB1*03-01 vs DRB4*01:01	9.014	No	ns	
DRB1*03:02 vs DRB1*04:01	-3.667	No	ns	
DRB1*03:02 vs DRB1*07:01	-17.00	No	ns	
DRB1*03:02 vs DRB1*15:01	-5.818	No	ns	
DRB1*03:02 vs DRB1*15:02	-5.071	No	ns	
DRB1*03:02 vs DRB3*01:01	-1.250	No	ns	
DRB1*03:02 vs DRB1*16:01	-12.83	No	ns	
DRB1*03:02 vs DRB4*01:01	-4.111	No	ns	
DRB1*04:01 vs DRB1*07:01	-13.33	No	ns	
DRB1*04:01 vs DRB1*15:01	-2.152	No	ns	
DRB1*04:01 vs DRB1*15:02	-1.405	No	ns	
DRB1*04:01 vs DRB3*01 :Q1	2.417	No	ns	
DRB1*04:01 vs DRB1*16:01	-9.167	No	ns	
DRB1*04:CT vs DRB4*01:01	-0.4444	No	ns	
DRB1*07:01 vs DRB1*15:01	11.18	No	ns	
DRB1*07:01 vs DRB1*15:02	11.93	No	ns	
DRB1*07:01 vs DRB3*01:01	15.75	No	ns	
DRB1*07:01 vs DRB1*16:01	4.167	No	ns	
DRB1*07:01 vs DRB4*01:01	12.89	No	ns	
DRB1*15:01 vs DRB1*15:02	0.7468	No	ns	
DRB1*15:01 vs DRB3*01:01	4.568	No	ns	
DRB1*15:01 vs DRB1*16:01	-7.015	No	ns	
DRB1*15:01 vs DRB4*01:01	1.707	No	ns	
DRB1*15:02 vs DRB3*01:01	3.821	No	ns	
DRB1*15:02 vs DRB1*16:01	-7.762	No	ns	
DRB1*15:02 vs DRB4*01:01	0.9603	No	ns	
DRB3*01:01 vs DRB1*16:01	-11.58	No	ns	
DRB3*01:01 vs DRB4*01:01	-2.861	No	ns	
DRB1*16:01 vs DRB4*01:01	8.722	No	ns	

Table IV

Table Analyzed		A1c Vs HLA DR type	
Kruskal-Wallis test			
P value		0.6081	
Exact or approximate P value?		Gaussian Approximation	
P value summary		ns	
Do the medians vary signif. (P < 0.05)		No	
Number of groups		9	
Kruskal-Wallis statistic		6.350	
Dunn's Multiple Comparison Test	Difference in rank sum	Significant? P<0.05?	Summary
DRB1*03-01 vs DRB1*03:02	-3.321	No	ns
DRB1 *03-01 vs DRB1*04:01	5.750	No	ns
DRB1*03-01 vs DRB1*07:01	15.58	No	ns
DRB1*03-01 vs DRB1*15:01	2.023	No	ns
DRB1*03-01 vs DRB1*15:02	-2.250	No	ns
DRB1*03-01 vs DRB3*01:01	-5.500	No	ns
DRB1*03-01 vs DRB1*16:01	0.5833	No	ns
DRB1*03-01 vs DRB4*01:01	9.028	No	ns
DRB1*03:02 vs DRB1*04:01	9.071	No	ns
DRB1*03:02 vs DRB1*07:01	18.90	No	ns
DRB1*03:02 vs DRB1*15:01	5.344	No	ns
DRB1*03:02 vs DRB1*15:02	1.071	No	ns
DRB1*03:02 vs DRB3*01:01	-2.179	No	ns
DRB1*03:02 vs DRB1*16:01	3.905	No	ns
DRB1*03:02 vs DRB4*01:01	12.35	No	ns
DRB1*04:01 vs DRB1*07:01	9.833	No	ns
DRB1*04:01 vs DRB1*15:01	-3.727	No	ns
DRB1*04:01 vs DRB1*15:02	-8.000	No	ns
DRB1*04:01 vs DRB3*01 :Q1	-11.25	No	ns
DRB1*04:01 vs DRB1*16:01	-5.167	No	ns
DRB1*04:CT vs DRB4*01:01	3.278	No	ns
DRB1*07:01 vs DRB1*15:01	-13.56	No	ns
DRB1*07:01 vs DRB1*15:02	-17.83	No	ns
DRB1*07:01 vs DRB3*01:01	-21.08	No	ns
DRB1*07:01 vs DRB1*16:01	-15.00	No	ns
DRB1*07:01 vs DRB4*01:01	-6.556	No	ns
DRB1*15:01 vs DRB1*15:02	-4.273	No	ns
DRB1*15:01 vs DRB3*01:01	-7.523	No	ns
DRB1*15:01 vs DRB1*16:01	-1.439	No	ns
DRB1*15:01 vs DRB4*01:01	7.005	No	ns
DRB1*15:02 vs DRB3*01:01	-3.250	No	ns
DRB1*15:02 vs DRB1*16:01	2.833	No	ns
DRB1*15:02 vs DRB4*01:01	11.28	No	ns
DRB3*01:01 vs DRB1*16:01	6.083	No	ns
DRB3*01:01 vs DRB4*01:01	14.53	No	ns
DRB1*16:01 vs DRB4*01:01	8.444	No	ns

Using Kruskal-Wallis test and Dunn's multiple comparison test statistical tool to analyzed glycated hemoglobin verse HLA-DR type by comparison, the P value was 0.73 23 (P>0.05). There was no significant difference between glycated hemoglobin and HLA-DR Type. Theses is shown in **table IV**.

Discussion

Human major histocompatibility complex (MHC) or human leukocyte antigen (HLA) is a cell surface protein that plays an important role in the adaptive immune response. These proteins form complexes with antigenic peptides presented on the cell surface. This complex is recognized by T-cell receptors and triggers adaptive immune responses by inducing cell death and/or antibody production. A strong association of specific human leukocyte antigen (HLA) class II (DR and DQ) subtypes with T1D was demonstrated very consistently across all populations analyzed. Although specific risk alleles (and

especially their frequencies) vary by ethnic group and/or geographic region⁵. For example insulin dependent diabetes mellitus (IDDM) has been clearly associated with certain specific HLA class II alleles (like with HLA DR3 and DR4 in India 7 and DRB1*04 in Saudi Arab¹⁰, Various HLA alleles associated with non-insulin dependent diabetes mellitus (NIDDM) have been identified as HLA DRB1 *04 and DRB1*07 while HLA antigens associated with the disease include DR3, DR4, DR7, DR11 and DR13. The complex multifactorial etiology of NIDDM requires extensive research to identify predisposing factors in order to implement preventive measures such as dietary management and regular exercise. WHO estimates that Nigeria has the highest number of people with diabetes in Africa, with an estimated burden of about 1.7 million, rising to 4.8 million by 2030⁸⁻⁹.

Few studies have been conducted in Nigeria to determine the association between diabetes and genetic markers such as HLA-DR. Michael etc. DR3 has been found to be the most common antigen in her type 1 diabetic patients

living in Yoruba, southwestern Nigeria. Their study found no association between type 2 diabetes and HLA¹¹.

In Bahrain, DRB1*040101 ($p = 0.019$) and DRB1 *070101 ($p < 0.001$) were positively associated with the disease while DRB1*110101 ($p = 0.014$) and DRB1 *160101 ($p = 0.038$) were reported to be negatively associated⁸. Almawi *et al.* have found DRB 1*070101 ($p = 0.001$) to be positively associated with N1DDM in Bahraini and Lebanese population⁹.

However, since HLA is one of the most polymorphic genes known and there are large differences in HLA allele frequencies between different ethnic groups and geographic regions, the differences in these findings are expected increase. In the current study, the most common of DRB 1*15, DRB 1*03, and DRB4+01 may be factors contributing to the increased risk of developing diabetes in the study population. Mean results for glucose and her HbA1c levels were normal and showed no significant difference when compared according to their alleles. Correlations using the Kruskal-Wallis test and Dunn's multiple comparison test showed no significant differences across groups. HbA1c vs HLA-DR antigen

and glucose levels vs. HLA-DR antigen $P=0.7325$ and $P=0.6081$. However, alleles HLA-DRB4*01 (17.5%), DRB1*03 (29.2%) and DRB1*15 (35%) showed higher frequencies in the investigated group. This suggests that these alleles may predict Enugu's diabetes.

Conclusion

HLA-DRB1 + 15, DRB1*03 and DRB4*01 are genetic markers that may be associated with an increased risk of developing diabetes in the Nigerian Enugu population. High-resolution typing can further resolve specific DRB1*15, DRB1*03, and DRB4*01 alleles associated with disease and identify individuals at high risk of developing type 1 diabetes mellitus may help improve our understanding of genetic risk factors as prognostic/predictive value in diabetes and may contribute to the development of new therapeutic targets in the future.

Conflict of Interest

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

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ORIGINAL

Dietary intakes of Ethiopian Orthodox Tewahedo Christian lactating mothers during the fasting and non-fasting periods in rural Ethiopia: A prospective cohort study

Ingesta dietética de las madres lactantes cristianas ortodoxas tewahedo etiopes durante los periodos de ayuno y no ayuno en la Etiopía rural: Un estudio de cohorte prospectivo

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Abstract

Background: Even if Ethiopian Orthodox Tewahedo Christian lactating mothers are exempted from religious fasting, a significant proportion of these mothers are practicing it. However, there were little evidence generated on the effect of Orthodox fasting on the energy and nutrient intake of lactating mothers in Ethiopia. Therefore, this study was designed to evaluate the dietary nutrient intake of Ethiopian Orthodox Tewahedo Christian lactating women during Lent fasting and non-fasting periods in rural Ethiopia.

Materials and methods: A prospective study was conducted on 513 Ethiopian Orthodox Tewahedo Christian lactating mothers (157 fastings and 356 non-fastings) from rural Genta Afeshum district, during the lent fasting and non-fasting periods of 2017. Energy and nutrient intake was calculated from a 24-hr individual dietary recall using CIMI Ethiopia software. Nutrient intake below the estimated average requirement (EAR) was used to identify participants at high risk of inadequate intake.

Results: The median dietary intake of energy, zinc, magnesium, niacin, vitamin B12, and D for both study groups; and protein, iron, vitamin B1, and pantothenic acid for fasting mothers and vitamin A for non-fasting mothers were significantly ($p < 0.05$) higher in the non-fasting period compared to fasting period. Similarly, the prevalence of high risk for inadequate of protein, zinc and vitamin B1, both for the fasting and non-fasting mothers' group were significantly lower ($p < 0.05$) during the non-fasting compared to fasting period. Additionally, the prevalences for high risk of inadequate intake of dietary magnesium and niacin was significantly ($p < 0.05$) higher during fasting period than the non-fasting period, in the fasting mothers' group. However, there was a slight, but a significant ($p < 0.05$) increment in the prevalence of inadequate intake of vitamin A in the non-fasting period than the fasting period, in the non-fasting mothers' group.

Conclusion: The dietary energy and nutrient intake of fasting and non-fasting mothers were affected during lent fasting period, but they were substantially improved in the non-fasting period, thus the proportions of lactating mothers at higher risk of inadequate intake of nutrients were reduced during the non-fasting period. The results call for a strong integration and involvement of church leaders in the existing nutrition interventions, by preaching the exemption of the lactating mothers' group from fasting to improve the consumption of ASFs, both during fasting and non-fasting seasons. Therefore, this aims to improve the quality of diet consumed by the lactating mothers in general.

Key words: Ethiopian Orthodox Tewahedo Christian, lactating mothers, lent fasting period, dietary intake, CIMI Ethiopia.

Resumen

Antecedentes: Aunque las madres lactantes cristianas ortodoxas etíopes están exentas del ayuno religioso, una proporción significativa de estas madres lo practican. Sin embargo, se han generado pocas pruebas sobre el efecto del ayuno ortodoxo en la ingesta de energía y nutrientes de las madres lactantes en Etiopía. Por lo tanto, este estudio se diseñó para evaluar la ingesta de nutrientes en la dieta de las mujeres lactantes cristianas ortodoxas etíopes Tewahedo durante los períodos de ayuno y no ayuno de la Cuaresma en las zonas rurales de Etiopía.

Materiales y métodos: Se realizó un estudio prospectivo en 513 madres lactantes cristianas ortodoxas etíopes Tewahedo (157 ayunantes y 356 no ayunantes) del distrito rural de Genta Afeshum, durante los períodos de ayuno y no ayuno de Cuaresma de 2017. La ingesta de energía y nutrientes se calculó a partir de un recuerdo dietético individual de 24 horas utilizando el software CIMI Ethiopia. Se utilizó la ingesta de nutrientes por debajo del requerimiento medio estimado (EAR) para identificar a los participantes con alto riesgo de ingesta inadecuada.

Resultados: La mediana de la ingesta dietética de energía, zinc, magnesio, niacina, vitaminas B12 y D para ambos grupos de estudio; y de proteínas, hierro, vitamina B1 y ácido pantoténico para las madres en ayunas y de vitamina A para las madres sin ayuno fue significativamente ($p < 0,05$) mayor en el período sin ayuno en comparación con el período de ayuno. Del mismo modo, la prevalencia de alto riesgo de insuficiencia de proteínas, zinc y vitamina B1, tanto en el grupo de madres en ayunas como en el de madres sin ayuno, fue significativamente menor ($p < 0,05$) durante el período de no ayuno en comparación con el de ayuno. Además, la prevalencia de alto riesgo de ingesta inadecuada de magnesio y niacina en la dieta fue significativamente mayor ($p < 0,05$) durante el período de ayuno que durante el período sin ayuno, en el grupo de madres en ayunas. Sin embargo, hubo un ligero, pero significativo ($p < 0,05$) incremento en la prevalencia de ingesta inadecuada de vitamina A en el período de no ayuno que en el de ayuno, en el grupo de madres que no ayunan.

Conclusión: La ingesta de energía y nutrientes en la dieta de las madres en ayunas y sin ayuno se vio afectada durante el período de ayuno, pero mejoró sustancialmente en el período sin ayuno, por lo que las proporciones de madres lactantes con mayor riesgo de ingesta inadecuada de nutrientes se redujeron durante el período sin ayuno. Los resultados exigen una fuerte integración e implicación de los líderes eclesíasticos en las intervenciones nutricionales existentes, predicando la exención del grupo de madres lactantes del ayuno para mejorar el consumo de FAS, tanto en la época de ayuno como en la de no ayuno. De este modo, se mejorará la calidad de la dieta consumida por las madres lactantes en general.

Palabras clave: Cristiana ortodoxa etíope Tewahedo, madres lactantes, período de ayuno de cuaresma, ingesta dietética, CIMI Etiopía.

Introduction

Religious fasting plays a pivotal role in changing the dietary pattern of households. It affects the nutritional status of individuals living in the households, especially the nutritionally vulnerable groups such as pregnant and lactating women, and children¹⁻⁶. In Ethiopia, more than two-thirds of the population are either followers of Ethiopian Orthodox or Islam religions. In these religions, fasting during their fasting period is a strict/mandatory religious practice⁷. However, the fasting traditions and the number of fasting days in the calendar year are prominently different between these two religions⁸.

Unlike in Islam, the fasting practices in the Ethiopian Orthodox religion include avoiding any animal source foods for more than 180 days in a year. It is also coupled with abstaining from any foods and water until mid of the day or 3:00 pm afternoon by skipping breakfast during the fasting days, except Saturday and Sunday^{4,9,10}. However, pregnant and lactating mothers are among the groups of people exempted and permitted to eat animal source foods during the fasting days, and any foods and water during the day or during fasting periods without any restriction^{4,11-13}. However, this is not happening, as significant proportions of the Ethiopian Orthodox

pregnant and lactating mothers are fasting in the seven official fasting periods of the religion throughout the year^{2,4}. Studies in northern Ethiopia where the majority of the people are followers of the Orthodox religion reported that 28 - 77% of the pregnant or lactating women were fasting during the fasting periods^{4,14}. A study in Oromia region was also revealed that 38% of pregnant women were also practicing fasting in the Ethiopian Orthodox fasting period².

Our previous study in the Tigray region also found that the frequency of meals, diet diversity, and consumption of animal source foods (ASFs) was low in lactating women regardless of their fasting status during the Lent fasting season. However, the dietary pattern was improved during the following non-fasting period⁴. Yet, to the best of the authors' knowledge, less is known about the effect of Ethiopian Orthodox fasting on the dietary energy and nutrient intake of lactating mothers in Ethiopia. Therefore, this study was initiated to assess whether and to what extent the Ethiopian Orthodox fasting period affects the energy and nutrient intake of fasting and non-fasting Orthodox Christian lactating mothers.

Materials and methods

Study settings

The study was conducted in Genta Afeshum, which is one of the districts under the Misraqawi zone of Tigray regional state in Ethiopia. The district lies between 14° 20' N and 32° 29' E and resides in an altitude between 2045 and 3314 meters above sea level. The district is about 120 km far from the regional capital, Mekelle, and Addis Ababa (921 km), the capital city of the country. In the district, an estimated 99,112 people are living, and most of them are followers of the Ethiopian Orthodox religion^{4,15,16}.

Study design and period

This study is part of a larger longitudinal community-based study. In this study, two surveys were conducted during the Ethiopian Orthodox Tewahedo lent fasting (15 February – 15 April 2017) and non-fasting (1-30 May 2017) periods.

Sample size, sampling procedure, and study participants

Due to the larger study that included mother-child pairs, different sample sizes were calculated using the single population proportion formula and a finite population with a prevalence of underweight in lactating mothers, underweight, wasting, and stunting in children elsewhere in the Tigray region. Amongst this, the largest sample size was calculated using the assumption: prevalence of stunting in children (57.0%), 95% of confidence interval for true prevalence, and a relative precision (d) of 5% was high (n = 384) and selected for this study. Additionally, we also considered the 1.5 design effect in the calculated sample size, so that the final sample size was 576. The multi-stage systematic random sampling procedure was used to select the study participants.

Inclusion and exclusion criteria

Lactating mothers who had 6-23-months-old children, who were permanent inhabitants (lived > 6 months), were included, whereas those mothers who were not healthy or had even 6-23-months-old children but with an apparent health problem or gave birth to a twin with the indexed child were excluded from the study.

Data Collection

Before conducting the quantitative 24hr dietary survey, the principal investigator identified food items, recipes, cooking and serving materials, and how they were served commonly to women in the study area. Food items and prepared recipes were measured using a laboratory weight balance (2 kg maximum weight: Model CS 2000, Ohaus Corporation, New York, NJ, USA) to estimate the amount/weight of food consumed by the mothers. Pictures were also taken of the commonly consumed food items. Typical utensils for food preparation were used by the data collectors to support the estimation of quantities in the 24hr recall.

Ten experienced data collectors were recruited and trained before the survey. A pretested questionnaire which was translated to the local language (Tigrigna), was used to collect information on the socio-demographic and economic, and health-related characteristics of the mothers. Interactively, the mothers were asked to recall the dietary information for the last 24-hr using the multiple-pass technique¹⁷.

Ethical Consideration

Ethical clearances were obtained from the Ethical Review Committees in Ethiopia (Hawassa University and Tigray Region Health Bureau) and Germany. Furthermore, the aim of the study and the confidentiality of information to be collected during the study was told to the mothers. The participated mother was also informed about their right to withdraw with their children from the participation whenever they felt discomfirmed during the data collection time. Their agreement to participate with their indexed child in the study was documented by signing in the informed consent.

Data Management and Analysis

The amount of food items consumed by the mothers in the last 24-hr was estimated. The estimated amount of food items were sorted out into the 31 food groups of the CIMI Ethiopia software (Calculator for Inadequate Micronutrient Intake for Ethiopia)¹⁸. Then, food items that are categorized in the same food group were summed up together and the data were entered into CIMI Ethiopia, a nutritional assessment software. CIMI Ethiopia is recently developed and validated for calculating energy and nutrient intake and identifies the inadequacy of energy and nutrients in a person diet. Statistical analysis was performed using SPSS for Windows version 25 (IBM Corporation, Armonk, NY, USA). Nutrient intake data were not normally distributed (Kolmogorov-Smirnov test), therefore differences in energy and nutrient (n = 14) intake between the fasting and non-fasting mothers during the fasting period were determined using Mann Whitney U Test. Whereas, to determine the differences in the intake of fasting mothers between the fasting and non-fasting period, and similarly for the non-fasting mothers, Wilcoxon Signed Ranks Test was used. Average results were presented as mean (SD) and median with an interquartile range. To identify the prevalence of high risk for inadequate intake, the estimated average requirement (EAR) for each nutrient was used as a cutoff point^{19,20}. Because there is no EAR for energy and pantothenic acid, inadequacy was not calculated for them. To calculate a potential risk of inadequacy for a protein, individual body weight was considered. Then, the difference in the proportion of mothers with a high risk for inadequate intake between the fasting and non-fasting periods was determined in both groups using McNemar's test.

Results

Socio-demographic, economic, and health-related characteristics

A total of 513 lactating mothers are included in this study. The mean age and height of the fasting and non-fasting mothers were comparable. While the average number of children of the fasting mothers was higher than those of mothers who were not fasting. However, the mean MUAC for the fasting mothers was lower than those of mothers in the non-fasting group. Details of the characteristics of lactating mothers are presented in **table I**.

Comparison of energy and nutrient intake of fasting and non-fasting mothers during the lent fasting period

The median intake of energy, protein and most micronutrients by the non-fasting mothers were higher

than the fasting mother group during the fasting period. However, these differences were not statistically significant ($p > 0.05$), except for niacin ($p = 0.042$) (data not shown).

Energy and nutrient intake of fasting mothers

The median intake of energy and 9 nutrients (including protein) were significantly higher ($p < 0.05$) during the non-fasting than fasting period. Even though there was an increase in the median intake of calcium during the non-fasting period for fasting mothers, it was not significantly different ($p = 0.703$) from the fasting period. However, there was no significant difference in the median take of vitamin B6 between fasting and non-fasting period. Similarly, the median intake of vitamin C by the fasting mothers was comparable in the fasting and non-fasting periods. Besides these, the median intakes of vitamin A, B6, B12, C, D and calcium were below the EARs (**Table II**).

Table I: Socio-demographic, economic, and health-related characteristics of mothers in northern Ethiopia.

	Fasting status of mothers		
	Fasting mothers (n = 157) Number (%)	Non-fasting mothers (n = 356) Number (%)	Total (n = 513) Number (%)
Marital status			
Married	139 (88.5)	296 (83.1)	435 (84.8)
Others	18 (11.5)	60 (16.9)	78 (15.2)
Maternal education			
No formal education attended	63 (40.1)	115 (32.5)	178 (34.7)
Completed primary school	57 (36.3)	125 (35.1)	182 (35.5)
Completed secondary school and above	37 (23.6)	116 (32.6)	153 (29.8)
Maternal occupation			
Housewives	131 (83.4)	276 (77.5)	407 (79.3)
Farmers	21 (13.4)	51 (14.3)	72 (14.0)
Daily /causal laborers	1 (0.6)	14 (3.9)	15 (2.9)
Petty traders	2 (1.3)	12 (3.4)	14 (2.7)
Employed	2 (1.3)	3 (0.8)	5 (1.0)
	Mean (SD)	Mean (SD)	Mean (SD)
Age of the mother (years)	30.36 (6.27)	29.53 (6.47)	29.78 (6.42)
Height of the mothers(cm)	156.51 (5.49)	156.66 (5.51)	156.62 (5.50)
MUAC of the mothers (cm)	22.75 (2.20)	23.57 (2.28)	23.32 (2.29)
Number of children of the mothers	3.59 (1.92)	3.24 (2.02)	3.35 (1.99)
Household monthly income (Birr)	1591 (965)*	2141 (1119)**	1974 (1103)***

*n=155 **n=354***n=509

Table II: Comparison of dietary energy and nutrients intake of fasting mothers during the Ethiopian Orthodox Lent fasting and non-fasting periods in northern Ethiopia.

Nutrients	Fasting mothers (n= 157)				Sign
	Lent fasting period		Non-fasting period		
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
Energy (kcal)	1752 (725)	1769 (1147, 2248)b	2017 (462)	2059 (1665, 2363)a	<0.001*
Protein (g)	56 (27.9)	53.4 (32.9, 78.2)b	59.6 (15.6)	61.7 (49.3, 69.0)a	<0.001*
Iron (mg)	36.8 (18.3)	35.2 (22.6, 47)b	41.2 (10.9)	42.2 (34.0, 47.1)a	0.001*
Zinc (mg)	13.43 (6.1)	13.21 (8.65, 17.90)b	15.31 (3.7)	15.97 (12.60, 17.81)a	<0.001*
Vitamin A (µg RE)	219 (273)	155 (80, 248)a	236 (237)	187 (57.3, 362)a	0.102
Calcium (mg)	341 (184)	304 (194, 460)a	336 (102)	323 (268, 394)a	0.703
Magnesium (mg)	627 (273)	626 (407, 810)b	714 (167)	746 (586, 833)a	<0.001*
Vitamin B1 (mg)	1.69 (0.78)	1.61 (1.04, 2.26)b	1.86 (0.45)	1.93 (1.54, 2.19)a	0.006*
Niacin (mg)	13.2 (5.4)	13.8 (9.1, 16.1)b	15.6 (3.9)	15.8 (13.1, 18.1)a	<0.001*
Vitamin B6 (mg)	0.89 (0.58)	0.76 (0.45, 1.15)a	0.80 (0.52)	0.64 (0.42, 1.03)a	0.128
Vitamin B12 (µg)	0.008 (0.068)	0.000 (0.000, 0.000)b	0.065 (0.255)	0.000 (0.000, 0.000)a	<0.001*
Pantothenic acid (mg)	3.18 (1.43)	3.09 (2.03, 4.17)b	3.45 (0.84)	3.52 (2.84, 3.99)a	0.03*
Vitamin C (mg)	61.2 (28.9)	58.8 (39.6, 79.7)a	62.9 (30.9)	58.7 (41.8, 79.1)a	0.881
Vitamin D (µg)	0.04 (0.14)	0.02 (0.01, 0.03)b	0.07 (0.18)	0.03 (0.01, 0.06)a	<0.01*

Data analysis using Wilcoxon Signed Ranks Test ($p < 0.05$).

Energy and nutrient intake of non-fasting mothers

The median dietary intakes of energy, zinc, magnesium, vitamin A, B12, D, and niacin by the non-fasting mothers were significantly ($p < 0.05$) higher during the non-fasting period compared to the fasting period. Although the median intakes for majority of the rest of nutrients included in this study were not statistically significant ($p > 0.05$) between the two periods; their intakes by the non-fasting mothers were increased during the non-fasting period. Despite,

they were not statistically different ($p > 0.05$), the median intakes of dietary vitamin B6 and C by non-fasting mothers were decreased during the non-fasting period. While the median intakes of iron, zinc, magnesium, vitamin B1, and niacin by non-fasting mothers were above the EARs, the median intakes of nutrients such as vitamin A, B6, B12, C and calcium were below the EARs, in both study periods (Table III).

Table III: Comparison of dietary energy and nutrients intake of non-fasting mothers during the Ethiopian Orthodox lent fasting and non-fasting periods in northern Ethiopia.

Nutrients	Non-fasting mothers (n = 356)				Sign
	Lent fasting period		Non-fasting period		
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
Energy (kcal)	1878 (703)	1929 (1338, 2365) b	2075 (491)	2095 (1763, 2404) a	<0.001*
Protein (g)	60 (27.9)	59.7 (37, 78) a	60.9 (15.6)	60.5 (50.6, 70.6) a	0.302
Iron (mg)	39.2 (17.0)	39.4 (25.7, 49.7) a	41.5 (14.3)	41.6 (34.5, 47.5) a	0.058
Zinc (mg)	14.6 (6.8)	14.7 (9.7, 18.4) b	15.7 (4)	15.8 (13.2, 18.0) a	<0.01*
Vitamin A (µg RE)	242 (366)	154 (90, 243) b	244 (253)	202 (77.8, 345) a	0.004*
Calcium (mg)	366 (197)	323 (270, 386) a	341 (124)	324 (270, 387) a	0.106
Magnesium (mg)	676 (270)	688 (468, 869) b	726 (181)	741 (622, 843) a	<0.005*
Vitamin B1 (mg)	1.812 (0.78)	1.823 (1.174, 2.315) a	1.888 (0.47)	1.922 (1.601, 2.196) a	0.087
Niacin (mg)	14.2 (5.3)	14.2 (10.2, 17.9) b	16.3 (4.1)	16.3 (13.7, 18.4) a	<0.001*
Vitamin B6 (mg)	0.896 (0.64)	0.762 (0.442, 1.229) a	0.898 (0.64)	0.708 (0.459, 1.133) a	0.550
Vitamin B12 (µg)	0.005 (0.042)	0.000 (0.000, 0.000) b	0.077 (0.278)	0.000 (0.000, 0.000) a	<0.001*
Pantothenic acid (mg)	3.43 (1.58)	3.46 (2.31, 4.32) a	3.51 (0.94)	3.47 (2.93, 4.02) a	0.219
Vitamin C (mg)	68.5 (36.9)	64.9 (44.5, 85.6) a	64.6 (28.1)	62.7 (42.9, 82.4) a	0.122
Vitamin D (µg)	0.037 (0.09)	0.023 (0.014, 0.037) b	0.067 (0.201)	0.034 (0.014, 0.057) a	<0.001*

Data analysis using Wilcoxon Signed Ranks Test ($p < 0.05$)

Comparison of the prevalence of energy and nutrients intake below EAR

The prevalence of high risk for inadequate intake of protein, zinc, magnesium, niacin, and vitamin B1 by fasting mothers were significantly ($p < 0.05$) higher during the fasting than the non-fasting period. Similarly, for the non-fasting mothers, the prevalence for high risk of inadequate intake of protein, zinc, vitamin A and vitamin B1 were significantly ($p < 0.05$) higher during the fasting

period compared to the non-fasting period. Furthermore, over 96% of the lactating mothers included in this study were at high risk of inadequate intakes of vitamin A, B12, D, and calcium. Moreover, the majority of fasting and non-fasting mothers showed a high risk for an inadequate intake of vitamin C (78.1% - 89.9%) and vitamin B6 (91.1% - 93%) regardless of the study period (Table IV).

Table IV: Comparison of the prevalence of energy and nutrient intake below the EAR by fasting and non-fasting mothers during Ethiopian Orthodox Lent fasting and non-fasting periods.

Nutrients	Lactating mothers					
	Fasting mothers (n= 157)			Non-fasting mothers (n= 356)		
	Intake <EAR			Intake <EAR		
	Fasting period n (%)	Non-fasting period n (%)	Sign.	Fasting period n (%)	Non-fasting period n (%)	Sign.
Protein (g)	83 (52.9)	56 (35.7)	0.003*	161 (45.2)	126 (35.4)	0.008*
Iron (mg)	0 (0.0)	0 (0.0)	NA	1 (0.3)	0 (0.0)	NA
Zinc (mg)	54 (34.4)	13 (8.3)	<0.001*	102 (28.7)	29 (8.1)	<0.001*
Vitamin A (µg RE)	152 (96.8)	154 (98.1)	0.727	342 (96.1)	351 (98.6)	0.049*
Calcium (mg)	153 (97.5)	157 (100.0)	NA	347 (97.5)	352 (98.9)	0.267
Magnesium (mg)	14 (8.9)	0 (0.0)	0.001*	28 (7.9)	28 (7.9)	NA
Vitamin B1 (mg)	50 (31.8)	11 (7.0)	<0.001*	93 (26.1)	30 (8.4)	<0.001*
Niacin (mg)	74 (47.1)	39 (24.8)	<0.001*	143 (40.2)	65 (18.3)	0.597
Vitamin B6 (mg)	143 (91.1)	146 (93.0)	0.678	328 (92.1)	326 (91.6)	0.888
Vitamin B12 (µg)	157 (100.0)	157 (100.0)	NA	356 (100.0)	356 (100.0)	NA
Pantothenic acid (mg)	-	-	-	-	-	-
Vitamin C (mg)	141 (89.8)	138 (87.9)	0.701	307 (86.2)	278 (78.1)	0.275
Vitamin D (µg)	157 (100.0)	157 (100.0)	NA	356 (100.0)	356 (100.0)	NA

Data analysis using McNemar's test, significant level at $p < 0.05$; NA = Not appropriate for analysis; ns- not significantly different at $p < 0.05$; * = significantly different at $p < 0.05$. For the lactating mothers, the EARs were: calcium (800mg), iron (6.5mg), zinc (10.4mg), vitamin B1 (1.2mg), niacin (13mg), vitamin C (70mg), vitamin B6 (1.7mg), and magnesium (265mg). High risk for inadequacy of energy and pantothenic acid was not calculated using the EAR, due to the data inappropriateness and absence of cut points; for protein, 1.05 g/kg/day was considered for identifying the EAR cut point to declare inadequacy (FAO/WHO/UNU, 2001, 2002; FAO/WHO, 2001; Institute of Medicine (IOM), 2005, 2011).

Discussion

In the present study, the energy, protein, and most micronutrients intake between the fasting and non-fasting mothers during the Ethiopian Orthodox Lent fasting period were not significantly different, but their intakes were lower compared to the non-fasting period. This indicates that not only the energy and nutrient intake of fasting mothers, but also that of non-fasting mothers were also affected during the Lent fasting period. A study in Addis Ababa reported that the availability of meat was scarce due to the closure of most of the abattoirs during the Orthodox fasting period; otherwise it was also very expensive if available^{20,21}. Our previous study also revealed a significant reduction in the intake of ASFs, DDS, and the number of meals by mothers during fasting than the non-fasting periods⁴. Thus, the involvement of the church leaders in preaching the exemption of lactating mother group from fasting is important. As a result, the consumption of ASFs could be increased, both during the fasting and non-fasting seasons. Thus, the quality of diet consumed by the lactating mothers of Ethiopian Orthodox Tewahado mothers could be improved in general.

Unlike the other nutrients, the intake of niacin by the fasting mothers was significantly lower compared to the non-fasting mothers, which might be due to the high consumption of pulses majorly by the non-fasting group⁴. Furthermore, the median intakes of calcium, vitamin A, B6, B12, C, and D of the fasting and non-fasting mothers were below the EARs in both study periods. A study in Tigray region also reported lower intakes of calcium, vitamin A, and C by lactating mothers than the recommended nutrient intake²³. Whereas, the present study demonstrated that the median intakes of iron, zinc, magnesium, vitamin B1, and niacin were above the EARs at the study population level. Similarly, studies in northern Ethiopia also reported that the intake of iron by children and adults was above the daily recommendations²³⁻²⁶. This could be mainly due to the consumed staples in the area, which are mainly cereals such as wheat, barley, and teff, and also include pulses such as chickpea and broad bean, and pepper, in which iron, zinc, magnesium, vitamin B1 and niacin contents are relatively high.

Energy intake of the mothers during the fasting and non-fasting periods was in the range of 1769-1929 kcal and 2059-2095 kcal/individual/day, respectively. However, these findings were higher than reported for the rural mothers in Ethiopia, Kenya and Tanzania²⁷⁻³¹. In our study, the median intakes of protein were between 53.4-59.7g kcal/individual/day for fasting period and 60.5-61.7g kcal/individual/day for the non-fasting period. These results were higher than reported for the women at different physiological stages elsewhere in Ethiopia, Kenya and Nigeria^{24,27,29-31}. The lower protein intake by the pregnant women could be related with restriction of the amount and type of food consumed due to a fear of

obstetric complications associated with the delivery of a bigger baby, plastering on the fetal head, fear of abortion, evil eye and fetal abnormality^{2,29,32-34}.

The present study showed that the median intake of pantothenic acid was between 3.2-3.5 mg/individual/day in the study population level. It was higher than that reported for women of reproductive age (1.9-2.2 mg)/individual/day in southern Ethiopia²⁷. However, it was lower than that found in South Africa³⁵. The former inconsistency could be due to the consumption of higher amount of pulses in our case, but for the later, due to differences in the physiological stage of the participants and dietary habits in the two study areas^{4,35,36}.

In the present study, the median intakes of energy, protein, iron, zinc, magnesium, vitamin B1, and niacin were significantly increased during the non-fasting period for the fasting mothers. As a result, the prevalence of high risk due to inadequate intake of protein, zinc, magnesium, vitamin B1, and niacin was reduced significantly during the non-fasting period. Our findings on non-fasting mothers also showed significant improvements in energy, zinc, magnesium, and niacin intake and reductions in the prevalence of high risk due to inadequate intake of zinc and vitamin B1 after the fasting period. These increments were mainly due to an increased number of meals and a more diversified diet, specifically the consumption of ASFs and pulses⁴. Since cereals and pulses are the main staples of the study community, the intake of iron is not a problem; rather the quality of the diet is one of the challenges due to the presence of high amount of antinutrients, which may limit the absorption of minerals. Thus, activities which can improve the bioavailability of minerals such as consumption of vitamin C rich foods, ASFs, and processing techniques that can reduce the antinutrients content should be promoted.

Almost all lactating mothers (96.1-98.6%) didn't consume an adequate amount of vitamin A compared to the EAR cut method, regardless of the mothers fasting status and study period. This result was lower than what was found in women of the reproductive age of southern Ethiopia, in which the prevalence was between 23.7-47.5%. This disagreement could be due to the consumption of dark green leafy vegetables and fruits that are better available in southern Ethiopia than our study area²⁷. Furthermore, a study conducted in Ethiopia using a national survey also reported that 83% of the participating households were consuming vitamin A below the EAR in the last 7 days prior the survey³⁸.

Highest prevalence of calcium intake below the EAR was found in studies conducted in Sidama (84.7-97.1%), Gondar (90.4%), Butajira (99%) districts, and at the national (89-96%) level in Ethiopia^{23,27,31,37}. Our present study also reported a very high proportion (>97%) of fasting and non-fasting mothers who were at higher risk of

inadequate calcium intake, with no significant difference between the periods. Such a high level of risk for inadequate intake of dietary calcium in different areas of the country may demonstrate the need for implementation of the proposed universal calcium supplementation in Ethiopia after identifying the individual calcium intake level to reduce the risk related to high intake using validated testing tool³⁹. Even if the intake of vitamin C was not significantly affected by the fasting period, more than two-thirds of the lactating mothers achieved less than the EAR. Therefore, considering the persistent and high prevalent risk of inadequate intake of calcium and vitamin C in both study periods, the consumption of vitamin C and calcium rich foods are expected to be chronically low in the study area.

Improvements in the intake of vitamin B12 and vitamin D were observed during the non-fasting period in both groups, even if the intake of these nutrients in general was close to zero. Thus, almost all the lactating mothers were at higher risk of inadequacy of vitamin B12 and vitamin D. In line with our results, studies in Sidama district reported the absolute (100%) risk for inadequate intake of dietary vitamin D in all women^{28,40}. This problem is apparently observed in our study context due to poor consumption of vitamin D source foods like fish, milk, and eggs in both study periods for fasting and non-fasting mothers⁴. Similar to our findings for vitamin B12, the prevalence of vitamin B12 intake which was below the EAR was 100% in Sidama region and reported nationally in Ethiopia²⁸. However, a previous national study in Ethiopia using a blood biomarkers identified only 15.1% of nonpregnant women was deficient in vitamin B12⁴¹. Therefore, further investigation of the vitamin B12 status should be done using a functional biomarker like methyl malonic acid or homocysteine and additionally valid biomarkers of B12-status like holotranscobalamin for a better understanding of the situation in the study area⁴².

Despite the improvements in energy and nutrient intakes during the non-fasting period, our results also showed the co-existence of risk for multiple nutrient inadequacies in substantial proportions of fasting and non-fasting mothers diet. Thus, the risk to have or to develop different micronutrient deficiencies is expected to be high. Previous studies in Ethiopia also reported the co-existence of multiple micronutrient deficiencies in children and women at different physiological stages⁴³⁻⁴⁷.

Although the current study has much strength, some drawbacks were also observed. Thus, the longitudinal nature of the study, following the fasting and non-fasting mothers during the longest fasting and the immediate non-fasting periods are among the strengths of this study. Studying in an area where almost all population are Ethiopian Orthodox Christians also helps in generating sound evidence on the effect of Orthodox fasting on dietary nutrient intake of lactating mothers. However,

using a single 24-hr dietary recall data may not represent the usual intake of individuals. Because we didn't take blood samples, the consequences of an inadequate intake cannot be correlated with specific clinical markers of the associated deficiency.

Conclusions

Based on our findings, we conclude that, during the fasting period, not only the energy and nutrient intakes of the fasting mothers, but also the non-fasting mothers were affected. Therefore, the prevalence for a higher risk of inadequate intake of most nutrients by the lactating mothers were high during the fasting period at the study population level. Regardless of the mothers' fasting status and fasting period, almost all lactating mothers (>96%) were at higher risk of inadequate intake of vitamin A, B12, and D, and calcium from their diet. Similarly, the majority of the lactating mothers were at risk of inadequacy of vitamin B6 (91.1-93%) and vitamin C (78.1-89.9%). Therefore, vitamin A, B6, B12, and D, and calcium can be considered as serious public health important micronutrients among lactating mothers in the district. Thus, the involvement of the church leaders by preaching the exemption of lactating mother group from fasting, thus consumption of ASFs should be encouraged, both during fasting and non-fasting seasons. Therefore, the quality of diet consumed by the lactating mothers of the Ethiopian Orthodox Tewahedo religion followers can be improved in general. Besides this, initiation of universal calcium with the support of using a valid individual screening tools to minimize the risk of excess intake should be implemented. Furthermore, as cereals and pulses are the staple food in the district, activities which can improve the bioavailability and absorption of protein and minerals such as consumption of vitamin C rich foods, ASFs and processing techniques like soaking, germination and fermentation should be promoted.

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Epidemiological and clinicopathological features of breast cancer in Mauritania

Características epidemiológicas y clinicopatológicas del cáncer de mama en Mauritania

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Abstract

Background: Breast cancer is the leading cause of death in African women. The aim of this cross-sectional study was to assess the incidence, clinic-pathological characteristics, risk factors and outcome of breast cancer in Mauritania.

Methods: Demographic and clinic pathological features of breast cancer were gathered from 11174 patient files of all cancer types referred to the Centre National d'Oncologie (CNO) between January 2009 and December 2020.

Results: Breast cancer was the most common type of cancer identified in women (30.7%). The disease incidence increased from 69 in 2009 to 209 in 2020 with a mean age of 49 year sat cancer detection. Grade 3 tumor was diagnosed in 31.8% patients. Stage 3 and metastatic stage were found respectively in 44.9 % and 22.6% of screened women. 40.4% of cancer patients with satisfactory immunohistochemical data were triple negative breast cancer (TNBC) but no significant variation was found in these features between TNBC and non TNBC groups. A 3-year survival rate of 63% was observed.

Conclusions: These results support the already published studies on the likely genetic basis of breast cancer in our population.

Key words: Breast cancer, triple negative breast cancer, women.

Resumen

Antecedentes: El cáncer de mama es la principal causa de muerte en las mujeres africanas. El objetivo de este estudio transversal fue evaluar la incidencia, las características clínico-patológicas, los factores de riesgo y el resultado del cáncer de mama en Mauritania.

Métodos: Las características demográficas y clínico-patológicas del cáncer de mama se recogieron de 11174 expedientes de pacientes de todos los tipos de cáncer remitidos al Centre National d'Oncologie (CNO) entre enero de 2009 y diciembre de 2020.

Resultados: El cáncer de mama fue el tipo de cáncer más común identificado en las mujeres (30,7%). La incidencia de la enfermedad aumentó de 69 en 2009 a 209 en 2020 con una edad media de 49 años de detección del cáncer. Se diagnosticó un tumor de grado 3 en el 31,8% de las pacientes. El estadio 3 y el estadio metastásico se encontraron, respectivamente, en el 44,9% y el 22,6% de las mujeres examinadas. El 40,4% de las pacientes con cáncer con datos inmunohistoquímicos satisfactorios eran cáncer de mama triple negativo (TNBC), pero no se encontraron variaciones significativas en estas características entre los grupos TNBC y no TNBC. Se observó una tasa de supervivencia a 3 años del 63%.

Conclusiones: Estos resultados apoyan los estudios ya publicados sobre la probable base genética del cáncer de mama en nuestra población.

Palabras clave: Cáncer de mama, cáncer de mama triple negativo, mujeres.

Abbreviations

Breast cancer (BC), Centre National d'Oncologie (CNO), Triple negative breast cancer (TNBC), Immunohistochemical (IHC), The American joint committee on cancer /Union for international cancer control (AJCC/UICC), Receptors of estrogen (ER), Progesterone (PR), Hormone epidermal growth factor receptor 2 (HER-2).

Background

Although breast cancer (BC) survival is continually improving in developed states¹, the disease remained a leading cause of death in women from low- and middle-income countries likely due to a late diagnosis, often at advanced stage, combined to the scarcity of adequate and personalized primary treatment²⁻³. The incidence and mortality rate from BC was also affected by other major risk factors such as age, family history and ethnic ascendance⁴⁻⁶. However, studies on the underlying etiologies and the prospect of recovery from the disease remained particularly limited in sub-Saharan African women⁷⁻⁹. We presented here a cross-sectional study gathered from the registries of the Centre National d'Oncologie (CNO), on the frequency, demographics, clinic-pathological features and prognosis of breast cancer in Mauritania. These variables were specifically evaluated in triple negative breast cancer (TNBC) patients and compared with data from non TNBC women.

Methods

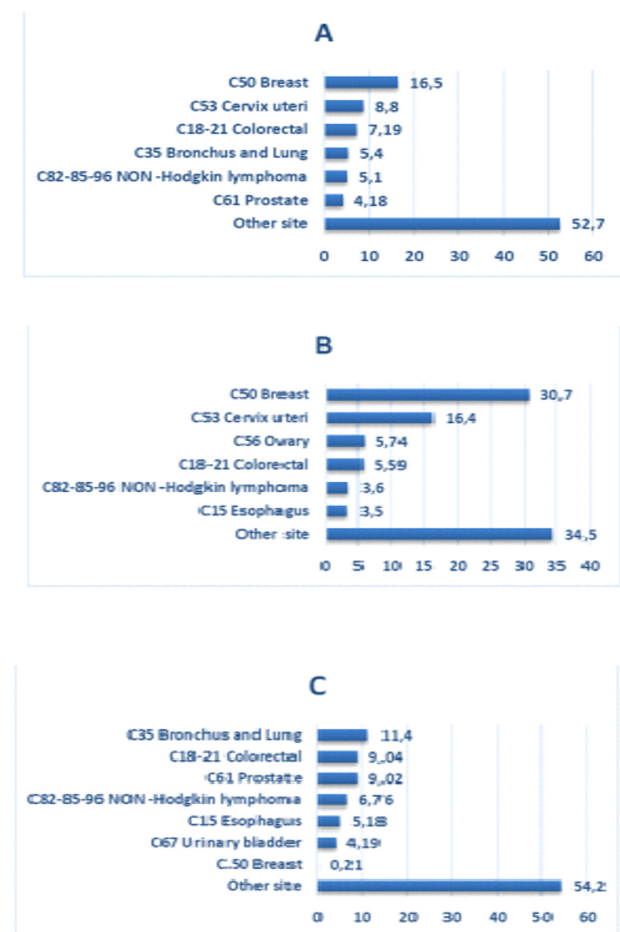
Medical files of 11174 patients of all cancer types followed at the CNO, the only referring center for oncology in the country, were examined from the period of January 2009, date of opening of the center, through to December 2020. Cancer type, Name and date of birth of each patient were recorded. In this study, detailed demographic and clinical characteristics, available at the center only from 01/2017 onwards, were analyzed for breast cancer patients and included age at diagnosis, body mass index (BMI) calculated as weight in kilograms/height in meters square (kg/m^2), family history of the disease, cancer staging, histological grading, received therapy and clinical outcome. Immunohistochemical staining (IHC) was carried out on patient tissue samples embedded in paraffin blocks. Patients with no slides or ambiguous pattern were excluded. Staging (from T0 to T4) was performed according to the American joint committee on cancer /Union for international cancer control (AJCC/UICC) systems. Evaluation (from 0 to 4) of cancer stage used TNM staging. Triple negative breast cancer (TNBC) subjects were patients with slides showing no antibody staining or a tumor cells fluorescence of less than 1% for, concurrently, receptors of estrogen (ER), progesterone (PR) and hormone epidermal growth factor receptor 2 (HER-2). Local or distant recurrence was defined by the time span from the end of primary treatment to date of return of the disease in the original site or other part of the body respectively. Survival duration was determined as the period between the dates of BC diagnosis to the patient death if recorded or the last missed appointment and loss of follow up. Data analysis was performed by SPSS version 23.0 software (Chicago, Ill). Comparison among clinical variables between TNBC and no TNBC was performed with Person Chi-square test using a statistical significance of $p < 0.05$.

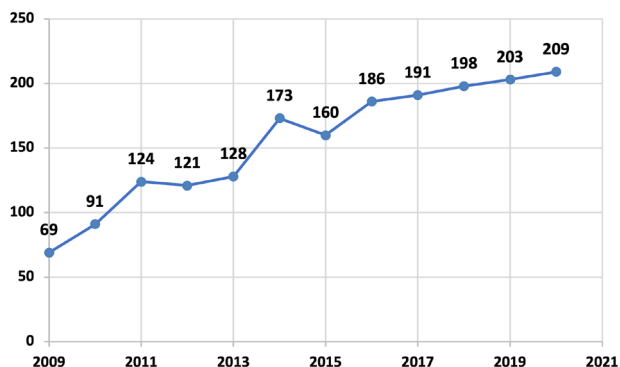
Results

Demographic findings

Globally, out of the 11174 cancer files of all types (5989 women and 5185 men) referred to CNO during the period from January 2009 to December 2020, breast cancer was found in 1853 (16.58%) patients (**Figure 1**). With a proportion of 30.75%, BC was the most common type of cancer identified in the female group. In the male group, the disease was much less frequent with only 11 cases (0.21%) of the total cancer male carriers. Overall, 99.79% of breast cancer cases were in females and less than 1% in males. The incidence rate showed a steady increase of the annual number of new women breast cancer cases with 69, 160 and 209 BC diagnosed in 2009, 2015 and 2020 respectively (**Graphic 1**). Adequate demographic and clinic-pathological characteristic, available from 01/2017 to 12/2020, concerned 793 women (**Table I**). Median age of patients, at cancer detection, was 49 years with most breast cancers diagnosed between 35 to 55 years (52.4%) followed by the group of above 55 years (31%). The fraction in the 20s to 35s age represented 16.6%. Premenopausal status was observed in 63.7% of the records.

Figure 1: Proportions (%) of common cancers referred to the CNO during the period of 2009 to 2020: A (whole cohort); B (females); C (males).



Graphic 1: Breast cancer incidence between 2009 and 2020.

Family history (first- and second-degree relatives with breast cancer) was reported by 95 (14.5%) of patients and 388 women (59%) had parents with shared common ascendant. Of 785 patients, 31.3% were overweight and 49.3 % obese. The ethnic distribution of BC women showed that 397 (50.1%) patients were white Moors, 263 (33.16%) black Moors and 133 (16.7%) of black African descent.

Pathological feature

Out of the 793 included women, breast cancer was bilateral in 25 (3%) of cases. In 417 patients (52.6%), the right breast was affected. The average diameter (measured at the widest point) of the primary tumor was 4 cm with 68.1% of recorded patients having a tumor size smaller than 5 cm against 31.9% showing a diameter above 5 cm. Cells abnormality was diagnosed with poorly differentiated status (grade III) in 185 (31.8%) patients. Moderately differentiated (grade II) and differentiated (grade I) tumors were found respectively in 334 (57.2%) and 67 (11.4%) women. Breast cancer was at stage I in 7 (0.13 %), stage II in 167 (31%), stage III in 242 (44.9%) and metastatic stage IV in 124 (22.6%) patients. Cancer stretching into breast surrounding tissues showed presence of invasive ductal carcinomas (IDC) in 618 (79.6%) and invasive lobular carcinoma (ILC) in 70 (9 %) slides. Less common types were also observed (11.4 %). In 425 breast cancer patients with satisfactory immunohistochemical data, 172 (40.4%) were classified triple negative breast cancer (TNBC) as no above cut off antibody staining was detected simultaneously for ER, PR and HER-2 receptors. Molecular classification of the remaining 253 (59.6%), non TNBC patients, gave in order 119 (28 %) luminal A, 27 (6.2 %) luminal B and 107 (25.4%) HER2-positive (**Table I**). Comparison of the relevant demographic, clinical and immunohistochemical characteristics between TNBC and NTNBC patients showed, despite slight differences in percentages, no statistically significant difference ($p < 0.05$) in median age at diagnosis, family history, ethnicity, menopausal status, proportion of cases with clinical stage or histological grade, treatment and recurrence was observed (**Table II**).

Outcome

Out of 189 women diagnosed with breast cancer in 2017, 120 were still alive and only 26% of those diagnosed in 2018 have died giving a 3- and 2-year observed survival rate of 63% and 74% respectively. BC did not return in most of these patients, as 88% and 95% of women diagnosed respectively in 2017 and 2018 did not show any local or distant recurrence.

Table I: Demographic and clinico-pathological characteristic of the study population.

Parameters	Cases (N)	Percentage (%)
Age, years (N=793)		
<35	132	16,6
[35-55]	416	52,4
>55	245	31
Menopausal status (N=793)		
Premenopausal	505	63,7
Postmenopausal	288	36,3
Family history (N=658)		
Present	95	14,5
Absent	563	85,5
Consanguinity (N=658)		
Yes	388	59
Non	270	41
Body Mass Index kg/m² (N=785)		
Underweight <18	24	3
Normal weight [18-25[128	16,3
Overweight [25-30[246	31,4
Obesity [30-35]	354	45,1
Morbid obesity >35	33	4,2
Ethnicity (N=793)		
White Moors	397	50,1
Black Moors	263	33,2
Black Africans	133	16,7
Breast affected (N=793)		
Right	417	52,6
Left	351	44,3
Bilateral	25	3,1
Tumor size (N=404)		
<5 cm	275	68,1
>5cm	129	31,9
Histological grading (N=586)		
Grade I	67	11,4
Grade II	334	57
Grade III	185	31,6
Staging (N=540)		
STAGE I	7	1,2
STAGE II	167	31
STAGE III	242	44,9
STAGE IV	124	22,9
Histological type (N=777)		
Invasiv Ductal Carcinoma (IDC)	618	79,6
Invasive Lobular Carcinoma (ILC)	70	9
Other type	89	11,4
Immunohistochemistry (N=425)		
TNBC	172	40,4
luminal A	119	28
luminal B	27	6,4
HER2+	107	25,2
Treatment (N=777)		
Curative	604	77,7
Palliative	138	17,7
Not treated	35	4,6

Table II: Comparison of epidemiological and clinico-pathological features between TNBC and NON-TNBC patients.

Parameters	NON-TNBC (N=253)	TNBC (N=172)	X ² Value	P Value
Age			4,845	0,088
< 35	39 (15,67%)	34 (19,56%)		
[35-55]	147 (58,2%)	75 (43,475%)		
>55	67 (26,11%)	63 (36,9%)		
Family history			1,616	0,204
Present	15 (6%)	32 (18,93%)		
Absent	238 (94%)	139 (80,07%)		
Ethnicity			5,343	0
Moors white Moors	103 (40,7%)	49 (28,5%)		
Black Moors	16 (9,3%)	107 (62,7%)		
Black Africans	56 (22,13%)		16 (9,3%)	
Menopause			,704	0,401
Premenopause	149 (59%)	113 (66%)		
Postmenopause	104 (40%)	59 (34%)		
Histological type			,099	0,753
Invasive carcinoma	209 (83,58%)	143 (83,5%)		
Others	44 (16,4%)	29 (16,5%)		
Histological grading			4,813	0,185
Grade I	30 (11,11%)	6 (3,2%)		
Grade II	158 (62,8%)	111 (64,8%)		
Grade III	65 (26,11%)	55 (32%)		
Staging			3,652	0,455
STAGE I	2 (0,14%)	0(0%)		
STAGE II	70 (27,6%)	56 (32,9%)		
STAGE III	101 (40,2%)	66 (38,4%)		
STAGE IV	48 (19%)	24 (14,2%)		
Treatment			2,549	0,28
Curative	208 (82,2%)	146 (84,6%)		
Palliative	45 (17,8%)	26 (15,4%)		
Local recurrence or distant metastasis	(n=58) 22,9%	(n=68) 39,5%	4,041	0
Local recurrence	2	3		
Distant metastasis	56	65		

Discussion

In this study, we have first addressed the main demographic and clinical characteristics of breast cancer in a cohort of patient women referred to the CNO (Centre National d'Oncologie) and assessed the outcome of cancer in the context of these factors. Out of 11175 patient files of all cancer types, BC was the most common in the cohort population (16.56%), particularly in women (30.9%). This standing was also reported by a ten years study (from 2000 to 2009) which included 3305 histological samples analyzed by the department of anatomic pathology (Hopital National de Nouakchott) and showed a prevalence of 14.6% in the whole cohort and 25.2% among the female population¹⁰⁻¹¹. As our study was conducted in the following decade of the previous work and covered the single state referring facility for cancer, the data generated were therefore likely representative of the disease evolution in the country. Their concordance reflected an increase in the incidence of breast cancer in our population. Similar percentages of breast cancer in women were reported in neighboring populations such as in Morocco (36%)^{8,12} and Senegal (26.1%)¹³. Most women diagnosed with breast cancer (69%) in our study were ages 55 or less. Registries and community-based studies showed that 70% of women with breast cancer

in Sub-Saharan Africa were in the same age group¹⁴. The mean age of 49 years we observed was thus close to the 48 years reported globally in Africa¹⁵ and 46 years in British black women¹⁶. This relatively early onset of breast cancer was lower than late age of 67 years at presentation in white British women [16]. Pre-menopausal status was also predominant in our cohort (63 %) as in two-thirds of black African women with BC¹⁷⁻¹⁸ while most of European women (80 %) were postmenopausal at presentation with the disease¹⁹. We also observed that most patients (66%) had moderate to poorly differentiated tumors with widely spread stage 3 (44%) or metastasized (22%) cancer when diagnosed with BC. A similar outline was reported in a 12 sub-Saharan countries study (Zimbabwe, Benin, Seychelles, Ethiopia, Mauritius, South Africa, Kenya, Mozambique, Mali, Namibia, Uganda and Cote d'Ivoire) showing that 64.9% of women patients were diagnosed in late stages, when treatment became weakly effective, of which 18.4% being metastatic at diagnosis²⁰. This late advanced stage at presentation, very likely accentuated by poor socioeconomic conditions and lack of access to adequate healthcare. Therefore could be determinant in the low 2- and 3-year observed survival rate of 74% and 64% observed in our cohort and the overall relative

survival (RS) of 61.4% (59.1–63.5) at year 3 and 52.3% (49.9–54.6) at year 5²⁰ in BC patients across sub-Saharan Africa. In contrast, 79% and 89% of women with breast cancer respectively in Europe and the US had not died from their cancer 5 years later after diagnosis²¹. Despite evidences reported from many large cohort studies linking overweight to breast cancer risk²²⁻²³, nearly 40% of women worldwide were overweight in 2020²⁴. We have shown a high cumulative prevalence of overweight and obesity among our patients. Obesity was for centuries desirable and a sign of wealth in various African countries²⁵. A traditional practice of force-feeding teenage girls (known as leblouh in our country) has indeed been prevalent in Mauritania and several other African populations²⁶⁻²⁷. Although lifestyle choices and low provision of healthcare services in African populations may be determinant in the disease expected development, various studies have shown that other risk factors may take part in BC prognosis such as patient race or ethnic origin, parents 'consanguinity and age at onset²⁸⁻³⁰. The comparable early age at breast cancer onset observed in our cohort, globally in Sub-Saharan¹⁴ and British black women¹⁶ against a relatively late age of 67 years in white British women at presentation¹⁹ was in this context relevant. African-American women have also higher rates of grade 3 than their Caucasian counterparts³¹⁻³². Race related differences among BC patients have been attributed to various hereditary grounds including breast cancer susceptibility genes and endogenous hormones³³. For instance, in the US, the frequency of samples tested negative for receptors of progesterone, estrogen and HER2 protein (TNBC) was higher in African-American women (28%) compared to Caucasian women (12%)³⁴. The Mauritanian population is composed of three main groups all Muslims but of different race origin³⁵: the white Maures (WM) speaking Hassaniya, a berber-arab dialect. This group ethnically and culturally self-identifies with the neighboring North Africa populations. The black Maures (BM) also speaking Hassaniya but share the same race origin with the third group, the black African Mauritians (BAM), as both descended from native sub-Saharan Africans.

The global TNBC prevalence (40.4%) observed in this study was intermediate between the percentages of 28.5% in the white Moors and 71.51% in the black Moors-black Africans group respectively. The frequency observed in the white Moors (28.5%) although slightly higher, was comparable to the percentages in North African populations³⁶⁻³⁷. The frequencies in black Moors-black Africans group, is also similar to those reported in sub-Saharan African women-based studies³⁸⁻³⁹ which is consistent with the common African ascendance above mentioned. This ethnically associated repartition of percentages in TNBC also concords with the distribution of other biomarkers we reported previously in our population⁴⁰⁻⁴¹. However, although differences of percentages between TNBC and NTNBC patients were

observed, all parameters we analyzed did not reach the level of statistical significance set.

Limitations

One of the limitation of this study was that all the parameters were not available in all patients for various reasons of which we could mention disappearance of patients and lack of consent to participate. As a result of this failing we could not set a statistical significance of all patient characteristics.

Conclusion

We have provided data from a representative cohort on the frequencies of BC in Mauritania, evaluated the main demographic and clinical characteristics, which may affect the disease prognosis. The results, consistent with already published studies support a genetic basis of breast cancer in our population. Further studies increasing the cohort size and extending the time span of following the patients may optimize data for significant correlation assessment.

What is already known on this topic

- High prevalence of breast cancer in sub-Saharan African women
- Poor outcome due to late diagnosis
- Gene susceptibility is reported to a great extent

What this study adds

- Present recent epidemiological and clinic-pathological data on breast cancer in Mauritania
- Provide first data (diagnosis, incidence and survival rate) on triple negative breast cancer patients in Mauritania.
- Compare the data found with data available in neighboring populations

Ethics approval and consent

Approval to this study was given by the ethics committee of the Université de Nouakchott Al-Asriya, Mauritania. The informed consent of patients referred to the CNO was obtained. All methods were carried out in accordance with relevant guidelines and regulations.

Availability of data and materials

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

Competing interests

The authors declare no competing interest.

Funding

No specific funding was obtained for this study carried out between the UNA and the CNO.

Authors' contributions

Selma MOHAMED BRAHIM: collected and organized all cancer files; She contributed to epidemiological and Immunohistochemistry data analysis;

Cheikh Tijani HAMED: contributed in pathological data analysis;

Ekht Elbenina ZEIN: initiated the paper conception and contributed to the manuscript progress; MS contributed to epidemiological data analysis;

Fatimetou VETEN: contributed to epidemiological data analysis;

Mohamed Vall ZEIN: contributed to pathological data analysis;

Meriem KHYATTI: contributed in paper conception and paper writing;

Ahmed HOUMEIDA: were the major contributor in coordinating all data analysis and writing the manuscript;

Ahmedou TOLBA: examined Immunohisto chemical slides (IHC) and contributed in paper conception and writing.

All authors read and approved the final manuscript.

Annex

STROBE Statement—checklist of items that should be included in reports of observational studies.

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction Background/rationale Objectives	2	Explain the scientific background and rationale for the investigation being reported	3
	3	State specific objectives, including any prespecified hypotheses	3
Methods Study design Setting Participants Variables Data sources/ measurement Bias Study size Quantitative variables	4	Present key elements of study design early in the paper	3
	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
	6	Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	3
	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3
	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	3
	9	Describe any efforts to address potential sources of bias	3
	10	Explain how the study size was arrived at	3
	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	3
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	2
		(e) Describe any sensitivity analyses	
	Results Participants Descriptive data Outcome data Main results Other analyses	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
(b) Give reasons for non-participation at each stage			4
(c) Consider use of a flow diagram			4
14*		(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	4
		(b) Indicate number of participants with missing data for each variable of interest	4
		(c) Cohort study—Summarise follow-up time (eg, average and total amount)	4
15*		Cohort study—Report numbers of outcome events or summary measures over time	4
		Cross-sectional study—Report numbers of outcome events or summary measures	4
16		(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	4
		(b) Report category boundaries when continuous variables were categorized	4
	(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	4	
17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	4	
Discussion Key results Limitations Interpretation Generalisability	18	Summarise key results with reference to study objectives	4
	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	5
	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	6
	21	Discuss the generalisability (external validity) of the study results	6
Other information Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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Body Image Satisfaction among Aesthetic Surgery Clients

Satisfacción con la imagen corporal entre los clientes de cirugía estética

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Abstract

Methods: The descriptive cross-sectional study design approach is done by interrogating members of the study population, with the aim of describing the studied phenomenon in terms of its nature and degree of existence only. To conduct the study, a non-probability (purposive) sample of (150) clientele who attend beauty facilities in Babylon Province was chosen. The contentment with one's body image is addressed in the used questionnaire. The questionnaire's dependability was established through a pilot research, and it was subsequently presented to experts for validation. The questionnaire contained a total of 30 questions. The information was gathered through self-reporting and analyzed using descriptive and inferential statistical data analysis.

Results: Out of 150 participants aged 20-25 years at mean age is 26 (± 4.98), the female clients predominated (82.7%), urban residents (86.0%), the single clients were composed the highest percentage (60.7%), the students clients were constituted the majority (92.0%), clients hasn't had any previous plastic surgery (72.7%), clients wants to have a rhinoplasty (50.7%) to improve their appearance (89.3). The findings demonstrated that the (52%) of clients were unsatisfied with their body image. There were significant association in body image with regards clients age ($p=0.020$) and gender ($p=0.000$).

Conclusions: Body image of aesthetic clients have been influenced by clients age and gender (age 20-25 years more unsatisfied than others age groups, female more unsatisfied than male). Preparing radio and television programs that encourage young people to engage effectively and positively with their appearance.

Key words: Body Image, aesthetic surgery, clients.

Resumen

Métodos: El enfoque de diseño de estudio transversal descriptivo se realiza interrogando a los miembros de la población de estudio, con el objetivo de describir el fenómeno estudiado en términos de su naturaleza y grado de existencia únicamente. Para realizar el estudio, se seleccionó una muestra no probabilística (intencionada) de (150) clientes que asisten a centros de belleza en la provincia de Babilonia. La satisfacción con la propia imagen corporal se aborda en el cuestionario utilizado. La confiabilidad del cuestionario se estableció a través de una investigación piloto y posteriormente se presentó a expertos para su validación. El cuestionario contenía un total de 30 preguntas. La información fue recopilada a través de autoinforme y analizada mediante análisis de datos estadísticos descriptivos e inferenciales.

Resultados: de 150 participantes de 20 a 25 años con una edad media de 26 ($\pm 4,98$), predominaron los clientes del sexo femenino (82,7%), residentes urbanos (86,0 %), los clientes solteros fueron el porcentaje más alto (60,7%). los clientes estudiantes constituyeron la mayoría (92,0%), clientes que no han tenido ninguna cirugía plástica anterior (72,7%), clientes quieren hacerse una rinoplastia (50,7%) para mejorar su apariencia (89,3). Los resultados demostraron que el (52%) de los clientes estaban insatisfechos con su imagen corporal. Hubo asociación significativa en la imagen corporal con respecto a la edad de los clientes ($p=0,020$) y género ($p=0,000$).

Conclusiones: La imagen corporal de los clientes estéticos se ha visto influenciada por la edad y el género de los clientes (edad 20-25 años más insatisfecha que otros grupos de edad, mujeres más insatisfechas que hombres). Elaborar programas de radio y televisión que animen a los jóvenes a comprometerse de manera efectiva y positiva con su apariencia.

Palabras clave: Imagen corporal, cirugía estética, clientes.

Introduction

Aesthetic medicine can help with scars, sagging skin, wrinkles, moles, liver spots, excess fat, cellulite, undesired hair, skin discoloration, and spider veins¹. A 20 million plastic procedures were performed worldwide between 2014 and 2015². Plastic surgery is a major driver of medical tourism. In February 2018, the president of the British Society of Plastic Surgeons stated that operations were performed on people who were not candidates for surgery, that unscrupulous practitioners put their health at risk for profit, and that the British National Health Service covered the cost of correction for more than 1,000 patients per year³. Aesthetic medicine is concerned with enhancing a person's appearance. It can be used to treat a wide range of dermatological and surgical issues. Instructions for minimizing age signs like drooping skin, wrinkles, and liver spots are included. Cosmetic drugs can be used to treat excess fat, cellulite, and obesity. Laser-based therapy can be used to heal scars, unwanted hair, skin discoloration, and a change in quality of life⁴. Body image disorder is a mental illness characterized by unhappiness with one's physical appearance as the primary symptom. This somatic disease was only included in the DSM-III-list R's of diagnoses. A test to see if a person's fixation is severe enough to cause problems⁵. "The mental image or perception of one's body at rest or in motion at any time, drawn from internal sensations, changes in the body, contact with outside persons and objects, emotional experiences, and imaginations," according to the definition. That is, it is a person's perception of himself as he looks at his body and identifies his physical qualities, whether favorable or negative, as well as how others view him⁶. Therefore, thus aimed to investigate the body image satisfaction and associated socio-demographic variables among aesthetic surgery in Babylon Province/Iraq.

Methodology

The descriptive cross-sectional study design approach is done by interrogating members of the study population, with the aim of describing the studied phenomenon in terms of its nature and degree of existence only.

To conduct the study, a non-probability (purposive) sample of (150) clientele who attend beauty facilities in Babylon Province was chosen. The employed questionnaire, which measures physical appearance and body image satisfaction (Appearance Evaluation subscale MBSRQ-AE), was designed and adopted by Herbozo (2004)⁷.

Validity was determined by a panel of 11 arbitrators who were asked to comment on each component of the study questionnaire in terms of language appropriateness, correlation with the dimension of study variables to

which it was assigned, and suitability for the study population. Data was obtained from nurses to assess the questionnaire's reliability, and the test was delivered to 10 people from the study population who were not part of the initial sample. The Cronbach's alpha was found to be 0.82.

After obtaining the approval of the Babylon Health Directorate and verifying the validity and reliability of the questionnaire. The researcher interviewed himself (face to face) to the participants, explained the instructions, answered their questions regarding the form, urged them to participate and thanked them for the cooperation. The interview techniques was used on individual bases, and each interview took (15-20) minutes after taking the important steps that must be included in the study design.

The SPSS ver-20.0 software application was used to conduct statistical analysis. The information was evenly distributed. One-way analysis of variance and independent sample t test were used to examine variations in variables based on socio-demographic characteristics. For continuous variables, descriptive data is reported as mean standard deviation, and for categorical variables, it is shown as number (percent). Statistical significance was defined as a p 0.05.

Results

Tables I-IV shows the participants' ages; the average age is 26, with the age group 20-25 years old having the highest number of records (n=58; 38.7%). In terms of gender, female clients (n=124; 82.7 percent) outnumbered male clients (n=26; 17.3 percent). The bulk of study participants (n=129; 86.0 percent) were urban dwellers, compared to those who were rural residents (n=21; 14.0 percent). In terms of marital status, the findings show that single clients account for the biggest percentage (n=91; 60.7 percent) when compared to married and divorced individuals. In terms of occupation, the findings show that students clients made up the majority (n=138; 92.0 percent) as compared to working and unemployed clients. In terms of past plastic surgeries, the majority of clients (n=109; 72.7 percent) had never had any, compared to those who have had cosmetic rhinoplasty, dentistry, stomach tuck, and buttocks lift. The majority of the clients in this survey (n=76; 50.7 percent) seek a rhinoplasty to improve their appearance (n=134; 89.3%).

The analysis of body image satisfaction was demonstrate that aesthetic surgery clients experienced with average of 62.14 ± 19.791 ; the aesthetic surgery clients experienced unsatisfied towards body image (n=78; 52%) (**Table I**).

Table I: Socio-Demographic Characteristics.

Variables	Classification	Freq.	%
Age /years (M ± SD=26.57±4.982)	<20years old	9	6.0
	20-25years old	58	38.7
	26-30years old	56	37.3
	31-35years old	17	11.3
	36-40years old	9	6.0
	>40years old	1	.7
Gender	Male	26	17.3
	Female	124	82.7
Residents	Urban	129	86.0
	Rural	21	14.0
Marital status	Single	91	60.7
	Married	56	37.3
	Divorced	3	2.0
Occupation	Students	138	92.0
	Employment	6	4.0
	Unemployed	6	4.0
Types previous plastic surgeries	No	109	72.7
	Rhinoplasty	7	4.7
	Cosmetic dentistry	17	11.3
	Tummy tuck	6	4.0
	Botox and filler	11	7.3
Type of current plastic surgery	Rhinoplasty	76	50.7
	Cosmetic dentistry	14	9.3
	Tummy tuck	13	8.7
	Botox and filler	18	12.0
	Tighten the buttocks	22	14.7
	Chin surgery	7	4.7
Motivation for plastic surgery	Appearance improvement	134	89.3
	Therapeutic and cosmetic	16	10.7

Table II: Body Image Satisfaction Levels.

Weighted	Freq.	%	M ± SD
Unsatisfied (M=28-65)	78	52.0	62.14 ± 19.791
Satisfied to certain limit (M=66-103)	68	45.3	
Satisfied (M=104-140)	4	2.7	
Total	150	100.0	

"M: Mean of total Scores, SD: Standard Deviation for total scores".

Table III: Significant Differences in Body Image Satisfaction with regard Clients Age.

Age Variables	Source of variance	Sum of Squares	d.f	Mean Square	F	p≤ 0.05
Body Image	Between Groups	6.523	5	1.305	2.766	.020 Sig,
	Within Groups	67.922	144	.472		
	Total	74.445	149			

The findings revealed that body image satisfaction varies significantly depending on the age of the client (p=0.020)

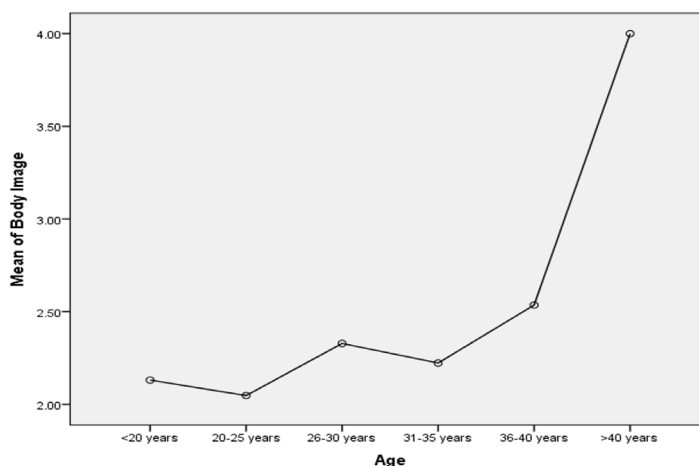


Figure 1: Distribution of Body Image Satisfaction According Age Groups.

Table IV: Significant Differences in Body Image Satisfaction with regard Clients Gender.

Body Image	Gender	Mean	S.D	t-value	d.f	p≤ 0.05	Sig
	Male	2.81	0.840	5.061	148	0.000	Sig.
	Female	2.09	0.610				

There were extremely significant variations in body image satisfaction between male and female clients ($p=0.000$), according to the findings.

Table V: Significant Differences in Body Image Satisfaction with regard Residents.

Residents Variables	Source of variance	Sum of Squares	d.f	Mean Square	F	p≤ 0.05
Body Image	Between Groups	.006	1	.006	.011	.916
	Within Groups	74.439	148	.503		
	Total	74.445	149			

There were no significant variations in body image satisfaction between clients and residents ($p=0.916$).

Table VI: Significant Differences in Body Image Satisfaction with regard Marital Status.

Marital Variables	Source of variance	Sum of Squares	d.f	Mean Square	F	p≤ 0.05
Body Image	Between Groups	1.787	2	.893	1.808	.168
	Within Groups	72.658	147	.494		
	Total	74.445	149			

There were no significant changes in body image satisfaction based on marital status ($p=0.168$).

Table VII: Significant Differences in Body Image Satisfaction with regard Occupation.

Occupation Variables	Source of variance	Sum of Squares	d.f	Mean Square	F	p≤ 0.05
Body Image	Between Groups	2.700	2	1.350	2.766	.066
	Within Groups	71.745	147	.488		
	Total	74.445	149			

There were no significant differences in body image satisfaction between customers' occupations ($p=0.066$).

Table VIII: Significant Differences in Body Image Satisfaction with regard Type Previous Plastic Surgeries.

Type of previous surgeries	Source of variance	Sum of Squares	d.f	Mean Square	F	p≤ 0.05
Body Image	Between Groups	.885	4	.221	.436	.782
	Within Groups	73.560	145	.507		
	Total	74.445	149			

There were no significant changes in body image satisfaction based on the type of previous plastic surgery ($p=0.782$).

Table IX: Significant Differences in Body Image Satisfaction with regard Type Current Plastic Surgery.

Current surgery	Source of variance	Sum of Squares	d.f	Mean Square	F	p≤ 0.05
Body Image	Between Groups	1.486	5	.297	.586	.710
	Within Groups	72.959	144	.507		
	Total	74.445	149			

There were no significant differences in body image satisfaction based on the type of current plastic surgery that consumers desired ($p=0.710$).

Table X: Significant Differences in Body Image Satisfaction with regard Motivation to Plastic Surgery.

Motivation	Source of variance	Sum of Squares	d.f	Mean Square	F	p≤ 0.05
Body Image	Between Groups	.049	1	.049	.097	.710
	Within Groups	74.396	148	.503		
	Total	74.445	149			

There were no significant variations in body image satisfaction when it came to motivation for plastic surgery ($p=0.756$).

Discussion

A range of mental diseases have been connected to body image issues. Previous studies on body image have exclusively concentrated on women, leaving men's body image largely unexplored. Furthermore, there have been few research that have looked at gender variations in body image over time. Body image is frequently rated only on the basis of unhappiness with the body, ignoring other elements such as appreciating the body and the relevance of attractiveness when it comes to measurement. One of the goals of this study is to show that plastic surgery patients have a mean body image satisfaction of 62.14 19,791; patients having plastic surgery have a dissatisfied body image, according to the study criteria. This study backs up the findings of Yazdandos et al. (2016), who reported that the majority of the 532 participants (92.5 percent) were dissatisfied with their body image⁸. Body image disorder is more prevalent in aesthetic patients⁹. Dissatisfaction with one's physical appearance and body image is a prevalent psychological problem in Western civilization¹⁰. Overweight persons are more prone to be unhappy with their appearance, although people of average weight are also affected¹¹. For both groups of persons, body image dissatisfaction has an impact on self-esteem and quality of life¹². It's also thought to be the driving force behind a number of appearance-enhancing practices, including weight loss and physical activity¹³. Body image's relevance as a psychological factor. Previous research have indicated that dissatisfaction with one's appearance influences one's decision to seek out the wide range of body shaping procedures available from aesthetic practitioners. Individuals who undergo these treatments usually report an increase in body image dissatisfaction, increased attention on the trait they desire to modify with treatment, and improved body image following treatment. Excessive physical discontent, on the other hand, is a symptom of a number of established mental problems. Furthermore, the majority of people are believed to be dissatisfied with their appearance. To some extent, physical attractiveness is an important component of self-esteem. Plastic surgery enhances a person's physical appearance while also promoting a positive self-image¹⁴.

Body image satisfaction varied considerably depending on the client's age ($p = 0.020$), according to the findings. The difference was in favor of those aged 40 and up, who were more content with their bodies, while those aged 20-25 were less satisfied with their bodies on average than the other age groups. Younger age groups exhibited much lower body image satisfaction than older age groups. Younger people are more dissatisfied with their bodies and have a higher level of awareness about their looks than older people¹⁵. Being beyond 30 years old, on the other hand, has been demonstrated to improve body image satisfaction because aging carries with it additional issues unrelated to beauty¹⁶.

According to the data, there were highly substantial variations in body image satisfaction between male and

female clients ($p = 0.000$). Differences favored male consumers (M SD = 2,810,840) who were more satisfied with their body image than female clients (M SD = 2,090,610). In the Walter & Shenaar-Golan study (2017)¹⁷, there was a statistically significant difference in satisfaction with body views between males and females, with males' average body image being higher than females¹⁸. Females had a considerably higher mean level of body image dissatisfaction than males¹⁹. Female customers were much less satisfied with their body image because they feared others would reject them because of their appearance, which could lead to plastic surgery acceptance and suggest a wish for a masculine body type. To back this up, females made up 82.7 percent of those who took part in the study, while males made up 17.3 percent. According to the data, there were no significant differences in satisfaction with body image between clients and residents ($p = 0.916$). There is no difference in body image assessment between urban and rural people, implying that the population component has no bearing on body image and is ignored. Residents have no effect on body image, i.e. there is no difference in satisfaction or unhappiness with rural versus urban housing²⁰. The study findings reveal that there is no association between self-perception of body image and where one lives, which is an extension of research on body image in adolescent females²¹.

According to the data, there were no significant differences in body image satisfaction based on marital status ($p=0.168$). According to these findings, there is no difference between married, divorced, and single women. They had similar views on body image, suggesting that marital status has minimal impact on body image satisfaction. Social status has no bearing on body image²². Despite the fact that body image is a main indication of marital pleasure, it is an irrelevant aspect²⁴.

According to the findings, there are no statistically significant differences in satisfaction with body image between clients' jobs ($p=0.066$). Body image is unaffected by whether the client is a student, employee, or non-employee, implying that occupation is a non-significant predictor of body image, as evidenced by the fact that respondents' dissatisfaction with body image is unaffected by their occupation, with dissatisfaction expressed at similar levels in various professions²⁴.

There were no significant changes in body image satisfaction based on the type of previous plastic surgery ($p=0.782$), according to the findings. Because they showed equal degrees of unhappiness with body image, there was no difference in satisfaction with body image and past cosmetic procedures, whether it was rhinoplasty, teeth, stomach tuck, or filler and Botox. The previous operation, regardless of its nature, had no effect on body image satisfaction. There were no significant differences in body image satisfaction based on the type of current plastic surgery that consumers desired

($p=0.710$), according to the findings. The majority of the auditors for rhinoplasty (50.7%) and the fewest for chin surgery (4.7%) expressed similar average scores for their dissatisfaction with their body images, implying that the type of plastic surgery is unimportant in evaluating body image because the satisfaction or dissatisfaction is the same regardless of the type of plastic surgery⁹. There were no significant variations in body image satisfaction when it came to motivation for plastic surgery ($p=0.756$), according to the findings. The main reason for the operation was to improve one's looks, which translates to dissatisfaction with one's body image. On the other hand, the majority of the clients (89.3%) had plastic surgery to improve their appearance and thus expressed similar levels of dissatisfaction with their body images, indicating that there is no difference between having plastic surgery to improve appearance and having plastic surgery for

therapeutic reasons. Whatever the reasons for plastic surgery, it has little influence on body image satisfaction.

Conclusion

Body image of aesthetic clients have been influenced by clients age and gender (age 20-25 years more unsatisfied than others age groups, female more unsatisfied than male). Preparing radio and television programs that encourage young people to engage effectively and positively with their appearance.

Interests conflict

The researchers declare that they have no conflict of interest.

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Comparison of Rectal and Sublingual Misoprostol Prescription to Reduce Bleeding During and After Cesarean Section: double blind, randomized clinical trial

Comparación de la prescripción de misoprostol rectal y sublingual para reducir la hemorragia durante y después de la cesárea: ensayo clínico aleatorio doble ciego

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Abstract

Introduction: Postpartum hemorrhage is an important cause of mortality and morbidity in pregnant women. There are various ways to control bleeding during and after childbirth. The aim of this study was to compare the rectal and sublingual misoprostol administration in reducing bleeding during and after cesarean section.

Materials and methods: This double-blind clinical trial study was performed on 80 pregnant women who referred to Shahid Sadoughi Hospital in Yazd for elective cesarean section. Mothers were randomly divided into two groups. Immediately after the birth of the infant, 20 units of oxytocin were infused in 500 ml ringer serum in both groups. In the first group 400 µg rectal misoprostol was administered after spinal anesthesia and in the second group 400 µg sublingual misoprostol. The data were collected by a questionnaire and the data were analyzed by SPSS 22 software.

Results: The results of the study showed that intraoperative hemorrhage was 393.37 ml in the rectal misoprostol group and 404.25 ml in the sublingual misoprostol group ($p = 0.73$). Also, there was no significant difference in the amount of bleeding in recovery between the two groups ($p = 0.91$). Mean preoperative hemoglobin level was 12.86 in rectal group and 12.26 in sublingual group ($p = 0.07$). Postoperative mean hemoglobin was 11.85 in rectal group and 11.4 in sublingual group ($p = 0.18$). None of the patients needed transfusions during the study and the side effects such as shivering, nausea and vomiting were not different between the two groups ($p > 0.05$).

Conclusion: The findings of this study showed that sublingual misoprostol is as effective as rectal misoprostol and that sublingual form may be used as a drug in the prevention of postpartum hemorrhage rather than rectal form.

Key words: Postpartum hemorrhage, misoprostol, sublingual administration, rectal administration, cesarean section.

Resumen

Introducción: La hemorragia posparto es una causa importante de mortalidad y morbilidad en las mujeres embarazadas. Existen varias formas de controlar la hemorragia durante y después del parto. El objetivo de este estudio fue comparar la administración de misoprostol rectal y sublingual en la reducción de la hemorragia durante y después de la cesárea.

Materiales y métodos: Este ensayo clínico doble ciego se realizó en 80 mujeres embarazadas que fueron remitidas al Hospital Shahid Sadoughi de Yazd para realizar una cesárea electiva. Las madres fueron divididas aleatoriamente en dos grupos. Inmediatamente después del nacimiento del bebé, se infundieron 20 unidades de oxitocina en 500 ml de suero ringer en ambos grupos. En el primer grupo se administraron 400 µg de misoprostol rectal tras la anestesia espinal y en el segundo 400 µg de misoprostol sublingual. Los datos se recogieron mediante un cuestionario y los datos se analizaron con el software SPSS 22.

Resultados: Los resultados del estudio mostraron que la hemorragia intraoperatoria fue de 393,37 ml en el grupo de misoprostol rectal y de 404,25 ml en el grupo de misoprostol sublingual ($p = 0,73$). Tampoco hubo diferencias significativas en la cantidad de sangrado en la recuperación entre los dos grupos ($p = 0,91$). El nivel medio de hemoglobina preoperatoria fue de 12,86 en el grupo rectal y de 12,26 en el grupo sublingual ($p = 0,07$). La hemoglobina media postoperatoria fue de 11,85 en el grupo rectal y de 11,4 en el grupo sublingual ($p = 0,18$). Ninguno de los pacientes necesitó transfusiones durante el estudio y los efectos secundarios como escalofríos, náuseas y vómitos no fueron diferentes entre los dos grupos ($p > 0,05$).

Conclusión: Los resultados de este estudio demostraron que el misoprostol sublingual es tan eficaz como el rectal y que la forma sublingual puede utilizarse como fármaco en la prevención de la hemorragia posparto en lugar de la forma rectal.

Palabras clave: Hemorragia posparto, misoprostol, administración sublingual, administración rectal, cesárea.

Introduction

One of the leading causes of maternal mortality in the world is postpartum hemorrhage. According to WHO reports, 585,000 maternal deaths are reported annually, the leading cause of postpartum hemorrhage as a result of active birth control in a way that reduces this serious risk¹. Due to the increased rate of cesarean section, the risk of postpartum hemorrhage is more common with moderate bleeding during cesarean section. Post-cesarean hemorrhage control prevents morbidity from blood transfusion¹. Postpartum hemorrhage is defined as loss of more than 500 cc after normal delivery and 1000 cc after cesarean section².

There are various ways to control bleeding during and after childbirth. Although routine use of oxytocin may reduce blood loss, in preeclampsia, heart failure and cesarean section in the long term are not appropriate due to hypotension, tachycardia and antidiuretic effect³. Misoprostol is a synthetic analogue of prostaglandin E1 whose benefits over other prostaglandins include its stability in high temperature, low cost and availability. It has been shown to be rapidly absorbed and its effect on the uterus has been shown to be rapid, as well as concerns about the misoprostol administration before the birth of the baby did not have a detrimental effect on the studies⁴.

Many studies have shown the beneficial role of oral or rectal misoprostol in preventing or controlling postpartum hemorrhage⁵. But proving its usefulness in rectal consumption as compared to oral consumption needs further investigation. Since the sublingual type is better for the patient than the rectal, it is easier for the patient to use and also reaches the highest plasma concentration in a shorter time, so this study we aimed to investigate the effect of sublingual and rectal misoprostol administration on reducing bleeding during and after cesarean section.

Materials and Methods

This prospective, randomized, double-blinded trial was conducted at shahid sadoughi hospital, Yazd, Iran. Approval was obtained from ethical committee of department of obstetrics and gynecology, shahid sadoughi university of Yazd.

This study was performed on 80 pregnant women who were candidates for elective cesarean section. Pregnant women (gestational age 37 weeks and older), and pregnant women with preeclampsia and eclampsia, polyhydramnios hypersensitivity to misoprostol, asthma, coagulopathy, myomectomy history, macrosomia, Placenta Previa, post-partum history, uterine fibroids, fetal distress and Placental abruption were excluded.

The recruited women were divided into two groups using random number table. Immediately after the birth of the infant, 20 units of oxytocin were infused in 500 ml ringer

serum in both groups. The first group received 400 µg rectal misoprostol after spinal anesthesia and the second group 400 µg sublingual misoprostol. The researcher and the patient did not know the type of medication and the groups. In the sublingual group, the study drug was given sublingual and placebo was prescribed rectally, but in the rectal group, the study drug was given rectal and placebo was prescribed sublingually. If there is excessive uterine bleeding due to atony, the uterus is initially massaged, and if the bleeding continues, the rate of oxytocin infusion is increased and then intramuscular methergine (0.2 mg) is given.

The primary outcome was the estimation of the intraoperative blood loss. The volume of bleeding was estimated by weighting blood gases, which Each gram of overweight equals 1cc of bleeding and the amount of blood aspirated in the suction bag. Other outcomes were: the hemodynamic variables, the change of hematocrit and hemoglobin values, need for transfusion and uterotonic drugs and occurrence of side effects related to misoprostol such as fever, chills and nausea and vomiting.

Vital signs (systolic, diastolic and mean arterial pressure and heart rate) were measured every 5 minutes during cesarean section and every 15 minutes at recovery time. Hemoglobin and hematocrit were measured before and 6 hours after cesarean section. Intraoperative adverse events up to two hours later and fever up to 1 hour postpartum were recorded at 20, 40 and 60 minutes. Finally, Statistical analysis of the data was performed using IBM® SPSS® Statistics version 22 (IBM® Corp., Armonk, NY).

Results

In this study 80 women were randomly divided into two group. All groups were demographically homogenous with no statistical significance, as shown in **table I**.

There was no significant difference in intra-operative blood loss between the two groups. Similarly, there was no significant difference in the amount of bleeding in recovery room between the two groups (**table II**).

The results showed that there was no significant difference between hemoglobin and hematocrit after surgery. Accordingly, there was no significant difference between groups regarding hemoglobin and hematocrit changes. It can therefore be said that sublingual misoprostol administration is as effective as rectal misoprostol (**table III**).

There was no significant difference regarding any of side effects such as fever, chills and nausea/vomiting between group. Also, the need for oxytocin and methergine in two group was similar (**table IV**).

The mean of systolic, diastolic, heart rate and mean arterial blood pressure were not significantly different between the two groups at the time of surgery and recovery.

Table I: Demographic and preoperative Hb and Hct of patients.

	Rectal group N=40	Sublingual group N=40	p-value
Age (year)	32.07 ± 4.5	30.2 ± 5.8	0.11
BMI (kg/m ²)	29.77 ± 3.27	30.58 ± 3.57	0.29
Pre Hb (g/dL)	12.86 ± 1.22	12.26 ± 1.71	0.07
Pre Hct (%)	38.38 ± 3.32	37.11 ± 4.28	0.14

Table II: Comparison the estimated blood loss between groups.

	Rectal group N=40	Sublingual group N=40	p-value
Intra-operative Blood loss (mL) Mean ± SD	393.37 ± 143.69	404.25 ± 145.88	0.73
Recovery Blood loss (mL) Mean ± SD	78 ± 35.67	77.25 ± 26.21	0.91

Table III: comparison between groups regards postoperative Hb, Hct and their changes (Δ Hb, Δ Hct).

	Rectal group N=40	Sublingual group N=40	p-value
Post Hb (g/dL) Mean ± SD	11.85 ± 1.21	11.4 ± 1.72	0.18
Post Hct (%) Mean ± SD	34.96 ± 3.1	34.57 ± 4.2	0.64
Δ Hb (g/dL) Mean ± SD	1.01 ± 0.7	0.86 ± 0.65	0.34
Δ Hct (%) Mean ± SD	3.41 ± 2.7	2.54 ± 2.3	0.12

Table IV: Comparison of outcome variables among the groups.

	Rectal group N=40	Sublingual group N=40	p-value
Need for oxytocin patients (%)			
20 unit	34 (85%)	30 (75%)	0.4
40 unit	6 (15%)	10 (25%)	
Need for methergine patients (%)			
Yes	5 (12.5%)	8 (20%)	0.36
No	35 (87.5%)	32 (80%)	
Fever (%)			
Yes	0 (0%)	0 (0%)	Not available
No	0 (0%)	0 (0%)	
Chills (%)			
Yes	9 (22.5%)	11 (27.5%)	0.6
No	31 (77.5%)	29 (72.5%)	
Nausea/vomiting (%)			
Yes	4 (10%)	7 (17.5%)	0.33
No	36 (90%)	33 (82.5%)	

Discussion

Bleeding, hypertension, and infection are the three leading causes of maternal mortality. In developing countries, postpartum hemorrhage is still one of the causes of maternal mortality¹³. Active control of bleeding using a uterotonic drug reduces postpartum hemorrhage¹³. But despite the fact that researchers agree on the use of uterotonic drugs to prevent postpartum hemorrhage, the choice of the best drug is still under discussion¹⁴.

Misoprostol is a synthetic analogue of prostaglandin E1 that can be used to treat uterine atony and prevent postpartum hemorrhage. Unlike methergine and carboprost, misoprostol is also prescribed for women with hypertension and asthma¹⁵. Various type and doses of misoprostol have been used in various studies to control bleeding including 400 micrograms rectal^{16,17}, 200, 400 or 600 micrograms oral^{20-18,15}, 400 micrograms sublingual^{21,22}, 400 micrograms of oral powder misoprostol (23 micrograms) or 400 micrograms in rectal enema²⁴. Studies have shown that misoprostol is effective in reducing bleeding but there is controversy regarding the dosage and method of administration.

In this study Patients were similar in both groups, and gravidity, age and BMI were not significantly different between the two groups. None of the patients in the two groups needed transfusions during the study. There was also no difference between the two groups in the amount of oxytocin and methergine needed. The findings of the present study showed that there was no significant difference in the amount of intraoperative bleeding and the bleeding in the recovery room between the two groups. Therefore, sublingual misoprostol administration may be as effective as rectal misoprostol. In addition to confirming the effect of sublingual misoprostol, the results showed that the mean hemoglobin and hematocrit were not different between the two groups before and after the surgery. Side effects were not observed in any patients. Also, the hemodynamic variables in this study were not significantly different between the two groups during surgery and recovery.

The study of Beigi et al. Was conducted on 542 nulliparous mothers in one group receiving 400 µg of sublingual misoprostol and in the other group receiving 20 units of intravenous oxytocin immediately after the birth of the newborn, the results of which showed postnatal hemorrhage in the misoprostol group 96.3 ml and in the oxytocin group was 395.78 ml. In the present study, postpartum hemorrhage in recovery was 77.25 ml. Unlike the Beigi study, all subjects received 20 units of oxytocin after birth in the present study. Also, in the Beigi study, fever and body temperature, headache, diarrhea, chills, vomiting, nausea and hiccups were significantly higher in the misoprostol group, which is inconsistent with the present study, which may be due to the sample size and type of drug comparisons²². Because Beigi study compared the sublingual misoprostol study with oxytocin and the present study sublingual misoprostol with rectal misoprostol. In another study by Soleimani et al, who evaluated the effect of sublingual misoprostol on the prevention of bleeding in cesarean section, 186 pregnant women who volunteered for cesarean section were evaluated. One group received 400 µg of sublingual misoprostol with oxytocin and one group received placebo and oxytocin. Their findings, similar to those of Beigi's study, showed that mean fall in hemoglobin and

hematocrit level were significantly lower in the misoprostol group than in the placebo group, and the need for additional uterine contraction factors was significantly lower in the misoprostol group. Similar to the present study, unlike other studies, there were no significant differences between the two groups in case of side effects. There was no significant difference between the two groups in the need for blood transfusion²⁵.

Fazel et al.'s study comparing rectal misoprostol and oxytocin showed that 400 µg of rectal misoprostol were as effective as 10 units of oxytocin and there was no significant difference between intraoperative bleeding and hemoglobin differences before and after the operation. However, the bleeding rate was lower in the misoprostol group. The rate of intraoperative bleeding was 578 ml in the misoprostol group and 620 ml in the oxytocin group. In the present study, bleeding rate was 393.3 ml in the misoprostol group and 404.25 ml in the sublingual group. Similar to the present study in Fazel et al., None of the patients needed transfusion and side effects such as nausea, vomiting and chest pain were not significantly different between the two groups and shivering was higher in misoprostol group¹².

Another study by Nasr et al, comparing rectal misoprostol and oxytocin, showed that 800 mg of rectal misoprostol compared to 5 units of oxytocin were equally effective in controlling hemorrhage. There was no significant difference between the two groups in terms of hemoglobin before and after surgery and postoperative bleeding. Hemodynamic variables were also examined in this study, but there was no difference between the two groups. Similar to other studies, only shivering and fever were higher in the misoprostol group than in oxytocin²⁶.

In the study of Uncu et al., 248 pregnant women were studied (in one group 400 mg oral misoprostol; second group 400 mg oral and one 400 mg vaginal dose; third group 400 mg rectal and fourth group 400 mg vaginal). The results of their study showed that there was no significant difference between hemoglobin and postpartum hematocrit levels. However, the difference between their study and the present study was the type of delivery and the sample size. In their study, the effect of drugs on normal delivery and in the present study was cesarean delivery. Finally, their study showed that although misoprostol is useful in the treatment of postpartum hemorrhage, it has no significant effect on the prevention of atony causing postpartum hemorrhage¹¹.

Studies of the effect of misoprostol on postpartum hemorrhage have examined the efficacy of this drug over other drugs. One study showed that the combination of misoprostol and oxytocin was better in controlling bleeding than misoprostol alone (26). In a study by Singh et al. In India, the results showed that 600 µg of sublingual misoprostol had a greater and more effective effect on

reducing bleeding than 400 micrograms of misoprostol, oxytocin, and even syntometrine²⁷. However, a meta-analysis study by Hofmayer et al. found that administration of oxytocin and ergot products during the third stage of labor had a greater effect than misoprostol on preventing postpartum hemorrhage as well as maternal mortality²⁸. In another study by NG et al., The results showed that 400 µg of oral misoprostol had a similar effect on post-operative hemoglobin compared to muscular syntometrine but shivering was higher in the misoprostol group (19). Also, the findings of various studies showed that nausea, fever and chills were common findings for oral misoprostol administration³¹⁻²⁹.

In a study in 2018 by Sweed et al., A comparative study of the sublingual and rectal misoprostol was performed. Results of their study showed that intraoperative bleeding was 457.5 ml in rectal group, 357.8 ml in sublingual group and 641.7 ml in control group. In the present study bleeding rate was 393.37 cc in rectal group and 404.25 cc in sublingual misoprostol group. In contrast to the present study, the results of the Sweed study showed that there was a significant difference between the two groups in bleeding and the rate of bleeding was lower in the sublingual group. The prescribed dose of misoprostol in Sweed et al. Was similar to the present study, but the dose of oxytocin was different, probably due to the large sample size and lack of brand equity in the Sweed study. In the Sweed study, hemoglobin and hematocrit changes in the pre- and postoperative were also lower in sublingual group compared to the rectal group³².

Limitations of this study include failure to evaluate other drugs, different doses of misoprostol, and lack of sample size. But the strengths of the study were the matched study groups for age, BMI, and pregnancy gravid and double blind. According to the results of this study and the same effect of misoprostol with other drugs and also the effect of sublingual form of misoprostol compared to rectal form, also because of the easier storage method at room temperature, no need for injections, cheaper and Easier consumption sublingual form Compared to rectal one, misoprostol sublingual form can be used to control bleeding during and after delivery. If there are any side effects, they are not dangerous and may be temporary and can be resolved within a maximum of 12 hours and in addition to their many benefits, these side effects can be neglected. However, there are still disagreements in various studies on the dosage used and its forms, and more extensive studies with larger sample sizes are recommended.

Interests conflict

The researchers declare that they have no conflict of interest.

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ORIGINAL

Pregnancy obesity, weight gain during pregnancy, and its association with birth outcomes

Obesidad en el embarazo, aumento de peso durante el mismo y su asociación con los resultados del parto

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Abstract

Introduction: Obesity is one of the major risk factors for various adverse outcomes for mother and fetus. This study aimed to determine the prevalence and perinatal, intrapartum, and neonatal outcomes of obese women giving birth in Kosovo from January 2019 to December 2020.

Methods: This retrospective cohort study used data from the Ferizaj Hospital system. We analyzed the pregnancy and birth data (mother-child pairs) to assess maternal body mass index and its associations with pregnancy risk factors and childhood health outcomes in this population.

Results: In the overall study population ages 18-45 years, the prevalence of maternal pregnancy obesity was 59%. More than half of maternal obesity (673/1052) was in severe and severe obesity categories at 44.8% and 19.2% respectively. Maternal obesity was inversely associated with preterm birth among those older than 30 years (adjusted OR 0.89, 95% CI [0.63–1.28]), but positively associated with preterm birth among those aged 30 years or younger (adjusted OR 0.921, 95% CI [0.92–2.37]). Furthermore, women with pregnancy obesity, compared to those who did not have obesity, were more likely to report hypertension during pregnancy, gestational diabetes, and C-section delivery with a p-value <0.05.

Conclusion: The findings of this study suggest that the greatest risk of extremely preterm birth was observed in obese women. Also, maternal obesity was associated with increased pregnancy and birth complication rates. We recommend promoting healthy lifestyle changes that could reduce the prevalence of preterm birth among obese women.

Key words: Obesity, maternal pregnancy, complication.

Resumen

Introducción: La obesidad es uno de los principales factores de riesgo adversos para la madre y el feto. Este estudio tuvo como objetivo determinar la prevalencia y los resultados perinatales, intraparto y neonatales de las mujeres obesas que dan a luz en Kosovo desde enero de 2019 hasta diciembre de 2020.

Métodos: Este estudio de cohorte retrospectivo utilizó datos del sistema del Hospital Ferizaj. Se analizaron los datos del embarazo y el parto (pareas madre-hijo) para evaluar el índice de masa corporal materno y sus asociaciones con los factores de riesgo del embarazo y los resultados de salud de la infancia en esta población.

Resultados: En la población general del estudio de 18 a 45 años, la prevalencia de obesidad materna en el embarazo fue del 59%. Más de la mitad de la obesidad materna (673/1052) se encontraba en las categorías de obesidad grave y severa, con un 44,8% y un 19,2% respectivamente. La obesidad materna se asoció de forma inversa con el parto prematuro entre las mayores de 30 años (OR ajustado 0.89, IC 95% [0,63-1,28]), pero se asoció de forma positiva con el parto prematuro entre las menores de 30 años (OR ajustado 0.921, IC 95% [0,92-2.37]). Además, las mujeres con obesidad en el embarazo, en comparación con las que no tenían obesidad, eran más propensas a informar de hipertensión durante el embarazo, diabetes gestacional y parto por cesárea con un valor p <0,05.

Conclusión: Los resultados de este estudio sugieren que el mayor riesgo de parto extremadamente prematuro se observó en las mujeres obesas. Además, la obesidad materna se asoció con un aumento de las tasas de complicaciones en el embarazo y el parto. Se recomienda promover cambios en el estilo de vida saludable que podrían reducir la prevalencia del parto prematuro entre las mujeres obesas.

Palabras clave: Obesidad, embarazo materno, complicaciones.

Introduction

Over the past few decades as the result of economic, technological, and lifestyle changes the prevalence of obesity has increased worldwide. Nowadays has been created an abundance of cheap, high-calorie food has been coupled with decreased required physical activity¹. All of this is thought to have had an impact on the increase in obesity worldwide. Obesity is a significant public health concern and is likely to remain so for the foreseeable future.

Based on the World Health Organization data in 2016 about 39% of adults aged 18 years and above were overweight, while 13% were obese². This rise in obesity prevalence is more evident in women of reproductive age³. Moreover, the rates of obesity in pregnancy are increasing, particularly in developed countries⁴⁻⁶. At the global level, in 2014, the number of pregnant women overweight or obese was estimated 8.9 and 14.6 million, respectively⁷.

Flegal et al, in their survey in the USA, indicated that 55.8% of women of childbearing age (20-39 years) were overweight or obese, defined as having a BMI of 25 or higher⁸. Greve et al, highlight that pre-pregnancy weight is the most significant modifiable risk factor for stillbirth, with up to 100% increased risk for women with obesity⁹.

Maternal obesity is a complex condition strongly associated with socio-economic status and ethnicity inequalities^{10,11}, making it a public health priority in addition to being a priority area for clinical practice¹². On the other hand, many studies are reported that during pregnancy and childbirth, obese women are at greater risk of maternal-fetal complications than women with a normal body mass index (BMI)^{13,14}. Furthermore, there is evidence that maternal BMI influences also the gestational age at delivery¹⁵. Additionally, maternal obesity increases the risk of several pregnancy complications, including antenatal, intrapartum, postpartum, preeclampsia, and neonatal complications such as hypertensive disorders of pregnancy, gestational diabetes mellitus (GDM), cesarean delivery, macrosomia, and unexplained stillbirths¹⁶⁻²⁰. This study aimed to determine the prevalence and perinatal outcomes of obese women giving birth in Kosovo.

Methods

Subject

Regional Hospital of Ferizaj has its origins in June 1999, the day when the ZO-Nerodima military hospital with 65 wounded and medical personnel from the war zone was placed in one segment of the city's Health House, in which the hospital is still located today. In its beginner, this hospital started to work with three wards and one of them was the gynecology ward, while two others were

Emergency, and Surgery wards with about 110 medical staff. Nowadays, the Regional Hospital of Ferizaj is a University Clinical Center, – that offers services in many departments for all communities of Ferizaj. All the medical staffs are very specialized at their work and every time develops knowledge and skills for individual enrichment and to contribute to a healthy life.

Study population

This retrospective cohort study used data from the Ferizaj Hospital system between January 2019 to December 2020. We included in this study the data of 1780 mothers who gave birth at the Ferizaj hospital. We analyzed pregnancy and birth data (mother-child pairs) to assess maternal body mass index and its associations with pregnancy risk factors and childhood health outcomes in this population. The first information was obtained during their first antenatal visit between gestational weeks 6 and 10. Maternal BMI was derived from measured height and weight recorded according to scientific notation. BMI was categorized into six groups: underweight (≤ 18 kg/m²); normal weight (19-24 kg/m²); overweight (25-29 kg/m²); obese class I (30-34 kg/m²); and obese class II & III (35->39 kg/m²)

We have considered as maternal outcomes preeclampsia (mild and severe preeclampsia), chronic hypertension and pre-existing hypertension plus superimposed gestational hypertension, pregestational diabetes mellitus, gestational diabetes, antepartum hemorrhage (such as placenta previa, abruptio placentae, and third-trimester bleeding), cesarean section, induction of labor, and shoulder dystocia (diagnosed clinically by the delivering attending physician).

While on perinatal/neonatal outcomes we have considered the data for fetal presentation. We examine several measures of birth weight: macrosomia: Macrosomia was defined as ≥ 4000 g²¹, (birth weight in excess ≥ 4000 g, birth weight over ≥ 4500 g, low birth weight over < 2500 g), preterm birth > 37 weeks, meconium-stained amniotic fluid. An Apgar score (used to evaluate neonatal well-being immediately after birth) of ≤ 7 at 5 min was used as an indicator for referral to a neonatal morbidity meeting. Additionally, we have assessed also the information about admission to neonatal intensive care, and neonatal mortality from 0 to 28 days.

Statistical analyses of data

The data were analyzed using SPSS Statistics for Windows, Version 20.0 The demographic characteristics of the pregnant women (obese and normal) were analyzed using descriptive statistics followed by two-sided independent Student's t-tests for the continuous variables, and the chi-squared (χ^2) test or Fisher's exact test for the categorical variables. The Kolmogorov-Smirnov test was used to check whether continuous data were normally distributed. The data were presented as mean

and standard deviation unless otherwise indicated. To the deep analyses of our data, we performed the univariate and multivariate logistic regression analyses (controlling for maternal age, parity, gestational age, and chronic hypertension). We performed for estimation adjusted odds ratios (OR) and 95% confidence intervals (95% CI), and a value of $p < 0.05$ was considered statistically significant.

Results

Overall, 1780 pregnant women were included in this study, the age population was 18-45 years with an average of 27.5 ± 6.9 years old in all pregnant women and 29.2 ± 4.3 years old in maternal obesity. Related to the age of pregnant mothers, 67.7% (712/1051) were ≤ 35 years old while 32.3% were > 35 years old. Most than half 61.7% live in rural areas and 38.3% in urban areas. Regarding the education level, approximately 24% referred to the primary level, 55.1% to the high school level, and 20.8% to the university level, while less than 32% were employed. The mean of parity was 1.9 ± 0.4 with a dominance of primiparous 40%, and other mothers referred second,

third, and more than third pregnancies in percentages of 37.7%, 13.6%, and 8.6% respectively. The BMI mean in pregnant women resulted in 27.2 ± 3.01 , while maternal obesity resulted in 32.5 ± 4.2 . The prevalence of maternal pregnancy obesity was 59% (1051/1780). More than half of maternal obesity (673/1052) was in obese class I and obese class II & III categories at 44.8% and 19.2% respectively. Regarding maternal obesity outcomes, we have considered mild and severe preeclampsia, and chronic hypertension. Furthermore, we have evaluated the presentational diabetes mellitus, gestational diabetes, and also the use of alcohol, smoke, and drug during pregnancy. Women with pregnancy obesity were more likely to report hypertension and gestational Diabetes Mellitus compared to those who did not have obesity. So, based on the analysis data, about 27.9% of pregnant women have Gestational Diabetes Mellitus and 3.8% have Diabetes Mellitus Type 1&2, while 22% presented Chronic hypertension, 10.8% have mild hypertension, and 4.6% have severe hypertension. About 8.6% were alcohol users during pregnancy, 19.5% were smoker users during pregnancy, and 16.4% were drug users during pregnancy. **Table I** shows the characteristics demographic of pregnant women (**Table I**).

Table I: Baseline demographic characteristics of the pregnant mother.

Maternal variables 1780		Total number of mothers	Obese mothers	P value
Age (ean \pm SD)	27.5 \pm 6.9	29.2 \pm 4.3	0.001	
Age	≤ 35 years old > 35 years old	1257 523	712 339	0.001
Residence	Rural Urban	983 797	649 402	0.002
Education	Primary level High school University	429 734 617	252 580 219	0.03
Employed	No Yes	1096 684	724 327	0.0007
Parity mean (mean \pm SD)	1.7 \pm 0.2	1.9 \pm 0.4	0.03	
Parity	Primiparous Second Third More than third	708 634 246 192	420 397 143 91	0.04
BMI (mean \pm SD)	27.2 \pm 3.01	32.5 \pm 4.2	0.0001	
BMI	≤ 18 kg/m ² 19-24 kg/m ² 25-29 kg/m ² 30-34 kg/m ² 35-39 kg/m ²	177 552 378 471 202	- - 378 471 202	0.0001
Hyperglycemic disorders	No Gestational Diabetes Mellitus Diabetes Mellitus Type 1&2	1408 327 45	718 293 40	0.03
Hypertensive disorders	No Chronic hypertension Mild hypertension Severe hypertension	1284 288 151 57	658 231 114 48	0.005
Alcohol use during pregnancy	No Yes	1586 194	960 91	0.0008
Smoking use during pregnancy	No Yes	1381 399	855 205	0.0007
Drug use during pregnancy	No Yes	1544 236	879 172	0.0003

Table II shows the association between intrapartum and neonatal outcomes with maternal obesity. Maternal obesity was inversely associated with preterm birth among those older than 30 years (adjusted OR 0.89 [95% CI 0.63-1.28]), but positively associated with preterm birth among those aged 30 years or younger (adjusted OR 2.59 [0.89-3.37] with a p-value <0.05). On the other hand, the estimated prevalence of preterm birth was higher among the underweight (≤ 18 kg/m²) category compared to obese women. Underweight women were 2.5 times at risk for pattern delivery less than 37 weeks for 95% CI [1.49-3.7] p-value < 0.0001. We have evaluated also the antepartum hemorrhage (such as placenta previa, abruptio placentae, and third-trimester bleeding), cesarean section, induction of labor and induction of labor in late-term pregnancies, and duration of labor ≤ 360 minutes or ≥ 360 minutes. A significant association was seen for induction of labor in maternal women in obese class I (1.1 times in risk for induction labor for 95% CI [0.05-1.7], p-value 0.048) and maternal women in obese class II & III (2.4 times in risk for induction labor for 95% CI [1.09-3.6], p-value 0.009). While for the duration of labor, a significant association was seen among

underweight women and the duration of labor was ≤ 360 minutes. Underweight women have a predisposition 2.4 times for the duration of labor was ≤ 360 minutes in risk for 95% CI [0.7-4.5], p-value 0.008. Related to the birth mode obese women have a predisposition for cesarean birth compared to women in normal or underweight. Overweight women were 1.5 times at risk for cesarean [0.7-2.3], women obese in class I was 1.9 times at risk for cesarean [0.9-3.6], while women obese in classes II&III were 3.5 times at risk for cesarean [1.07-7.5], with p-value less than 0.05.

Additionally, we have considered the data on neonatal outcomes in maternal obesity. We have evaluated the meconium-stained amniotic fluid, shoulder dystocia (diagnosed clinically by the delivering attending physician), measures of birth weight such as macrosomia ≥ 4000 g, birth weight over ≥ 4500 g, low birth weight < 2500 g, Apgar score of ≤ 7 at 5 min. Additionally, we evaluated also the data on umbilical cord arterial pH < 7.1 , cases that were admitted to neonatal intensive care, and neonatal mortality from 0 until 28 days. The multiple linear regression analysis shows newborn weight was

Table II: Association between intrapartum and neonatal outcomes with maternal obesity.

Variables	Underweight (≤ 18 kg/m ²)		Normal weight (19-24 kg/m ²)		Overweight (25-29 kg/m ²)		Obese class I (30-34 kg/m ²)		Obese class II & III (35->39 kg/m ²)	
	odds ratio 95% CI	P value	odds ratio 95% CI	P value	odds ratio 95% CI	P value	odds ratio 95% CI	P value	odds ratio 95% CI	P value
Preterm delivery < 37 weeks	2.5 [1.49-3.7]	0.0001	reference		0.2 [0.05-1.4]	0.3	1.4 [1.00-2.7]	0.04	0.3 [0.00-1.1]	0.11
Induction of labor	0.4 [0.01-1.2]	0.2	reference		0.1 [0.06-1.3]	0.3	1.1 [0.05-1.7]	0.048	2.4 [1.09-3.6]	0.009
Induction of labor in late-term pregnancies	0.1 [0.02-1.3]	0.4	reference		1.6 [0.7-2.6]	0.03	1.9 [1.01-3.5]	0.02	3.4 [1.2-7.1]	0.01
Duration of labor ≤ 360 minutes	2.4 [0.7-4.5]	0.008	reference		0.4 [0.02-1.5]	0.5	0.2 [0.04-1.7]	0.3	0.6 [0.01-1.9]	0.7
Duration of labor ≥ 360 minutes	0.01 [0.00-0.8]	0.7	reference		0.02 [0.00-1.1]	0.9	0.7 [0.03-2.0]	0.8	0.5 [0.02-1.9]	0.7
Bleeding during labor	1.01 [0.07-1.4]	0.6	reference		1.2 [0.4-2.2]	0.045	1.5 [0.2-2.4]	0.03	1.3 [0.1-1.9]	0.04
Birth mode										
Spontaneous vaginal	1.7 [0.3-2.5]	0.03	reference		0.1 [0.07-1.4]	0.9	0.6 [0.02-1.2]	0.7	1.1 [0.4-1.8]	0.8
Caesarean	0.3 [0.04-1.1]	0.5	reference		1.5 [0.7-2.3]	0.04	1.9 [0.9-3.6]	0.004	3.5 [1.07-7.5]	0.0001
Instrumental vaginal	1.7 [1.04-2.8]	0.03	reference		0.01 [0.00-0.8]	0.7	0.9 [0.2-1.8]	0.8	0.7 [0.1-1.5]	0.4
Meconium-stained amniotic fluid	0.2 [0.3-1.9]	0.1	reference		1.4 [0.4-2.6]	0.03	2.0 [1.08-3.4]	0.009	2.7 [1.24-6.2]	0.0001
Shoulder dystocia	1.5 [0.2-2.4]	0.04	reference		0.2 [0.01-0.8]	0.3	0.4 [0.1-0.9]	0.5	0.8 [0.02-1.7]	0.6
Apgar score ≤ 7 at 5 min	2.1 [0.8-3.9]	0.005	reference		1.9 [1.04-3.08]	0.008	1.4 [0.6-2.8]	0.03	1.7 [0.45-3.2]	0.02
Umbilical cord arterial pH < 7.1	0.1 [0.00-1.1]	0.2	reference		0.02 [0.00-0.6]	0.7	0.5 [0.01-1.0]	0.9	0.3 [0.01-1.04]	0.4
Birth weight										
Low birth weight	1.3 [0.8-1.7]	0.007	reference		0.2 [0.04-1.3]	0.5	1.4 [0.9-1.8]	0.03	0.2 [0.01-0.9]	0.4
Macrosomia ≥ 4000 kg	0.01 [0.00-0.7]	0.8	reference		1.8 [0.3-2.9]	0.03	2.1 [0.7-4.8]	0.004	2.7 [0.1-7.5]	0.0007
Macrosomia ≥ 4500 kg	0.03 [0.00-0.7]	0.5	reference		1.2 [0.4-1.8]	0.04	2.4 [1.08-3.5]	0.002	1.9 [0.8-3.4]	0.004
Admission of the baby to the neonatal intensive care unit	0.1 [0.00-0.8]	0.2	reference		1.7 [0.3-2.6]	0.03	2.1 [1.02-4.5]	0.002	2.3 [1.3-5.1]	0.0001
Neonatal mortality 2-28 days	1.4 [0.7-1.9]	0.048	reference		0.2 [0.06-1.3]	0.7	0.9 [0.5-1.7]	0.3	1.3 [0.4-1.9]	0.04

statistically different between the BMI groups ($p < 0.05$). Admission of the baby to the neonatal intensive care unit appeared a significant association with obese women ($p < 0.05$). Neonatal mortality 2-28 days was apparently more significant in underweight and obese classes II&III women. Moreover, the neonatal variables such as Apgar score, fetal birth trauma (shoulder dystocia), and umbilical cord arterial $pH < 7.1$ were not different between the obese women and non-obese women.

Discussion

Giving life to a child is a miracle, but on the other hand, it requires a lot of sacrifices, commitment, and care on the part of the pregnant woman. This is because the mother must be very careful in maintaining this pregnancy, especially in her nutrition to maintain a normal weight without becoming obese. According to Davis's study (2015), for the past 20 years, the rising obesity pandemic has received a great deal of press, policy, and research. Among women of childbearing age, obesity is paramount because of its association with multiple adverse health outcomes for both mother and fetus and even future generations²². Having a high body mass index during pregnancy can increase the risk for an array of maternal and perinatal complications, and the risks are amplified with the increasing severity of the condition. It has been estimated that one-quarter of pregnancy complications (like gestational hypertension, preeclampsia, gestational diabetes, preterm birth, and macrosomia) are attributable to maternal overweight or obesity²³. We undertake this study to determine the prevalence and perinatal, intrapartum, and neonatal outcomes of obese women giving birth in Kosovo for two years. One of the years when this was carried out this study coincides with the time when the global pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, COVID-19) appeared. Not much is known about the specific risk factors for maternal obesity and excessive weight gain during pregnancy. Identification of these risk factors and critical periods of gestational weight gain might be useful for the development of preventive strategies (24). The multifactorial etiology of obesity is a consensus in the literature, involving genetic, environmental, socioeconomic, and behavioral factors²⁵.

Cai et al, in their study highlight that some of the risk factors of obesity, rose significantly during the COVID-19 quarantine²⁶. Home quarantine made people more vulnerable to overeating and intake of high-calorie food²⁷. Furthermore, social distancing home quarantine limits physical activity, making sedentary daily life adopted obesity to the pregnant women, which will translate in the future to maternal and neonatal outcomes.

The prevalence of obesity in this study resulted in 59% (1051/1780), and from that more were in obese class I

and obese class II & III categories at 44.8% and 19.2% respectively. As we highlighted before maternal obesity is strongly associated with socioeconomic status. For example, Hazlehurst et al, in their study found that socioeconomic status varies between obesity classes, and pregnant women in the highest obesity class (class III, $BMI \geq 40 \text{ kg m}^2$) are significantly more likely to reside in deprived locations (odds ratio 4.7, 95% CI [3.2-6.9]) compared with women in obesity class I ($BMI 30.0-34.9 \text{ kg m}^2$; OR 2.2, 95% CI 2.1- 2.3)¹². In our study, more than half (61.7%) of pregnant women live in rural areas and 38.3% in urban areas with a statistical significance between them, (p -value < 0.05).

In one study conducted by Boudet-Berquier et al, there was found significant association between primiparae obesity with maternal age of 25-29 years (OR=2.09 [1.13-3.87]) (vs. 30-34 years), high school level (OR=2.22 [1.32-3.73]) (vs. university level), while among multiparae, primary school level (OR = 6.30 [2.40-16.57]), secondary school level (OR=2.89 [1.81- 4.63]), and high school level (OR = 1.86 [1.18-2.93]) (vs. university level), no follow-up antenatal classes (OR=1.77 [1.16-2.72])²⁸. Furthermore, a systematic review found that low maternal education, rather than other sociodemographic factors such as income and employment, tended to be associated with excessive gestational weight gain²⁹.

Disparities are also seen with maternal employment status. Pregnant women with a BMI in class I are more likely to be employed, while those in class III are more likely to be unemployed³⁰. The findings of our study were similar to the previous studies, but it was controversial to a study conducted by Cheng et al, which did not find any association between maternal education, employment status, or monthly family income and pregnancy BMI or Gestational weight gain (GWG) among pregnant women (31). So, in our study, there was found an association between age, education level, employment, and parity (p -value < 0.05).

Numerous studies have reported an association between abnormal pregnancy body mass index (BMI) and the onset of gestational diabetes, hypertension, and preeclampsia during pregnancy, cesarean delivery, and infant birth weight above 4000 grams (vs birth weight between 2500 grams and 4000 grams)³¹⁻³³.

Moreover, Leddy et al, highlight that obese women are at increased risk of complications at the time of labor and delivery. The rate of successful vaginal delivery decreases progressively as maternal BMI increases. Chu et al, in a meta-analysis of 33 studies showed that the ORs of cesarean delivery were 1.46 (95% CI, 1.34-1.60), 2.05 (95% CI, 1.86-2.27), and 2.89 (95% CI, 2.28-3.79) among overweight, obese, and severely obese women, respectively, compared with normal weight pregnant women^{34,35}. The findings of the previous study were

almost the same as our findings. Maternal overweight, obese classes I, and classes II & III were 1.5, 1.9, and 3.4 at risk for cesarean delivery compared to maternal in normal weight.

Few studies have shown that Maternal alcohol, smoking, and drug intake before and during pregnancy is associated with maternal obesity³⁶⁻³⁸. In this study, there was a significant association between the intake of alcohol, smoking, and drug in maternal obesity (p-value <0.05).

There is increasing evidence that maternal BMI influences gestational age at delivery (pre-term and/or birth post-term birth). Additionally, a post-term birth includes interventions to expedite birth, such as induction of labor and cesarean section, interrupting the natural gestation trajectory³⁹. Bhattacharya et al results showed that low birth weight was significantly less common in obese (p-value < 0.05) than in normal and overweight mothers⁴⁰. The findings of our study were similar to the previous study. While delivery after 41 completed weeks and macrosomia birth weight were significantly higher in the obese as compared to the normal BMI group and in the overweight group.

Minsart et al, highlight that the reason for this increased rate of neonatal complications in obese women is unknown but could be related to increased maternal pelvic soft tissue, as well as difficulty in estimating the fetal weight, and intrapartum complications such as the inability to adequately monitor the fetus and contractions⁴¹. On the other hand, there is strong evidence for the relation between macrosomia and shoulder dystocia, but the current evidence for an independent relation between maternal obesity and shoulder dystocia through the excess fat tissue in the birth canal is less clear^{42,43}. In our study, we found an association between obesity and macrosomia, while shoulder dystocia was associated with underweight women. The risk for macrosomia increased linearly with the increasing BMI of the mother, in an adjusted Odds Ratio of 1.8 (95% CI [0.3-2.9]) for overweight and 2.1 (95%CI [0.7-4.8]) in obese class I and 2.7 (95%CI [0.1-7.8]) mothers. These results are comparable with some studies^{44,45}.

Conclusion

The findings of this study suggest that the greatest risk of extremely preterm birth was observed in obese women. Also, maternal obesity was associated with increased pregnancy and birth complication rates. We recommend promoting healthy lifestyle changes that could reduce the prevalence of preterm birth among obese women.

Ethical Considerations

This study was approved by the Ferizaj Hospital Ethical Committee. During this study, we followed the guidelines of the Declaration of Helsinki of 1975, as revised in 2008. We have explained the purpose of the study to all our colleagues before starting this study. No personal data were recorded, and all the data collected will be used only for the current study. We warrant that all ethical guidelines for medical research were strictly respected.

Ethical Considerations

This study was approved by the Ferizaj Hospital Ethical Committee. Before enrollment of all contributors the researcher explained the purpose of the study. During this study, we followed the guidelines of the Declaration of Helsinki of 1975, as revised in 2008. No personal data were recorded. We warrant that all ethical guidelines for medical research "On the protection of personal data" were strictly respected.

Author contributions

All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

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Competing interests

All the authors played a significant role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

Conflicts of interest

The authors have no potential conflicts of interest to report in connection with this article.

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ORIGINAL

Assessing patient satisfaction with the quality of healthcare service in public hospitals. Evidence of a country with a primarily public healthcare system

Satisfacción de los pacientes con la calidad percibida del servicio de salud en hospitales públicos. Evidencia de un país con un sistema de salud mayoritariamente público

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Abstract

Introduction: Patient assessment of service quality is a very important component in evaluating the quality of healthcare services in a medical center. This study aims to identify and assess the factors that affect overall patient satisfaction with healthcare quality provided by medical centers in Albania.

Method: The study used empirical research to identify previously validated scales of service quality evaluation. From March to June 2022, 300 hospitalized patients participated in the study. The most relevant factors influencing patient satisfaction variation are identified using multiple regression and factor analysis. A structured questionnaire was used as a tool for assessing healthcare quality.

Results: There is a statistically significant relationship between patient education level ($F_{4;247} = 2.990$, Sig = 0.02) and income level ($F_{3;247} = 2.259$ and Sig = 0.042,) with overall patient satisfaction. Four of the five quality dimensions demonstrated a statistically significant relationship with overall satisfaction, explaining 60.5% ($R^2 = .605$) of the variation values of patient satisfaction. Patient satisfaction was significantly impacted by Tangibles ($\beta = .291$, Sig=.000), Reliability ($\beta = .212$, Sig=.003); Assurance ($\beta = .253$, Sig=.000); Empathy ($\beta = .141$, Sig=.018), while Responsiveness did not influence patient satisfaction ($\beta = .028$, Sig=.674).

Conclusions: The study proposes a validated conceptual model for the health sector detailing the relationships between the factors that influence patient satisfaction with the quality of medical healthcare services in the Albanian context. The findings have important implications for decision-makers in health care institutions in their continuous effort to improve healthcare services quality.

Key words: Quality of healthcare, patient satisfaction, sociodemographic factors.

Resumen

Introducción: La evaluación de la calidad del servicio por parte del paciente es un componente esencial en la evaluación de la calidad de los servicios de salud en un centro médico. Este estudio tiene como objetivo identificar y evaluar los factores que afectan la satisfacción general del paciente con la calidad de la atención médica brindada por los centros médicos en Albania.

Método: El estudio utilizó investigación empírica para identificar escalas previamente validadas de evaluación de la calidad del servicio. De marzo a junio de 2022 participaron en el estudio 300 pacientes hospitalizados. Los factores más relevantes que influyen en la variación de la satisfacción del paciente se identifican mediante regresión múltiple y análisis factorial. Se utilizó un cuestionario estructurado como herramienta para evaluar la calidad asistencial.

Resultados: Existe una relación estadísticamente significativa entre el nivel de educación del paciente ($F_{4;247} = 2,990$, Sig = 0,02) y el nivel de ingresos ($F_{3;247} = 2,259$ y Sig = 0,042) con la satisfacción general del paciente. Cuatro de las cinco dimensiones de calidad demostraron una relación estadísticamente significativa con la satisfacción general, explicando el 60,5% ($R^2 = 0,605$) de los valores de variación de la satisfacción del paciente. La satisfacción del paciente se vio significativamente afectada por Tangibles ($\beta = .291$, Sig=.000), Confiabilidad ($\beta = .212$, Sig=.003); Garantía ($\beta = .253$, Sig=.000); Empatía ($\beta = .141$, Sig=.018). La capacidad de respuesta no influyó en la satisfacción del paciente ($\beta = .028$, Sig=.674).

Conclusiones: El estudio propone un modelo conceptual validado para el sector de la salud que detalla las relaciones entre los factores que influyen en la satisfacción del paciente con la calidad de los servicios de atención médica en el contexto albanés. Los hallazgos tienen implicaciones importantes para los tomadores de decisiones en las instituciones de atención médica en su esfuerzo continuo por mejorar la calidad de los servicios de atención médica.

Palabras clave: Calidad asistencial, satisfacción del paciente, factores sociodemográficos.

Introduction

Linder-Pelz¹ emphasizes the importance of the patient's perspective when assessing the quality of health care. This concept has attracted the attention of service providers since the early 1970's in developed countries who became aware of the importance of patient satisfaction as well as researchers who strongly believed that the quality of health care should be studied from the patient's perspective^{2,3}. Patients provide valuable and unique information about the quality of care^{4,5} and it is even believed that the main indicator of health care is patient satisfaction and not health status.

To ensure quality, evaluating patients has the potential to be an educational process, identifying those moments or situations where improvements are possible, identifying best practices, and establishing a set of standards that include and incorporate potential patients⁶. Patient satisfaction studies are important for the success of health organizations because they must build and rely on mechanisms to enable changes based on consumer needs. Hall et al.⁷, reiterated that on the one hand studies regarding patient perspective are very important and on the other hand this very important issue was often ignored by service providers. The importance of service quality has been recognized long ago and its implementation has been and remains vital for organizations to increase organizational performance, customer satisfaction and loyalty⁸. One of the main concerns of any healthcare unit is to achieve a high level of patient satisfaction through the provision of better - quality services^{9,10}. Patient assessment is an essential determinant of the quality of health care provided by each hospital institution^{11,12}. Patient satisfaction analysis is also important in health care providers' decision-making regarding the management, planning, management, and control of services as part of the management process^{13,14}. According to a review of the literature, patient characteristics such as age, gender, education, or monthly income are likely to influence a patient's evaluation of the medical center's performance in providing health care¹⁵. Studies about age confirm that older respondents are more satisfied¹⁶ perhaps because they are more social and accepting than younger people or are more likely to regard and respect more the health care professionals. Studies show that male patients are more satisfied than female patients¹⁷. The education level was also found to be significantly associated with level of satisfaction of patients. It was noted that less educated patients were more satisfied as compared with high educated persons that is the mean satisfaction level was comparatively less in patients who were graduate or post-graduate¹⁸.

From the literature review it is noticed that the number of researchers who are using the SERVPERF instrument¹⁹, is increasing day by day²⁰⁻²². SERVPERF instrument is specifically proposed for use in patients in relation to the

quality of health care²³, and used also as an instrument in many studies to measure and evaluate quality²⁴⁻²⁶. Further, based on a meta-analytical summary of 17 years of research work on all five continents, Carrillat et al.,²⁷ concluded that SERVPERF is an appropriate and equally valuable predictor for assessing the quality of general service. While Adil et al.²⁸, in his study concluded that the SERVPERF instrument is more accurate for measuring service quality and can explain the greatest variance in the overall level of service quality.

Improving the quality of patient healthcare in medical centers is both a necessary and a vital activity. To obtain patient satisfaction, it is necessary to first identify those important factors that are responsible for or have a direct impact on influencing the level of patient satisfaction, as well as to demonstrate the significance of their relevance in improving the quality of services provided in public health care sector. In transition countries, public hospitals continue to be the primary and most important providers of health care, meeting the needs of the population for health care. The government faces daily challenges not only in finding new resources to finance high costs, but also in maximizing the use of existing resources. As a result, this study concentrated on public hospital centers and aims to: a) assess patient satisfaction with public hospital healthcare services; b) identify the variables that affect overall satisfaction with healthcare quality, ranking these variables according to the priorities of the patients themselves; c) provide additional recommendations for all types of health care centers and the respective decision makers; and d) generate a conceptual model and data that can assist managers and medical center staff in identifying factors that influence patient satisfaction levels;

Methods

The primary goal of this cross-sectional study is to assess the quality of health care services provided by Public Hospitals, from the perspective of the patients. Within a period of 4 months during March -June 2022 this survey had over 300 hospitalized patients' respondents. The final database only contains the answers of 247 because the rest did not have the necessary information to be included in the survey. An official request and an approval from the head of medical center is obtained. Data was collected face-to-face using structured questionnaires, and the questionnaires were self-administered from the patients. Participants were informed of the study's purpose and provided written consent confirming their voluntary participation and the right to withdraw at any time.

The primary research instrument is a structured questionnaire with two main parts. The first section collects socio-demographic information such as age, gender, educational level, Income level of respondents. The second section includes statements about health

care quality dimensions and patient overall satisfaction. The quality dimensions, as independent variables, according to SERVPERF: Tangibles (4 questions), Reliability (5 questions), Responsiveness (4 questions), Assurance (4 questions), Empathy (3 questions).

The research focuses on two main research questions:

- Do sociodemographic factors affect satisfaction levels with the quality of medical healthcare services?
- What healthcare quality dimensions impact patients' perceived satisfaction with the quality of health care services provided by medical centers?

Data analysis was performed through the Statistical Package for the Social Sciences SPSS 25 with a statistical significance 0.05. A series of statistical tests such as, ANOVA, Pearson Correlation, Multiple Regression, R^2 , Factor Analysis, VIF, was performed.

According to Cronin and Taylor¹⁹, their performance-based scale (SERVPERF) is a method of assessing service quality with total reliability variation between 0.884 and 0.964, depending on the type of industry. Referring to our case study, the reliability coefficient for all items together has coefficient value α of 0.892, which indicates a very high reliability value of these items (variables) that assess the quality of health care. Concerning the possibility of collinearity or factor interaction, the analysis shows that the correlation values are within the allowed norms and that there is no interaction between them to cause distortion of the results as indicated by the low VIF values (Variance Inflation Factor). A VIF greater than 4 or a tolerance less than 0.25 indicates multicollinearity (the inverse of VIF). Tolerance values in this case study range from 1.491-3.096. As a result, there is no collinearity between the factors that could lead to distorted study results.

Results

Patient sociodemographic factors and overall satisfaction with health care quality

Evaluating patient satisfaction is difficult because satisfaction is a complex concept influenced by a variety of factors, including patient sociodemographic characteristics.

The sociodemographic factors, considered in this study as control variables, are age, gender, educational level, and income level:

Age –Out of 247 interviewees, 33.6% were patients between the ages of 45 and 60, 26.7% were between the ages of 30-45, 23.5% were over 60, and 16.2% were between the ages of 16 and 30. There are no differences between different age groups of patients in terms of satisfaction with healthcare services $F_{3; 247} = 0.052$, $Sig = 0.984 > 0.05$.

This conclusion was reported also by O'Holleran²⁹ and K. Miles, et al.³⁰, according to whom the relationship between age and patient satisfaction is complex and cannot be evaluated simply as two isolated variables that affect each other.

Gender -49.8% of the respondents were female patients and the rest 50.2% were male. It seems patient gender does not affect the overall satisfaction with the health care quality. A value of $F_{1; 247} = 0.210$, $Sig = 0.647$ mean that there are no statistically significant differences between overall patient satisfaction and the patient gender. Same result is stated by Ayranci³¹.

Education -While regarding the level of education, the variable is divided in groups. Most of the patients in the study (44.5%) have a secondary education, followed by those with a university degree (27.5%). The analysis of variance shows that there is statistically significant relationship between patient education level and overall reported satisfaction, $F_{4; 247} = 2.990$, $Sig = 0.02$. Education and overall patient satisfaction were found to have a statistically significant linear negative relationship ($r = -.167$, $Sig = .000$). The reason behind this conclusion may be related to the greater amount of information that these patients have and consequently make them not only more demanding, but also being more involved. So, the more educated and informed, the higher the expectations for the quality of healthcare services³².

Income level - In terms of income, more than half of the respondents (52.7%) say their monthly income is up to 30,000 Albanian Lek (ALL), another third declares their monthly income ranges from 30,000 to 50,000 ALL, 10% say their income ranges from 50,000 to 70,000 ALL and only 5.3% say their income exceeds 70,000 ALL. The same conclusion for the income level variable as the value of Fisher $F_{3; 247} = 2.259$ and $Sig = 0.042$, show that the level of satisfaction is different in patients with different income levels. Overall patient satisfaction and the income level were found to have a statistically significant positive linear relationship ($r = .154$, $Sig = .000$) Patients with higher incomes are more likely to report lower levels of overall satisfaction with health care quality. Numerous studies have shown that there is a negative relation between income level and overall satisfaction, where low-income people are likely to be less satisfied³³.

Patient overall satisfaction and quality health care dimensions

This further analysis is related to the other research question of determining the relationship between quality health care service dimensions with the overall satisfaction. Multiple regression is used to analyze the relationship between patient satisfaction as a dependent variable and quality dimensions as independent variables.

Multiple regression is used to analyze the relationship between patient satisfaction as a dependent variable and quality dimensions as independent variables.

Referring to the regression analysis it was found out the five-quality dimension have a significant statistical relation with overall satisfaction, explaining 60.5% ($R^2=.605$) of the variation values of this satisfaction. These factors are statistically significant according to ANOVA, where $F_{5,247}=76.381$, $Sig = 0.000$. All the coefficients (β) are positive, indicating that increasing the values of the factors leads to an increase in patient satisfaction with the health care services quality.

The multiple linear regression equation (as shown below in **table I**) takes the form:

$$\text{Patient satisfaction} = 0.231 + 0.291 \text{ Tangibles} + 0.212 \text{ Reliability} + 0.253 \text{ Assurance} + 0.141 \text{ Empathy.}$$

The factor loadings are examined using Principal Component Analysis to identify the element that has the

greatest impact on each dimension, highlighting areas that require effort and concrete suggestions for improvement. Factor loadings are the Pearson correlations, measure the strength of the linear relationship between the items and the components. More specifically, the latest are shown in **table II** below. Every item's factor loading for a proven item should be 0.6 or greater³⁴. Facilities, contemporary equipment, and service-related materials, which make up three of this variable's four components, are shown to have a significant impact on the tangible variable aspects. As a result, these factors should be considered to raise the perceived quality of the health care services offered.

Since all five factors for the variable "reliability" have factor loadings greater than 0.6, they are significant in determining the quality of medical care, especially the factor that has the highest value and is closely related to patient-medical center reliability: the provision of medical care as promised by the medical center. For the elements of the other two variables Assurance and Empathy, the data show that for the variable Assurance, all 4 of its constituent elements are important as the factor loadings

Table I: Patient satisfaction with the quality of hospital healthcare service.

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Constant	.231	.161		1.429	.154
Tangibles	.291	.050	.284	5.800	.000
Reliability	.212	.069	.215	3.054	.003
Responsiveness	.028	.066	.027	.421	.674
Assurance	.253	.068	.259	3.699	.000
Empathy	.141	.059	.152	2.382	.018

Dependent variable: Patient Satisfaction; p value lower than 0.05 was considered statistically significant ($p < 0.05$)
Method: Multiple Regression Analysis

Table II: Healthcare quality dimensions factor loadings.

Quality Dimension	Factor Loading
Tangibles	
T1. The Medical Center facilities are visually appealing	.728
T2. The Medical Center has modern equipment	.724
T3. Service-related materials (such as pamphlets, signs, etc.) are visually appealing	.713
T4. The Medical Center staff is regular in appearance	.272
Reliability	
R1. When the Medical Center promises to do something, he does it when he promised to do it	.748
R2. The Medical Center offers its services at the time / schedule as promised	.733
R3. When you have a problem, the Medical Center shows a sincere interest in solving it	.691
R4. The Medical Center insists on maintaining, processing / distributing accurate and error-free data	.614
R5 The Medical Center does the right thing from the first time / attempt	.699
Assurance	
A1. The behavior of the staff builds trust in you	.783
A2. You feel safe in all actions you perform with the hospital	.743
A3. The Medical Center staff is always polite to you	.669
A4. The Medical Center staff has the right knowledge to answer all your questions	.655
Empathy	
E1. Medical Center staff give you individual attention	.780
E2. The Medical Center has at its center individual attention for each patient	.825
E3. The service delivery schedule it is a convenient one	.604

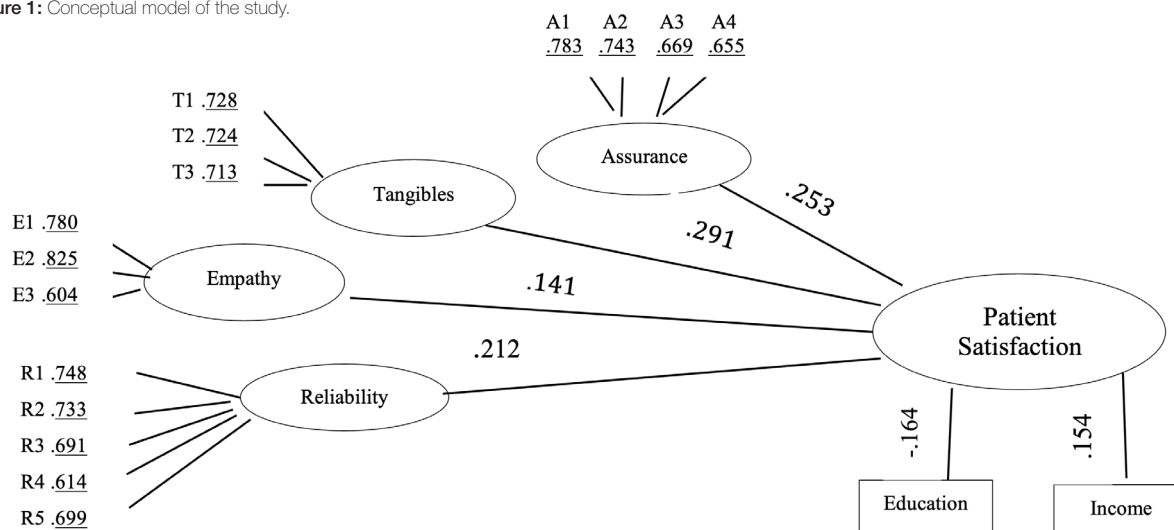
Method: Principal Component Analysis. Factor loadings greater than 0.6 are considered significant in determining the quality of health care services.

exceed the value 0.6 where among them stands out the first one with the highest value. This result is some what expected as the patient's life is entrusted to the professional skills and competencies of the medical staff. As for the dimension of empathy, the 3 elements are significant, where the perception of the patient as being

in the center of the medical center and the individual attention paid to each patient are among the most important of all the factors considered.

Finally, based on the preceding analysis and findings, the proposed conceptual model is presented in **figure 1**.

Figure 1: Conceptual model of the study.



Discussion

The study showed that patient satisfaction is a complex concept and it vary from health care related quality dimensions as by patient related sociodemographic factors.

According to the study, patient satisfaction appears to be significantly influenced by two sociodemographic factors: the degree of education and the level of income. These two variables, performing as control variables, have an impact on the correlation between patient satisfaction with health care quality. The negative statistical correlation between education level and general satisfaction is particularly noteworthy. Thus, it is likely that the more educated patients are, the better informed they are, the higher their expectations of health care, and the more demanding they are of staff, which may justify and explain the existence of a negative correlation with levels of overall satisfaction. In terms of incomes, it is noticed that individuals with incomes rated as average declare higher levels of satisfaction in relation to the two extremes. This is probably because individuals with lower incomes not being able to pay more, receive perhaps more limited service and thus declare somewhat lower levels of satisfaction. On the other hand, it is likely that these individuals, not being part of the public insurance schemes, will have to bear a large part of the expenses themselves because public hospitals provide health care only for the insured patients. Uninsured and unemployed

patients seem to be the category of patients who are forced to pay bills with fees set for services near public medical centers, the amount of which is considerable and burdens their economies. From the analysis of the study, it can be evidenced that the overall satisfaction regarding the quality of health care services measured according to the quality dimensions of SERVPERF is mostly influenced by: Tangibles, Reliability, Reliability, Empathy. These factors identified as the most important in determining patient satisfaction based on the dimensions of overall health care quality explain 60.5% of the values of variation of the overall satisfaction. These quality dimensions are statistically significant $F_{5; 247} = 76.381$, Sig = 0.000, indicating that increasing the values of the factors leads to an increase in patient satisfaction with the health care services quality. The study results expand and broaden comprehension of how patient satisfaction is impacted by many aspects of health care service quality. The model's output can assist managers in determining the areas where interventions can be addressed most effectively in terms of raising health care quality and increase patient satisfaction.

Conflicts of interest

The authors have no potential conflicts of interest to report in connection with this article.

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Análisis de eficacia de los principales patrones dietéticos en la reducción del riesgo cardiovascular

Analysis of the efficacy of the main dietary patterns in reducing cardiovascular risk

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Resumen

Introducción: las enfermedades cardiovasculares no sólo son la primera causa de muerte con un 30% de todas ellas en el mundo, sino que el importante aumento de su incidencia en estos últimos años las sitúa en una urgencia sanitaria. Estas patologías están muy relacionadas con patrones alimentarios poco saludables (consumo intensivo de sodio, azúcares, grasas saturadas; y un bajo consumo de frutas y verduras, cereales, fibra, legumbres, pescado y frutos secos). Un patrón dietético adecuado y ajustado individualmente a las características clínicas de cada paciente pueden ayudarnos a reducir tanto el peso corporal como el riesgo cardiovascular.

Objetivo: Analizar y comparar la eficacia de los principales patrones dietéticos en la reducción del riesgo cardiovascular.

Resultados: La dieta mediterránea sigue siendo el patrón con mayor evidencia y mejores resultados sobre la reducción de dicho riesgo cardiovascular y su mortalidad. Sin embargo, la dieta DASH es una buena alternativa sobre todo para pacientes hipertensos, a su vez, la dieta vegetariana ha demostrado multitud de beneficios cardiovasculares, presentando escasas desventajas. Otra alternativa más compleja pero muy de moda actualmente es la dieta cetogénica, que todavía no cuenta con suficiente respaldo científico en la reducción del riesgo cardiovascular.

Conclusiones: Realizar un adecuado patrón dietético es la medida más importante para prevenir la primera causa de muerte en el mundo, para ello disponemos de varios patrones alimentarios entre los que destaca la dieta mediterránea.

Palabras clave: Riesgo cardiovascular, patrones dietéticos, dieta mediterránea, DASH, dieta vegetariana, dieta cetogénica.

Summary

Introduction: cardiovascular diseases are not only the leading cause of death with 30% of all of them in the world, but the significant increase in their incidence in recent years places them in a health emergency. These pathologies are closely related to unhealthy eating patterns (intensive consumption of sodium, sugars, saturated fats, and low consumption of fruits and vegetables, cereals, fiber, legumes, fish and nuts). An adequate dietary pattern individually adjusted to the clinical characteristics of each patient can help us reduce both body weight and cardiovascular risk.

Objective: To analyze and compare the efficacy of the main dietary patterns in reducing cardiovascular risk.

Results: The Mediterranean diet continues to be the pattern with the most evidence and the best results on the reduction of said cardiovascular risk and its mortality. However, the DASH diet is a good alternative, especially for hypertensive patients. In turn, the vegetarian diet has shown many cardiovascular benefits, with few disadvantages. Another more complex but currently very fashionable alternative is the ketogenic diet, which still does not have sufficient scientific support in reducing cardiovascular risk.

Conclusions: Carrying out an adequate dietary pattern is the most important measure to prevent the first cause of death in the world, for this we have several dietary patterns among which the Mediterranean diet stands out.

Key words: Cardiovascular risk, dietary patterns, Mediterranean diet, DASH, vegetarian diet, ketogenic diet.

Introducción

La Enfermedad Cardiovascular:

Las enfermedades cardiovasculares (ECV) son trastornos crónicos y heterogéneos del sistema cardiaco y circulatorio, cuya causa subyacente de desarrollo es a menudo la aterosclerosis. Dicha patología resulta de un proceso inflamatorio crónico que afecta a las arterias de diferentes lechos vasculares y se caracteriza por la disfunción y el engrosamiento de la capa íntima y una pérdida de elasticidad en la mitad de los casos^{1,2}.

La ECV es la principal causa de muerte en todo el mundo, en ambos sexos; y en los países occidentales, representa alrededor del 30% de todas las muertes. 4 En los últimos años, en España entre 2.000 y 3.000 personas mueren al año por ECV, por cada millón de habitantes (**Figura 1**).

Además, el aumento de la incidencia de ECV en las últimas 3 décadas ha de convertirse en una prioridad sanitaria y socioeconómica, así como la necesidad de prevenirlas. Se estima que para el año 2030, 23,6 millones personas morirán de eventos cardiovasculares por año¹.

Las ECV son la consecuencia de varios trastornos diferentes, como el exceso de tejido adiposo abdominal, la hipertensión, la dislipidemia y la intolerancia a la glucosa, que aumentan el riesgo de desarrollar eventos cardiovasculares como accidente cerebrovascular y ataque cardíaco. A menudo se superponen varias de las comorbilidades mencionadas⁵.

Estas enfermedades están relacionadas con patrones de nutrición poco saludables (es decir, exceso de consumo intensivo de sodio y alimentos refinados; azúcares añadidos, grasas no saludables; bajo consumo de frutas y verduras, cereales, fibra, legumbres, pescado y frutos secos), consumo de alcohol, el estrés, el tabaquismo, y el sedentarismo¹.

La mala calidad de la dieta ha superado todos los demás factores de riesgo de mortalidad, contabilizando 11 millones de muertes, aproximadamente el 50% de las muertes por ECV a nivel mundial. Además, las ECV también conducen a discapacidades graves y disminuyen la calidad de vida de los pacientes. Por lo tanto, es urgente y necesario investigar las estrategias de prevención y tratamiento de las ECV^{6,7}.

Así, hay un gran porcentaje de evidencia científica que describe que la intervención dietética y la actividad física podrían ser los factores más importantes para su prevención⁵.

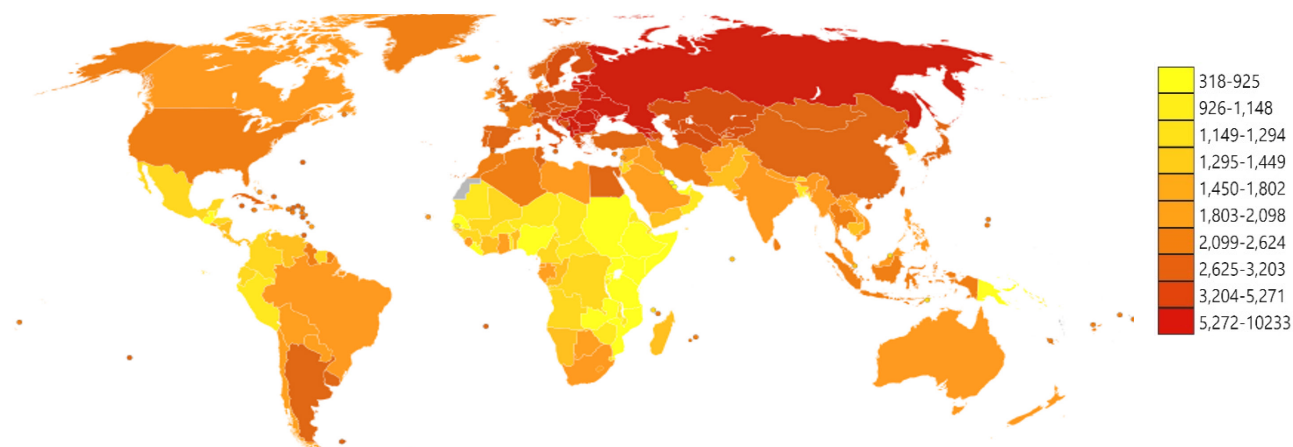
Sobrepeso y obesidad

En el contexto de riesgo cardiovascular, no se nos puede olvidar uno de los factores de riesgo más importante: La obesidad considerada por la Organización Mundial de la Salud (OMS) como la epidemia del siglo XXI; afectando a todas las edades, grupos sociales y países, sin distinciones⁸.

A pesar de varias décadas de lucha, el gran aumento de su prevalencia ha hecho que sea uno de los mayores desafíos de salud pública, siendo la obesidad la enfermedad metabólica más frecuente en el mundo occidental⁹.

El sobrepeso y la obesidad, clasificados como Índice de Masa Corporal (IMC) mayor o igual a 25 y 30 respectivamente, se deben a un exceso de acumulación de grasa almacenada en el tejido adiposo. Esta patología surge del desequilibrio energético: consumir más energía, kilocalorías (kcal) de la que se gasta; de ahí que la mayor parte de los enfoques para el control de peso se centran en reducir la ingesta de energía a través de la restricción calórica y el aumento del gasto energético a través de la actividad física¹⁰.

Figura 1: Muertes por enfermedad cardiovascular en 2016; por millón de personas (Estadísticas de la Organización Mundial de la Salud)⁹.



La OMS estima que hoy en día, más de 1500 millones de adultos en todo el mundo tienen sobrepeso y otros 600 millones son obesos¹¹.

En Europa, la prevalencia de la obesidad y la diabetes ha aumentado de dos a tres veces durante los últimos 30 años, por lo que es poco probable que se logre el objetivo de la OMS para 2025 de detener el aumento de estos factores de riesgo. Además, varios estudios estiman que para 2030, aproximadamente 2.000 millones de personas tendrán sobrepeso y 1,12 mil millones obesidad^{3,12}.

El IMC se utiliza para medir el grado de obesidad; sin embargo, no da información sobre la distribución de grasa, que es de gran importancia en el riesgo cardiovascular. Por lo tanto, nuevas mediciones clínicas (p. ej., abdominal circunferencia y el cálculo de la relación cintura/cadera) han sido introducidas con el objetivo de caracterizar la obesidad de central/androide o periférica. Numerosos estudios han demostrado una estrecha relación entre la obesidad central y las disfunciones cardiovasculares^{13,14}.

El sobrepeso y la obesidad están asociados a la aparición del síndrome metabólico y a la disfunción del tejido adiposo. Este tejido, particularmente la adiposidad central es metabólicamente activa y un órgano endocrino, cuya desregulación provoca un estado inflamatorio de bajo grado, que es la base de alteraciones metabólicas, como el efecto protrombótico, la disfunción endotelial, la resistencia a la insulina, la dislipidemia y la hiperuricemia¹⁵.

En consecuencia, el control eficaz del peso es un desafío y, aunque existe una enorme cantidad de programas de pérdida de peso disponibles, no todos están evaluados de manera exhaustiva; y muchos intentos de pérdida de peso dan como resultado una recuperación de peso y resultados deficientes a largo plazo¹³. Por lo tanto, es de vital importancia revisar la eficacia de los patrones dietéticos para apoyar un enfoque basado en la evidencia para el control del peso y el riesgo cardiovascular a largo plazo¹⁰.

Patrones dietéticos

Curiosamente, en griego antiguo, la palabra dieta significaba un conjunto de reglas de vida para mantener el estado de salud y bienestar del sujeto, incluyendo la nutrición y la actividad física, sin embargo, el significado moderno se refiere a la dieta como lo que se come⁵.

Los patrones de alimentación de la población están cambiando rápidamente en la mayoría de los países; habiendo un énfasis en el aumento del consumo de productos animales, especialmente carne roja^{16,17}. Dependiendo del tipo de dieta que se realice, estas pueden centrarse en unas u otras recomendaciones;

pero en general pretenden enfatizar el aumento del consumo de verduras, frutas, cereales integrales, frutos secos y legumbres, y desaconsejan o incluso recomiendan eliminar el consumo de carne roja, los dulces y las bebidas azucaradas, junto con alimentos procesados con alto contenido de azúcar, sal, grasa o bajo contenido de fibra. Además, sabemos que un alto consumo de alcohol, niveles elevados de estrés, el tabaquismo junto con una deficiencia de la actividad física promueve el riesgo de ECV. Es bien sabido que las dietas caracterizadas por el exceso de energía, que conducen a la obesidad, aumentan el riesgo cardiovascular. Los datos publicados indican que una reducción del 20-50% en la ingesta de energía, en ausencia de desnutrición, retrasa la aparición de estas enfermedades^{5,18}.

Múltiples estudios han evaluado las asociaciones de nutrientes o alimentos individuales con el riesgo de ECV; sin embargo, los nutrientes y los alimentos no se consumen de forma aislada sino en combinaciones numerosas y multifacéticas. Por lo tanto, los enfoques que combinan varios nutrientes y alimentos en "patrones dietéticos" podrían reflejar prácticas dietéticas del mundo real e integrar asociaciones interactivas y acumulativas de diferentes componentes dietéticos; lo que facilita la traducción de los hallazgos en recomendaciones dietéticas^{20,21}.

También es probable que el efecto de un solo elemento dietético sea demasiado pequeño como para ser detectado en estudios o ensayos. Por el contrario, parece lógico que el efecto acumulativo de muchos aspectos diferentes de la dieta sea considerablemente mayor; ya que los alimentos y los nutrientes podrían tener efectos sinérgicos o antagónicos cuando se consumen en combinación²². A nivel general, en la **Figura 2**, podemos observar las recomendaciones a nivel nacional en cuanto a las proporciones de alimentos a consumir.

Cabe destacar que la evaluación nutricional no es un estándar de práctica durante las visitas médicas de rutina, debido a numerosas barreras, incluida la falta de capacitación y conocimiento, la falta de tiempo, la falta de reembolso y la ausencia de herramientas validadas para la detección de malos hábitos dietéticos²³.

En consecuencia, y dado que es poco realista e ineficaz derivar a todos los pacientes a un dietista; es imperativo que los médicos estén familiarizados con la evidencia subyacente a las recomendaciones dietéticas saludables y que implementen asesoramiento personalizado en función de las condiciones y comorbilidades de los pacientes^{24,25}. Lamentablemente, muchos pacientes permanecen sin diagnosticar y, por lo tanto, sin una terapia adecuada, desafortunadamente, a veces la primera manifestación de ECV es la muerte repentina en esos pacientes¹.

Dieta mediterránea

La dieta mediterránea se basa en componentes de los

Figura 2: Pirámide de alimentación saludable, de la Sociedad Española de Nutrición Comunitaria (SENC)¹⁹.



patrones dietéticos tradicionales de países europeos mediterráneos y abarca no sólo los tipos de alimentos consumidos y sus contribuciones relativas a la ingesta diaria de nutrientes, sino también un enfoque de alimentación que es consciente de cómo se obtienen, se cocinan y se comen los alimentos, así como el estilo de vida consideraciones tales como participar en actividad

física regular^{26,27}.

La base principal de las comidas diarias en la dieta mediterránea es cereal como pan integral, pastas, cuscús y otros cereales sin refinar ricos en fibra y una variedad de frutas y verduras de diferentes colores y texturas ricas en micronutrientes, fibra y fitoquímicos. Productos lácteos, preferiblemente yogur bajo en grasa, queso, u otros productos lácteos fermentados, se recomiendan diariamente con moderación como fuente de calcio. El aceite de oliva virgen extra (AOVE) es la principal fuente de lípidos de la dieta y es complementado con aceitunas, nueces entre otros frutos secos y semillas²⁸. Se recomienda agua (1,5-2,0 L/día) como la principal fuente de hidratación, mientras que el vino y otras bebidas alcohólicas fermentadas son generalmente permitido con moderación. El pescado, la carne blanca y los huevos son las principales fuentes de proteína. Las legumbres también son una fuente de elección de proteínas de origen vegetal^{27,29}.

Este patrón también se caracteriza por una ingesta baja de productos lácteos ricos en grasas saturadas, carnes rojas, carnes procesadas, dulces; y bebidas alcohólicas destiladas³¹. Desafortunadamente hay una importante diferencia entre el consumo actual y real de alimentos y lo que recomienda una dieta mediterránea (Figura 3).

Cabe destacar que es un patrón dietético rico en grasas y bajo en carbohidratos, que proporciona un 35-45 % de la ingesta total de energía diaria de grasas, alrededor de un 15% de proteínas y un 40-45% de energía de CH. Sin embargo, el perfil de esta grasa es

Figura 3: Comparación de proporciones de alimentos entre la dieta mediterránea y el consumo promedio actual³⁰.

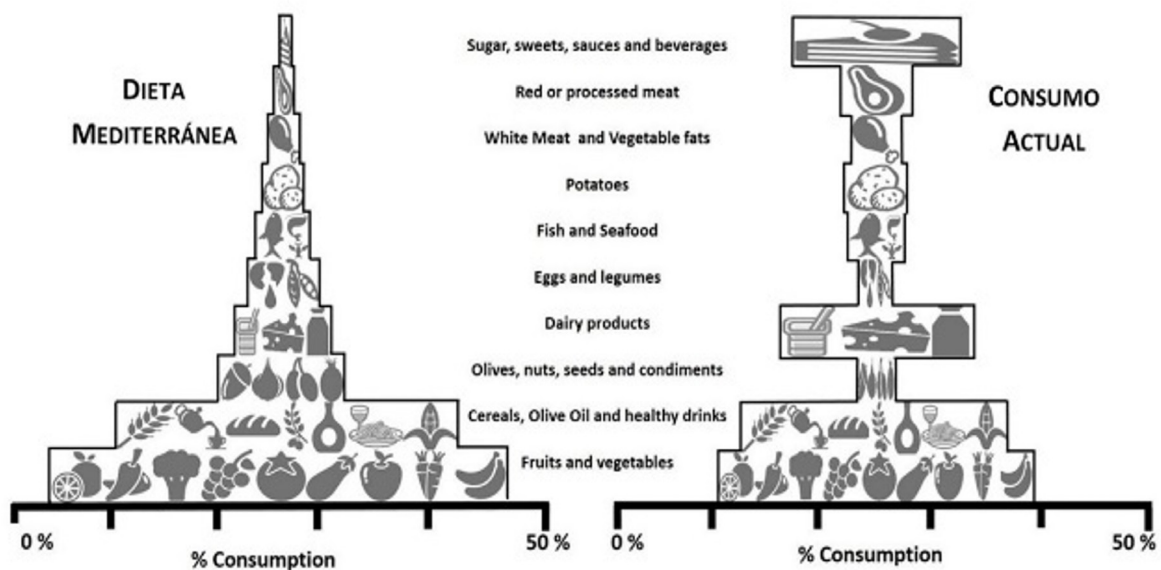


Figura 4: Encuesta (14 puntos) de valoración individual del grado de cumplimiento y adherencia a la dieta mediterránea³¹.

			PUNTOS
1	¿USA USTED EL ACEITE DE OLIVA COMO PRINCIPAL GRASA PARA COCINAR?	Sí=1 punto	
2	¿CUANTO ACEITE DE OLIVA CONSUME EN TOTAL AL DÍA (INCLUYENDO EL USADO PARA FREIR, COMIDAS FUERA DE CASA, ENSALADAS, ETC.)?	4 O MAS CUCHARADAS =1 punto	
3	¿ CUANTAS RACIONES DE VERDURA U HORTALIZAS CONSUME AL DÍA? (las guarniciones o acompañamientos = 1/2 ración) 1 ración = 200g	2 O MÁS (al menos 1 de ellas en ensalada o crudas) =1 punto	
4	¿CUANTAS PIEZAS DE FRUTA (INCLUYENDO ZUMO NATURAL) CONSUME AL DÍA ?	3 O MÁS AL DÍA =1 punto	
5	¿CUÁNTAS RACIONES DE CARNES ROJAS, HAMBURGUESAS, SALCHICHAS O EMBUTIDOS CONSUME AL DÍA? (ración: 100 - 150 g)	MENOS DE 1 AL DÍA = 1 punto	
6	¿CUANTAS RACIONES DE MANTEQUILLA, MARGARINA O NATA CONSUME AL DÍA? (porción individual: 12 g)	MENOS DE 1 AL DÍA = 1 punto	
7	¿CUÁNTAS BEBIDAS CARBONATADAS Y/O AZUCARADAS (REFRESCOS, COLAS, TÓNICAS, BITTER) CONSUME AL DÍA?	MENOS DE 1 AL DÍA = 1 punto	
8	¿BEBE VD. VINO? ¿CUÁNTO CONSUME A LA SEMANA?	3 a 7 COPAS A LA SEMANA =1 punto	
9	¿CUANTAS RACIONES DE LEGUMBRES CONSUME A LA SEMANA? (1 plato o ración de 150 g)	3 O MÁS A LA SEMANA =1 punto	
10	¿CUANTAS RACIONES DE PESCADO-MARISCOS CONSUME A LA SEMANA? (1 plato pieza o ración: 100 - 150 de pescado o 4-5 piezas o 200 g de marisco)	3 O MÁS A LA SEMANA =1 punto	
11	¿CUANTAS VECES CONSUME REPOSTERÍA o BOLLERÍA COMERCIAL (NO CASERA O ARTESANA) COMO GALLETAS, FLANES, DULCE O PASTELES A LA SEMANA?	MENOS DE 3 A LA SEMANA = 1 punto	
12	¿CUANTAS VECES CONSUME FRUTOS SECOS A LA SEMANA? (ración 30 g)	1 O MAS A LA SEMANA = 1 punto	
13	¿CONSUME USTED PREFERENTEMENTE CARNE DE POLLO, PAVO O CONEJO EN VEZ DE TERNERA, CERDO, HAMBURGUESAS O SALCHICHAS?	Sí =1 punto	
14	¿CUANTAS VECES A LA SEMANA CONSUME LOS VEGETALES COCINADOS, LA PASTA, ARROZ U OTROS PLATOS ADEREZADOS CON SALSAS DE TOMATE, AJO, CEBOLLA O PUERRO ELABORADA A FUEGO LENTO CON ACEITE DE OLIVA (SOFRITO)?	2 O MÁS A LA SEMANA =1 punto	

principalmente de ácidos grasos (AG) monoinsaturados y poliinsaturados^{32,33}.

Para valorar la adecuada adherencia a este patrón dietético se han desarrollado una serie de cuestiones relacionadas con el consumo alimentario individual (Figura 4).

Cabe destacar que es extremadamente heterogéneo y fuertemente influenciado por la disponibilidad de alimentos en cada zona geográfica³⁴.

En 2010, la UNESCO proclamó esta dieta como "Patrimonio Cultural de la Humanidad"; representando un modelo de comportamiento, una "forma de vida", que puede garantizar una mayor esperanza de vida y mejorar la calidad de vida en sí misma¹².

Dieta DASH

La dieta DASH (Dietary Approaches to Stop Hypertension) nació en USA con el objetivo de reducir presión arterial y, también, para prevenir las ECV, dicho patrón recomienda de forma relevante una reducción de la ingesta de sal, un factor principal para hipertensión arterial; además de otra serie de medidas dietéticas similares a las recomendaciones de la dieta mediterránea⁵.

En 1997, la dieta DASH se convirtió en una estrategia prometedora para el tratamiento de la PA alta, y los ensayos

clínicos han respaldado dicha evidencia. Este patrón de alimentación promueve la ingesta de cereales integrales, productos lácteos bajos en grasa o sin grasa, legumbres y frutos secos, al tiempo que restringe la ingesta de carnes rojas y procesadas y bebidas azucaradas. Además también se caracteriza por ser rica en verduras y frutas, lo que se traduce en un alto consumo de potasio, magnesio y fibra, que tienen un papel en el control de la PA y el metabolismo de la glucosa; y son la principal fuente alimenticia de antioxidantes y polifenoles, que se han relacionado con mejores niveles de glucosa e insulina en sangre³².

Destaca por su bajo contenido en grasas (27% de la ingesta calórica diaria), especialmente en grasas saturadas y colesterol (150 mg/d aproximadamente), y un reducido contenido en sodio, pero cabe destacar que es rica en fibra (>30 g/día), potasio, magnesio y calcio en comparación con otros patrones dietéticos³².

Permite hasta 2.300 mg de sodio al día, con una dosis aún más óptima de 1.500 mg, asociada a una mayor reducción de la presión arterial²⁴.

Dieta vegetariana

La dieta vegetariana, una de las 3 principales estrategias dietéticas apoyadas en el 2015 como "Pautas de alimentación saludable"²⁴.

Este patrón se caracteriza por una reducción o eliminación del consumo de productos animales;

enfazando vegetales, frutas, cereales, legumbres y frutos secos. Aunque falta una definición estandarizada, “vegetariano” generalmente describe como un patrón dietético lacto-ovo vegetariano, que está exento de carnes, aves y pescado. Aun así la palabra vegetariano se usa indistintamente para describir patrones dietéticos más restrictivos como “vegano” que elimina además los huevos, los productos lácteos e incluso la miel³⁵.

Las dietas basadas en plantas generalmente se definen en términos de la proporción y frecuencia de los alimentos de origen animal consumidos en la dieta, con poca consideración dada a los tipos y frecuencias de alimentos vegetales consumidos³⁶. Sin embargo, no todos los alimentos vegetales son iguales, existe una amplia diversidad de dietas basadas en la calidad de los alimentos vegetales incluidos; cada uno con efectos cardio metabólicos potencialmente distintos, lo que apunta a la importancia de definir las dietas en términos de la calidad de los alimentos vegetales que enfatizan³⁷.

Ingesta alta de alimentos vegetales más saludables, es decir, cereales integrales, frutas/verduras, frutos secos/legumbres y aceite de oliva/canola se asocian con un riesgo de cardiopatía coronaria sustancialmente menor, en comparación con las dietas vegetarianas que enfatizan alimentos vegetales menos saludables como granos refinados, patatas fritas y dulces²⁴. Por eso, la elección de alimentos saludables derivados de plantas es crucial para garantizar estos efectos cardiovasculares beneficiosos³².

El déficit de vegetales en la alimentación, puede atribuir un riesgo importante en la mortalidad cardiovascular

(Figura 4). El bajo aporte de vitamina B12 y ácido graso omega 3, y la elevada proporción de ácido graso omega 6, pueden aumentar el riesgo de desarrollar enfermedades cardiovasculares. Es por eso que, la suplementación con vitamina B12 y vitamina D en este tipo de dietas son necesarias²⁴.

Las dietas basadas en plantas tienen una baja densidad energética y un alto contenido de fibra, lo que puede contribuir a la prevención de las enfermedades cardiovasculares, la pérdida de peso y el mantenimiento del peso corporal a largo plazo³².

La dieta mediterránea es en muchos aspectos similar a una dieta vegetariana; como ser alta en vegetales, frutas, legumbres, nueces, granos, grasas insaturadas, y baja en carne^{38,39}.

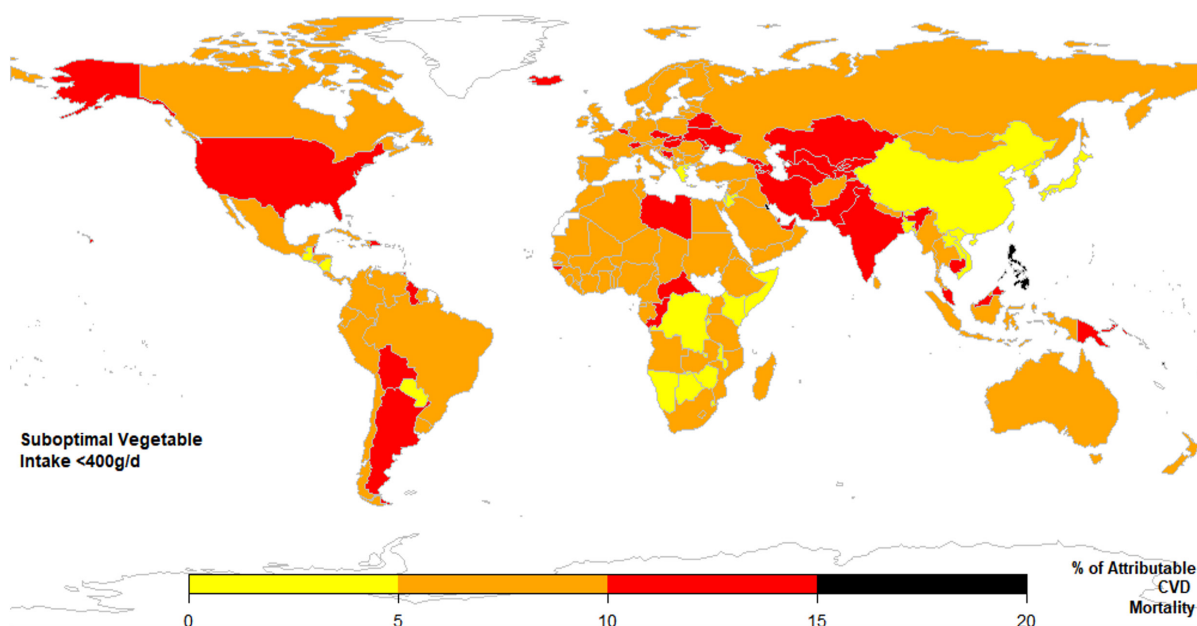
También cabe destacar que cada vez hay más evidencia que sugiere que las dietas ricas en proteínas, particularmente proteínas de origen vegetal, disminuyen significativamente las concentraciones séricas de lípidos en sangre⁴⁰.

Dieta cetogénica

El patrón de dieta cetogénica se desarrolló en la década de 1920 con el objetivo de controlar las convulsiones en la epilepsia, aunque su uso clínico recibió mayor atención en la década de 1990. Recientemente, también se ha utilizado como terapia para el tratamiento de la obesidad y la prevención de las ECV⁵.

Este patrón implica un alto contenido de grasas (60-80%) y proteínas (10-20%) y cantidad muy baja de CH (5-10%).

Figura 4: Porcentaje de muertes cardiovasculares atribuible al bajo consumo de verdura (menos de 400 gramos al día) en todo el mundo³.



Podría reproducir algunos de los efectos del ayuno, con los efectos benéficos principalmente atribuidos a la producción de cetonas, como β -hidroxibutirato, acetoacetato y acetona en el hígado⁴¹.

Los datos publicados hasta hoy describen cómo las personas con sobrepeso o la obesidad comen significativamente más productos dulces en comparación con personas con un peso corporal saludable y el riesgo de obesidad o sobrepeso aumenta alrededor del 14% con cada cucharada adicional de azúcar (5 g) consumida al día¹.

Una dieta restringida en hidratos de carbono se define con una ingesta por debajo del límite inferior del rango aceptable de macronutrientes, es decir el 45-65% del total. Aunque no existe una definición estandarizada, para hablar de una dieta cetogénica, y conseguir entrar en cetosis, debemos reducir el consumo de CH por debajo del 10%, es decir unos 50 gramos al día, en una dieta estándar de 200kcal; y por lo tanto un aumento relativo de la ingesta de grasas y proteínas³².

Este tipo de dieta se calcula con precisión para inducir cetosis (definida por un nivel plasmático de β -hidroxibutirato de 0.3 mmol/L) al tiempo que proporciona una nutrición adecuada para prevenir la desnutrición y promover el crecimiento y desarrollo normal en niños⁴².

Estas dietas pueden ser una opción para un período de pérdida de peso inicial a corto plazo (2-6 meses). Pero para el mantenimiento del peso a largo plazo y la salud cardiovascular, se recomienda aumentar gradualmente la ingesta de CH^{43,44}.

Es importante comentar que los profesionales de la salud deben considerar las dificultades para seguir una dieta cetogénica y tener en cuenta la ausencia de alimentos saludables como verduras, frutas y cereales integrales, cuya ingesta se asocia con un menor riesgo de desarrollar enfermedades como ECV³².

Objetivos

- El principal objetivo de esta revisión es analizar la eficacia de los principales patrones dietéticos a la hora de reducir el riesgo cardiovascular, como primera causa de morbimortalidad en el mundo.

Objetivos secundarios

- Analizar las principales ventajas y desventajas de cada patrón dietético.
- Evaluar la capacidad de adherencia a largo plazo entre los diferentes patrones dietéticos.
- Analizar que patrones serían los más recomendables para cada persona.

- Fomentar las recomendaciones dietéticas en el ámbito profesional, para reducir el riesgo cardiovascular.

Material y métodos

Para llevar a cabo este trabajo, se ha realizado una búsqueda bibliográfica, en la literatura científica sobre la eficacia de los principales patrones dietéticos a la hora de reducir el riesgo cardiovascular; utilizando las bases de datos de MEDLINE (Pubmed como motor de búsqueda) y Web of Science.

Con el fin de obtener un enfoque general sobre el tema a tratar, se hizo primeramente una búsqueda con los términos: diets AND cardiovascular risk. Posteriormente se incluyeron estudios utilizando las siguientes estrategias de búsqueda: dietary patterns AND cardiovascular risk; dietary patterns AND cardiovascular diseases; diets AND cardiovascular prevention; mediterranean diet AND cardiovascular risk; DASH diet AND cardiovascular risk; vegetarian diet AND cardiovascular risk; ketogenic diet AND cardiovascular risk; diets AND cardiovascular mortality.

A continuación, fueron filtrados por su relevancia, número de citas y por el idioma, en inglés.

Con los criterios citados, se obtuvieron un total de 184 artículos. Posteriormente de cada uno se evaluó su título, y su resumen con el fin de seleccionar sólo aquellos de mayor interés y utilidad para el trabajo; obteniendo finalmente 64 artículos para la revisión bibliográfica.

Los artículos seleccionados tenían una puntuación de 3,6/5 en Escala Jadad.

Resultados

Los médicos y resto de profesiones sanitarias deben centrarse en las dietas con más alto nivel de evidencia para apoyar un beneficio cardiovascular. Diferentes patrones dietéticos, incluyendo las dietas mediterráneas y las DASH se han relacionado ampliamente con un menor riesgo de morbimortalidad tanto cardiovascular como total. Aunque menos evidente, los médicos deben ser conscientes de los riesgos y beneficios de otras dietas como la dieta baja en carbohidratos y las dietas basadas en plantas²⁴.

Dieta mediterránea

Sin duda la dieta que más evidencia ha demostrado a la hora de reducir el riesgo cardiovascular es la dieta mediterránea. El principal estudio que dio relevancia a dicha dieta fue el estudio PREDIMED (2018), un ensayo multicéntrico en el que Estruch et al. asignaron 7.447

participantes (55 a 80 años de edad) en alto riesgo cardiovascular, pero sin ECV, a una de las tres dietas: una dieta mediterránea complementada con AOVE, otra complementada con frutos secos, o una dieta de control (con consejos para reducir grasa)³¹.

El punto final primario fue un ECV importante (infarto de miocardio, accidente cerebrovascular o muerte por causas cardiovasculares), cabe destacar que el estudio original fue retirado debido a problemas metodológicos, pero se volvió a publicar después de estas correcciones con las mismas conclusiones²⁴.

En el análisis por intención de tratar, hubo 96 eventos de punto final primario en el grupo asignado a una dieta mediterránea con oliva virgen extra-aceite (3,8%), 83 en el grupo adscrito con frutos secos (3,4%), y 109 en el grupo control (4,4%). La densidad de incidencia fueron 8.1, 8.0 y 11.2 por 1.000 personas-años, y los riesgos absolutos a 5 años fueron del 3.6%, 4.0% y 5.7%, respectivamente³¹.

Hubo diferencias significativas entre los diferentes grupos de estudio, cabe destacar que la dieta mediterránea suplementada con AOVE tuvo una mayor tasa de retención e implicó una importante reducción de la mortalidad cardiovascular: Hazard ratio 0,69 (IC 95%, 0,53 - 0,91). (Figura 5).

Estas reducciones de eventos cardiovasculares gracias a dichos patrones dietéticos son comparables a los de las estatinas.

Kris-Etherton et al. (2001); en el ensayo controlado aleatorizado "Lyon Diet Heart", observaron que las personas post-infarto de miocardio, que fueron asignadas aleatoriamente a dieta mediterránea (n=204) tuvieron

una reducción del 72% en muerte cardíaca e infarto de miocardio no fatal y reducción del 56% en la morbilidad total a los 4 años de seguimiento en comparación con aquellos asignados al azar a una dieta con recomendaciones de la American Heart Association (AHA), con un porcentaje de grasa total <30% (n=219). Así demostró además ser beneficiosa en el campo de la prevención secundaria en la estabilización de placa aterosclerótica⁴⁵.

En 2017, **Grosso et al.** realizaron un metaanálisis para explorar la asociación entre la adherencia a la dieta mediterránea y la incidencia / mortalidad por ECV. Los individuos en el cuartil más alto de adherencia tuvieron menor incidencia (RR: 0,76, IC del 95%: 0,68 - 0,83) y mortalidad (RR: 0,76, IC del 95%: 0,68 - 0,83) por ECV en comparación con los menos adherentes. También se encontró una reducción significativa del riesgo para la enfermedad coronaria (RR: 0,72), el infarto de miocardio (RR: 0,67) y la incidencia de accidente cerebrovascular (RR: 0,76).

Los análisis agrupados de los componentes revelaron que dichos efectos protectores parecen ser más atribuibles al AOVE, las frutas, las verduras y las legumbres³⁴.

Ninguna dieta excepto la mediterránea, se ha asociado con un aumento estadísticamente significativo en el colesterol c-HDL o la reducción de la PCR⁴⁵.

Hasta ahora, los principales beneficios de dieta mediterránea han sido asociados con un mejor control de los factores de riesgo cardiovasculares, para mejorar la presión arterial, el perfil lipídico, el metabolismo glucémico, el riesgo arrítmico o el microbiota intestinal. Pero recientemente, se ha demostrado que puede ejercer un efecto antiinflamatorio en la pared vascular, reduciendo

Figura 5: Curvas Kaplan-Meier de la incidencia acumulada de eventos de punto final en la población total de estudio. El Panel A muestra la incidencia del punto final primario (un compuesto de infarto agudo de miocardio, accidente cerebrovascular y muerte por causas cardiovasculares), y el Panel B muestra la mortalidad total³¹.

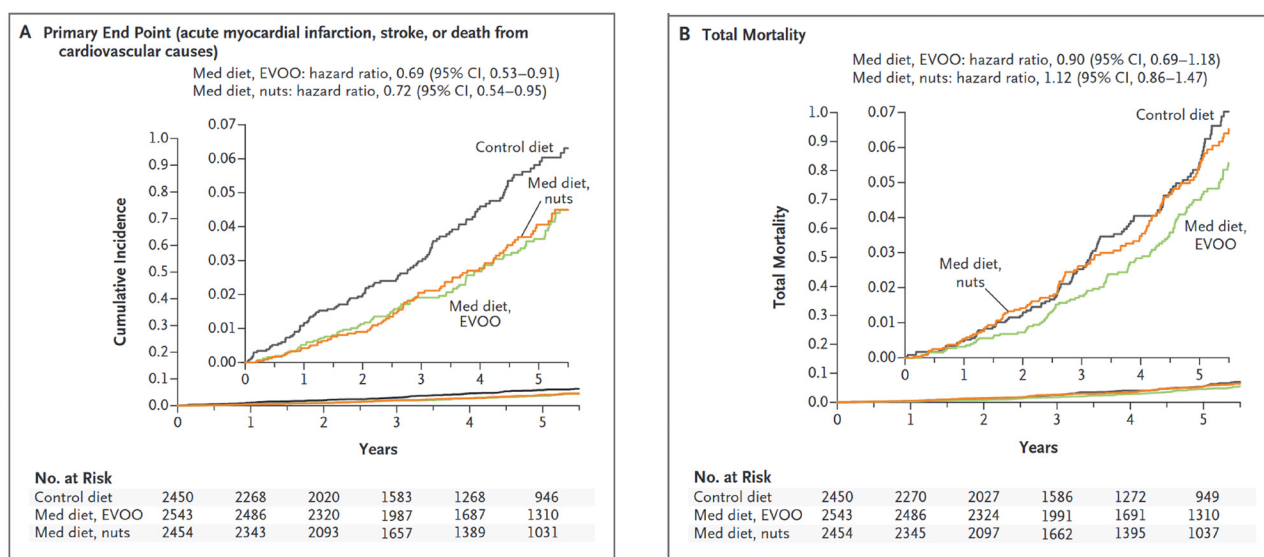
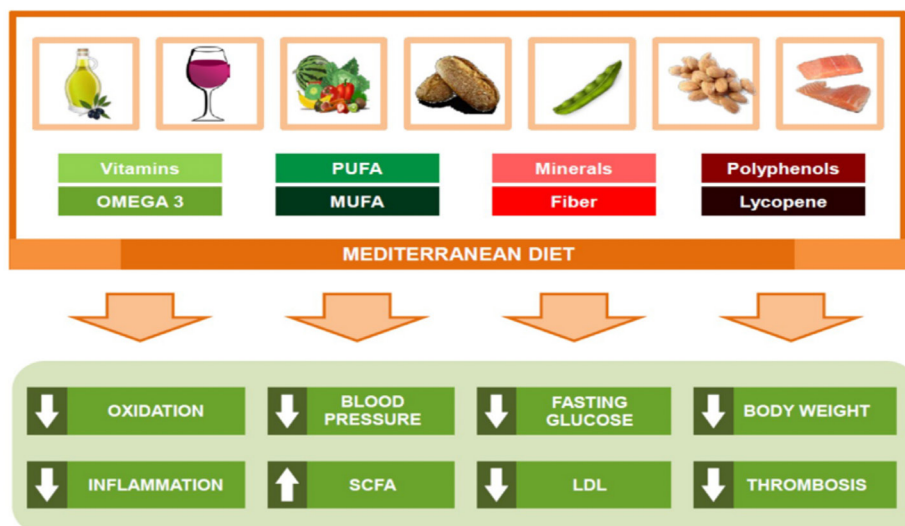


Figura 6: Principales mecanismos de protección de la dieta mediterránea frente a las enfermedades cardiovasculares⁴.



el espesor de la íntima media como un posible mecanismo cardioprotector (Figura 6). Curiosamente, también parece modular la expresión de genes proaterogénicos y proinflamatorios como ciclooxigenasa-2 y proteína quimioatrayente de monocitos, entre otros⁴.

En el año 2020, Hu et al. llevaron a cabo un análisis de 12.413 participantes (de 45 a 64 años) del Estudio de Riesgo de Aterosclerosis en Comunidades (ARIC), donde observaron asociaciones inversas para la puntuación de Healthy Eating Index-2015 basándose en una dieta mediterránea y la incidencia de ECV, mortalidad por ECV y mortalidad por todas las causas.

Las asociaciones más fuertes se observaron para la mortalidad por ECV, en la que la mayor adherencia (quintil 5) a los patrones dietéticos se asociaron con una reducción de riesgo del 21-34% y un HR: 0,84, en comparación con los participantes con la menor adherencia (quintil 1)⁴⁷.

En el mismo año, Dinu et al. realizaron un metaanálisis de ensayos clínicos aleatorizados, en el cual examinaron ochenta artículos, que cubren una amplia gama de dietas populares; para evaluar críticamente sus efectos sobre factores de riesgo cardiovasculares.

Los hallazgos más consistentes se observaron en estudios que incluyeron patrones dietéticos como la dieta mediterránea y la DASH. En dicho análisis, la mediterránea mostró evidencia significativa de una reducción en el peso, el IMC, el colesterol, la glucosa y la presión arterial, y evidencia débil de una mejoría en los triglicéridos, la insulina y la HbA1c. La dieta DASH, informó evidencia de un efecto beneficioso sobre el peso y la presión arterial, y evidencia débil para el IMC y el colesterol. Con respecto a los otros patrones, la evidencia fue menos consistente, porque la mayoría de los estudios tuvieron un tamaño de muestra limitado y muchos metaanálisis fueron de baja calidad metodológica⁴⁸.

Los componentes bioactivos del AOVE, han demostrado mejoras en el estado inflamatorio, el estrés oxidativo y la disfunción endotelial. Un metaanálisis reciente (2020) realizado por Schwingshackl et al. con 30 ECA (3106 participantes), con un consumo diario de 50 mg AOVE encontraron una disminución significativa en PCR (-0,64 mg/l, $p < 0,0001$) e IL-6 (-0,29 mg/l, $p < 0,04$) en comparación con el grupo control⁴⁹.

Tabla 1: Principales estudios y sus resultados sobre la dieta Mediterránea.

Autor (año)	Estudio	Participantes	Resultados
Estruch et al. (2018)	Ensayo Clínico Aleatorizado	7.447	Dieta Medit. (AOVE): 96/2.543 ECV. Dieta Medit. (Fr. secos): 83/2.454 ECV. Dieta control: 109/2450 ECV.
Grosso et al. (2017)	Metaanálisis	28 estudios	Mortalidad ECV: RR 0,76. Infarto de miocardio: RR 0,67. Accidente cerebro vascular: RR 0,76.
Hu et al. (2020)	Metaanálisis	12.413	Adherencia máx. (quintil 5): HR 0,84 Adherencia mín. (quintil 1): HR 1
Dinu et al. (2020)	Metaanálisis	80 estudios	Reducción significativa: IMC, PA, colesterol, triglicéridos, glucosa, HbA1c.
Schwingshackl et al. (2020)	Metaanálisis	3.106	Reducción significativa: PCR (-0,64 mg/l) e IL-6 (-0,29 mg/l) frente al grupo control.

Dieta DASH

Este tipo de patrón dietético tiene menos relevancia en nuestro medio; sin embargo, las guías de práctica clínica también la han recomendado para la reducción del riesgo cardiovascular, de hecho, actualmente es uno de los patrones con mayor evidencia científica en ECV además de una importante estrategia no farmacológica para controlar la HTA.

Ya en 2008 **Fung et al.** informaron hallazgos relevantes a partir de un seguimiento de 24 años, con enfermeras de mediana edad; en el estudio "Nurses' Health Study" sobre los enfoques dietéticos DASH, establecieron que las mujeres con antecedentes de hipertensión, actividad física inferior a la mediana, o fumadoras, el efecto de la dieta DASH fue más fuerte que entre las que no tenían estas características, RR: 0.68/0.76, respectivamente³⁸. Como conclusión, la situación clínica de los pacientes antes de la intervención, determina parte de su eficacia de en los factores cardiovasculares.

Siervo et al. (2015) en su metaanálisis sobre los efectos de la dieta DASH; demostraron que tanto la PAS como la PAD se reducían significativamente (-5,2mmHg, y -2,6 mmHg respectivamente); también se reducía el c-LDL en -0,1 mmol/L ($p=0,03$), colesterol total -0,2 mmol/L ($p<0,001$), el peso corporal -1,42 kg ($p<0,001$), y la insulina en ayunas -0,15 μ U/mL ($p<0,001$). Además, observaron que con dicha intervención la ECV disminuía en un 20%, el accidente cerebrovascular en un 19% y la insuficiencia cardíaca en un 29% ($p<0,001$)⁵⁰.

Cabe destacar que mayores reducciones en la PA pueden lograrse reduciendo aún más la ingesta de sodio, aunque supone un desafío práctico lograr una ingesta menor o igual a 1.200 mg/ día²⁷.

En el año 2018, **Soltani et al.** realizaron un metaanálisis que incluyó 6 ECA con 451 participantes que fueron seguidos durante 24 semanas, periodo en el cual se estudió el efecto de la dieta DASH en los biomarcadores inflamatorios. Los resultados mostraron que esta dieta reducía significativamente las concentraciones de PCR en comparación con otras dietas control⁵¹.

En el mismo año, **Phillips et al.** en un análisis transversal de 1.493 participantes (50-69 años), estudiaron las posibles asociaciones entre la calidad de la dieta (a través de una puntuación de calidad de la dieta DASH),

la adiposidad, el metabolismo de la glucosa, el perfil lipídico y la inflamación. Establecieron que una mayor la adherencia al patrón dietético DASH se asoció con mejoras en las medidas de adiposidad (IMC, perímetro de cintura), y menores concentraciones de TNF- α , IL-6, PCR, leucocitos, y PAI-1 como marcadores proinflamatorios, protrombóticos y proaterogénicos ($p<0,05$; en todos). También se mostraron mejoras en los parámetros del perfil de lipoproteínas (c-LDL y c-HDL)⁵².

No obstante, **Pickering et al.** remarcaron que los efectos potenciales para la salud de la dieta DASH dependen de la adherencia a dicho patrón, ya que los sujetos que anteriormente presentaban una menor adherencia a la dieta muestran un mayor beneficio de las intervenciones en el control de la PA que aquellos que tenían un patrón alimentario similar previamente. No obstante, el compromiso y la implicación del paciente son fundamentales en todas las intervenciones basadas en modificaciones dietéticas³².

Dieta vegetariana

La American Heart Association (AHA) emitió recomendaciones nutricionales entre las que se incluyen dietas vegetarianas como patrón dietético que puede ayudar a cumplir con las pautas establecidas; al igual que la dieta mediterránea y la DASH⁵.

Las grasas saturadas aumentan las concentraciones de c-LDL en plasma, y según un informe publicado por la AHA, reemplazar estas grasas por aceite vegetal insaturado puede reducir el riesgo de ECV en aproximadamente un 30%. El colesterol dietético se encuentra sólo en productos de origen animal, como carne, lácteos y huevos¹¹.

Es importante hacer hincapié en que el término "basado en plantas" no necesariamente significa "saludable". Existe evidencia que respalda los efectos adversos de la ingesta excesiva de algunos alimentos derivados de plantas, como granos refinados, patatas fritas, pasteles o bebidas azucaradas³².

Crowe et al. (2013) en su investigación prospectiva sobre el cáncer y el estudio de nutrición "EPIC-Oxford" con 44.561 participantes; encontró, entre un subgrupo de 1546 participantes, un 32% menos de riesgo de cardiopatía isquémica entre vegetarianos que entre los no vegetarianos (NV). La diferencia se atribuyó a una

Tabla II: Principales estudios y resultados sobre la dieta DASH.

Autor (año)	Estudio	Participantes	Resultados
Siervo et al. (2015)	Metaanálisis	20 estudios	PAS -5,2 mmHg (p significativa) PAD -2,6 mmHg (p significativa) c-LDL: -0,1 mmol/l (p significativa)
Soltani et al. (2018)	Metaanálisis	451	Reducción significativa: PCR = -1,01 mg/l; (IC) 95 %: -1,64 a -0,38;
Phillips et al. (2018)	Análisis transversal	1.493	Reducción significativa: IMC, perímetro de cintura, y marcadores inflamatorios (TNF- α , IL-6, PCR, leucocitos, y PAI-1)

protección sobre el colesterol no HDL y la PA, siendo el colesterol no HDL 3,97 (IC 95% 3,84 - 4,10) vs 4,42 (IC 95% 4,36 - 4,47) mmol/l y PAS siendo 130,7 (IC 95% 128,4 - 133,1) vs 134 (IC 95% 133 - 134,9) mmHg, respectivamente^{53,36}.

En un espectro de patrones dietéticos, parece que cuanto más basado en plantas sea la dieta, menor es la mortalidad por ECV y por todas las causas³⁸.

Dinu et al. en 2017 llevaron a cabo un metaanálisis de 86 estudios transversales y 10 estudios prospectivos de cohortes, cuyos resultados informaron un efecto protector significativo de la dieta vegetariana contra la incidencia y/o mortalidad por cardiopatía isquémica. La reducción del riesgo observada, en comparación con los patrones dietéticos no vegetarianos, fue del 25%⁵⁴.

Al año siguiente **Benatar et al.** en su metaanálisis incluyeron 40 estudios con 12.619 veganos y 179.630 omnívoros. En sus resultados obtuvieron que los veganos en comparación con los omnívoros consumían menos energía (-11%, IC95%: -14 a -8%) y menos grasa saturada (-51%, IC 95%: -57 a -45%). También tenían un IMC (-1,72 kg/m², IC 95% -2,30 a -1,16), un perímetro de cintura (-2,35 cm, IC 95% -3,93 a -0,76), c-LDL (-0,49 mmol/L IC 95% -0,62 a -0,36), TG (-0,14 mmol/L, IC 95% -0,24 a -0,05), glucosa en ayunas (-0,23 mmol/, IC 95% -0,35 a -0,10), PAS (-2,56 mmHg, IC 95%: -4,66 a -0,45) y PAD (-1,33 mmHg, IC 95%: -2,67 a -0,02), $p < 0,0001$ ⁵⁵.

Este tipo de patrón dietético destaca por su alto contenido antioxidantes, minerales y micronutrientes (**Figura 7**). Además, es probable que dicha dieta sea baja en calorías debido a su bajo contenido de grasas

saturadas y alto contenido de fibra, lo que podría ayudar con la pérdida de peso y el mantenimiento del peso a largo plazo⁵⁶. En particular, la fibra dietética podría reducir la ingesta de energía al desencadenar señales de saciedad; o su potencial efecto reductor del colesterol; probablemente mediada por una menor absorción de este y de grasa, una síntesis alterada de colesterol, una mayor síntesis de ácidos biliares y una disminución de la absorción de ácidos biliares³⁷.

En el año 2019 **Kim et al.** utilizaron datos de una cohorte comunitaria de adultos de mediana edad (n=12.168) en el estudio ARIC que fueron seguidos desde 1987 hasta 2016. La dieta de los participantes se clasificó utilizando 4 índices de dieta vegetariana. Los resultados mostraron que los participantes en el quintil más alto versus el más bajo de adherencia, tenían un riesgo 16%, 31% y 25% menor de ECV, mortalidad por ECV y mortalidad por todas las causas, respectivamente ($p < 0.05$)³⁵.

Wozniak et al. (2020) llevaron a cabo un estudio, con 10.797 individuos cuyo objetivo fue evaluar la prevalencia y la asociación de estas dietas con factores de riesgo cardiovascular, utilizando encuestas en la población de Ginebra y Suiza. Dicho estudio mostró que las diferentes dietas vegetarianas evaluadas se asocian con un mejor perfil de riesgo cardiovascular. Los participantes que se adhirieron a cualquier dieta que excluyera o redujera la ingesta de carne tenían un IMC, un colesterol total y una PA más bajos que los omnívoros⁵⁷.

Sin embargo, es importante no olvidarse de que la dieta vegetariana se caracteriza por una menor biodisponibilidad y absorción de proteínas, hierro, zinc y calcio, que son minerales importantes para mantener un adecuado estado de salud⁵.

Figura 7: Mecanismos potenciales de las dietas basadas en plantas para reducir el riesgo cardiovascular³⁷.

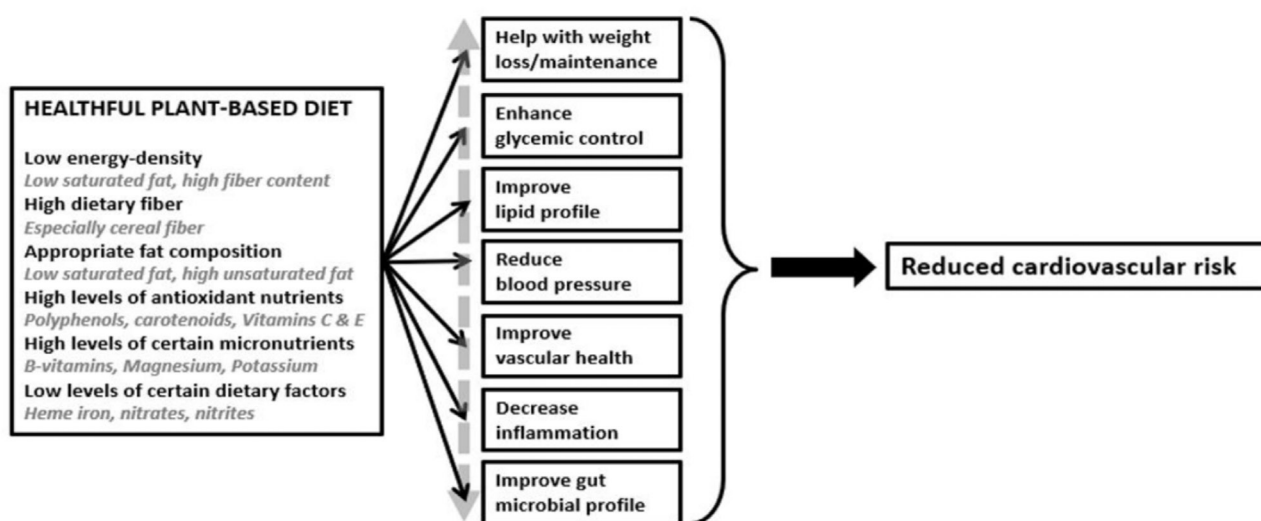


Tabla III: Principales estudios y sus resultados sobre la dieta vegetariana.

Autor (año)	Estudio	Participantes	Resultados
Crowe et al. (2013)	Cohortes	44.561	c-HDL: 3,97 mmol/l (vegetarianos) vs 4,42 mmol/l (NV) PAS 130,7 mmHg (vegetarianos) vs 134 mmHg (NV).
Dinu et al. (2017)	Metaanálisis	96 estudios	Reducción 25% incidencia y mortalidad por c. isquémica comparado con NV.
Benatar et al. (2018)	Metaanálisis	40 estudios	Veganos comparados con omnívoros: IMC más bajo (-1,72 kg/m ²), colesterol (-0,49 mmol/L), TG (-0,14 mmol/L), glucosa en ayunas (-0,23 mmol/l) y PAS (-2,56 mmHg).
Kim et al. (2019)	Cohortes	12.168	Quintil 5 respecto quintil 1: reducción significativa 16% en ECV; del 31% en mortalidad cardiovascular y 25% mortalidad por todas las causas.

Dieta cetogénica

Después de los decepcionantes resultados de las dietas bajas en grasas en la prevención de ECV, los carbohidratos se han convertido en el centro de un intenso interés en la epidemiología nutricional.

La cuestión de si la calidad de los CH en la dieta, en lugar de su cantidad relativa, puede tener un impacto positivo en los resultados de salud de la población se ha vuelto muy relevante. A este respecto, se han utilizado varios marcadores de calidad para investigar la relación entre dicha calidad y las mejoras en la salud.

Sin duda es importante un enfoque amplio y multidimensional basado en alimentos que contengan CH específicos (granos integrales, legumbres y frutas), evite los CH líquidos y reduzca los azúcares agregados con alto índice glucémico y bajo contenido en fibra³⁹.

Para abordar el vacío sobre las dietas cetogénicas en la literatura, **Bazzano et al.** en 2014 realizaron un ECA para analizar el efecto de una dieta baja en CH (<40% de energía total) frente a una dieta baja en grasas (<30% de la energía total, <7% grasas saturadas) sin restricción energética ni consejos de actividad física en adultos obesos. Después de 1 año de intervención, los sujetos con dieta baja en CH mostraron una mayor pérdida de peso: 3,5 kg (IC 95%: 5,6 a 1,4 kg), específicamente de masa grasa. Además, algunos factores de RCV como los triglicéridos, el c-HDL y el colesterol total también mejoraron más que en el grupo con la dieta baja en grasas^{58,59}.

Un estudio de **Sharman et al.** (2004) realizado en hombres adultos, indicó que la adaptación a esta dieta dio lugar a reducciones significativas de triglicéridos (-33%) y de insulina en ayunas (-34%). Curiosamente, dichos autores describieron un aumento significativo en el c-HDL después de 3 semanas de intervención.

Además, parece tener un gran beneficio en la pérdida de peso, que probablemente se deba a un mayor déficit de energía. Sin embargo, se necesitan estudios a largo plazo para describir completamente la evolución de la pérdida de peso y caracterizar mejor los mecanismos involucrados⁶⁰.

En el año 2019, **Liu et al.** llevaron a cabo un metaanálisis de 18 estudios con 69.554 pacientes con síndrome metabólico, y llegaron a la conclusión de que el riesgo de

desarrollar síndrome metabólico aumentaba un aumento del 2,5% por cada 5% de energía procedente de la ingesta de CH. Además, se observaron algunos efectos negativos sobre el perfil lipídico en individuos con una ingesta alta de CH, con niveles reducidos de c-HDL⁶¹.

En el mismo año **Reynolds et al.** revisaron 185 estudios prospectivos y 58 ensayos clínicos y evaluaron la relación entre los indicadores más utilizados de la calidad de los CH (fibra dietética, cereales integrales e índice glucémico de la dieta) y la incidencia y la mortalidad por una amplia gama de enfermedades crónicas. Los autores concluyeron que mayor a ingesta de fibra dietética o cereales integrales se asoció con una incidencia reducida de ECV, diabetes tipo 2 y algunos cánceres, así como con mortalidad cardiovascular y por todas las causas⁶².

Kirkpatrick. et al. (2019) llevaron a cabo un metaanálisis de 14 ECA en el cual examinaron las diferencias en la concentración de lípidos plasmáticos entre las dietas bajas en CH y otras dietas isocalóricas. Los resultados indicaron que estas dietas pueden provocar mejoras en los niveles de TG y c-HDL, control glucémico y reducciones en los medicamentos para el control de la diabetes, pero tienen efectos variables sobre los niveles de c-LDL; sin embargo, aproximadamente a los 2 años, no hubo diferencias con otras dietas para la mayoría de los marcadores de riesgo cardiovasculares.

La evidencia también demuestra que las dietas muy bajas en CH, desafían las recomendaciones nutricionales, ya que restringen o eliminan alimentos asociados con beneficios cardioprotectores y fomentan una alta ingesta de alimentos que se sabe que aumentan el riesgo cardiovascular⁴².

En el año 2020, **Ge L. et al.** incluyeron 121 ensayos con 21.942 pacientes que fueron clasificados en 14 dietas populares y tres dietas de control. En comparación con las dietas control, las dietas bajas en CH y bajas en grasas tuvieron un efecto similar a los seis meses sobre la pérdida de peso (4,63 vs 4,37 kg); la reducción de la PAS (5,14 mmHg, vs 5,05 mmHg) y la PAD (3,21 vs 2,85 mm Hg); sin embargo la dieta baja en CH aporta mayor beneficio en el perfil lipídico y en la pérdida de peso en los primeros meses⁴⁶.

En el mismo año **Dong T. et al.** llevaron a cabo un metaanálisis, donde incluyeron 12 estudios aleatorizados, que mostraron que una dieta baja en carbohidratos se asoció con una disminución en los niveles de triglicéridos. Las intervenciones que duraron menos de 6 meses se asociaron con una disminución de $-0,23$ mmol/l (IC 95%: $-0,32$ a $-0,15$), mientras que las que duraron de 12 a 23 meses se asociaron con una disminución de $-0,17$ mmol/l (IC 95%: $-0,32$ a $-0,01$).

El cambio en el peso corporal en los grupos de observación fue de $-1,58$ kg (IC 95%: $-1,58$ a $-0,75$); con menos de 6 meses de intervención, y durante 6-11 meses de intervención, este cambio fue de $-1,73$ kg (IC 95%: $-2,7$ a $-0,76$). El aumento en los niveles plasmáticos de c-HDL no fue significativo, y el nivel plasmático de c-LDL aumentó en $0,11$ mmol/l (IC95%: $0,02$ a $0,19$)⁶³.

Tabla IV: Principales estudios y sus resultados sobre la dieta cetogénica.

Autor (año)	Estudio	Participantes	Resultados
Bazzano et al. (2013)	Ensayo Clínico Aleatorizado	148	Mayor pérdida de peso (-3,5kg) y mejoría en niveles de triglicéridos, y relación colesterol total/c-HDL; respecto dieta baja en grasas.
Sharman et al. (2004)	Ensayo Clínico Aleatorizado	15	Reducciones significativas de triglicéridos, lipemia posprandial y de insulina en ayunas. Importante pérdida de grasa.
Kirkpatrick et al. (2019)	Metaanálisis	14 estudios	Reducción significativa de los niveles de TG, aumento leve c-HDL y mejora en la resistencia a la insulina.
Dong et al. (2020)	Metaanálisis	12 estudios	Mayor reducción de TG en intervenciones <6 meses. Pérdida de peso de 1,58 kg en <6 meses y de 1,73 kg en 6-11 meses de intervención. Cambios en los niveles de colesterol no significativos.

Discusión

Sin lugar a duda, la dieta es el factor de riesgo más importante para la primera causa de mortalidad en el mundo, y además también lo es para la discapacidad prematura. Los pacientes y los médicos a menudo tienen dificultades para mantenerse al tanto de las tendencias dietéticas, muchas de las cuales se centran en la pérdida de peso en lugar de la nutrición y la salud²¹.

Este estudio proporciona una visión general comprensiva y una evaluación crítica de los efectos de diferentes dietas populares sobre el peso corporal y los factores de riesgo cardiometabólicos.

Las 4 dietas analizadas en este estudio comparten muchas características comunes y todas podrían incluirse dentro de un plan de acción mundial para la prevención y el control de las ECV²⁷.

Sin embargo, los hallazgos más consistentes se observaron en estudios que incluyeron patrones dietéticos como las dietas mediterránea y DASH; ambos patrones dietéticos muy similares. Entre los diferentes tipos de dietas analizadas en esta revisión, la mediterránea aparece como la dieta con los mejores valores nutricionales ya que incluye cereales integrales, legumbres, fibras, PUFA sin excluir por completo los alimentos de origen animal como carne, pescado, productos lácteos, huevos y limitar el consumo de alcohol.

El estudio PREDIMED demostró por primera vez en un ensayo clínico aleatorizado que la dieta mediterránea protege contra las ECV y confirmó que influye beneficiosamente en los factores de riesgo

cardiovasculares. Los resultados muestran claramente que un patrón dietético alto en grasas insaturadas es mejor para la salud cardiovascular que una dieta baja en grasas. Además, se demuestra que nunca es demasiado tarde para cambiar los hábitos dietéticos para mejorar la salud cardiovascular; y que también puede ser útil como prevención secundaria de eventos cardiovasculares³¹.

De hecho, varios estudios demuestran que los sujetos que son adherentes a dieta mediterránea tienen menor riesgo de obesidad, diabetes, marcadores inflamatorios y todas las causas de riesgo de ECV sin ningún riesgo perjudicial⁶⁴. Por el contrario, a pesar de la evidencia científica que discutimos, las otras dietas analizadas no parecen tener suficiente evidencia para ser considerados mejores dietas que la mediterránea⁵.

Entre los componentes individuales el aceite de oliva, las verduras, frutas y legumbres parecen proporcionar las propiedades cardioprotectoras más fuertes y deben ser considerados como cruciales en la definición de futuros ECA para evaluar específicamente sus efectos³⁴.

La distribución nutricional y la calidad de esta dieta permite que los profesionales de la salud brinden consejos dietéticos fáciles de seguir para la mayoría de pacientes, sin la necesidad de una guía restringida³².

Además, ningún otro patrón dietético se ha sometido a una evaluación tan completa, repetida e internacional de sus efectos cardiovasculares. Ha superado con éxito todas las pruebas necesarias y se acerca al estándar de oro para la salud cardiovascular²².

En cuanto a la dieta DASH, aunque es similar en muchos aspectos a la mediterránea, el cuerpo de evidencia científica respecto al beneficio cardiovascular no es tan amplio, porque la mayoría de los estudios tuvieron un tamaño de muestra limitado y muchos metaanálisis fueron de baja calidad metodológica.

Si es cierto que se ha demostrado un beneficio significativo a la hora de reducir tanto la presión arterial sistólica como diastólica; en relación al consumo reducido de sodio. Es importante remarcar que mayores reducciones de sodio en la dieta, mayor fue este beneficio, por eso esta dieta sería especialmente recomendable para personas hipertensas. Por otro lado, varios estudios informaron además evidencia débil sobre la reducción del IMC y del perímetro de cintura, el colesterol total y sobre la incidencia de diabetes tipo 2.

El uso de dietas basadas en plantas como medio de prevención y tratamiento de enfermedades cardiometabólicas merece ser promovido a través de guías y recomendaciones dietéticas¹¹.

Además, las dietas vegetarianas adecuadamente planificadas son saludables y efectivas para el control del peso y la glucemia, y brindan beneficios metabólicos y cardiovasculares, incluida la reversión de la aterosclerosis y la disminución de los lípidos en sangre y la presión arterial. Los beneficios cardiovasculares parecen ser mayores con las dietas veganas puras que con las ovolactovegetarianas¹¹.

Para aquellos que prefieren un enfoque más moderado, los beneficios para la salud se pueden observar incluso con reducciones graduales en la ingesta de alimentos de origen animal cuando se reemplazan con alimentos vegetales saludables.

Todavía se necesitan estudios longitudinales con mayor número de participantes para determinar qué tipos de patrones dietéticos vegetarianos son los más eficaces en la reducción de ECV³⁸.

Deficiencias en algunos nutrientes como la vitamina B12, creatina, carnosina, taurina, vitamina D3, hierro-hemo y los ácidos grasos omega-3 también pueden influir de manera negativa en la salud cardiovascular. Sin embargo, el uso de suplementos, el consumo de alimentos fortificados, y la exposición a la luz solar pueden solventar estos problemas⁵⁵.

En cuanto a la dieta cetogénica, a pesar de ser unas de las dietas más de moda y con una fuerte repercusión a nivel general, todavía no está respaldada por estudios de peso que la recomienden para reducir el riesgo cardiovascular. Pero si cuenta con evidencia sobre una reducción significativa en el peso corporal, especialmente a corto plazo (6 meses); sobre todo en estudios con

restricción de carbohidratos más extrema; cuando el período de seguimiento o la cantidad de carbohidratos aumentaron, el efecto se atenuó.

En cuanto a los otros parámetros, observamos evidencia débil o sugestiva de una mejoría en el perfil glucémico y la presión arterial, y resultados contradictorios para el perfil lipídico, con un aumento en el colesterol total y LDL reportado en varios metaanálisis, que pueden estar relacionados con el hecho de que las personas con dietas bajas en carbohidratos tienden a comer menos verduras y frutas ricas en micronutrientes y fibra, y más alimentos de origen animal.

Aunque el c-LDL mostró un ligero aumento general en algunos resultados; se observaron cambios más favorables en otros parámetros lipídicos (c-HDL y TG), y no se observaron cambios significativos en el c-LDL después de más de 6 meses⁶³.

Este tipo de dietas pueden ser una buena opción para un período de pérdida de peso inicial a corto plazo (2-6 meses) en personas con sobrepeso / obesidad. Para el mantenimiento del peso a largo plazo y la salud CV, se recomienda aumentar gradualmente la ingesta de CH y se debe poner énfasis en los alimentos CH asociados con un menor riesgo cardiovascular, incluidas las verduras, frutas, granos enteros y legumbres²⁷.

Debe haber una discusión médico-paciente con respecto a la necesidad y supervisión de las dietas bajas/ muy bajas en CH antes de iniciar este tipo de dieta, ya desafían las recomendaciones nutricionales, restringiendo o eliminando severamente los alimentos asociados con los beneficios cardioprotectores y fomentan una alta ingesta de alimentos que se sabe que aumentan el riesgo de ECV.

Si se adopta una dieta muy baja en CH, las personas deberían, idealmente, recibir supervisión médica, evaluación basal y regular de lípidos/ lipoproteínas y, cuando sea factible, múltiples sesiones con un nutricionista para facilitar la adherencia dietética con asesoramiento nutricional personalizado y modificación del comportamiento, así como el reemplazo de CH con ácidos grasos insaturados y evitar la ingesta excesiva de grasas saturadas y colesterol⁴².

Podemos considerar que esta revisión cuenta con algunas limitaciones, como son el reducido número de estudios/ ensayos que comparen adecuadamente las dietas entre sí, a la hora de valorar la eficacia en la reducción de riesgo cardiovascular. También cabe destacar la falta de evidencia científica en cuanto a las dietas más modernas como son la vegetariana y la cetogénica.

Otro punto a tener en cuenta es que la mayoría de los metaanálisis carecían de validez externa, pues incluían

una población sesgada, con sobrepeso/obesidad u otras enfermedades, y esto debe considerarse antes de extender estos resultados a la población general. Además, los métodos utilizados para evaluar las dietas pueden variar entre los diferentes estudios

Un punto a favor es la utilización de estudios con gran relevancia y con una evidencia más que demostrada.

El enfoque futuro en el ámbito de patrones dietéticos debe seguir estudiándose; está más que demostrada

la eficacia a la hora de reducir el riesgo cardiovascular sin embargo la falta de grandes y potentes estudios hace más que necesaria una continua y actualizada investigación para que se puedan aplicar de manera rutinaria en la práctica diaria.

La ciencia es optimista y aunque la situación epidemiológica no sea favorable y el abordaje terapéutico sea complicado, hay que tener una visión esperanzadora y no parar de trabajar hasta llegar a conseguir los objetivos propuestos por las organizaciones sanitarias.

Tabla V: Patrones dietéticos y sus potenciales beneficios cardiovasculares.

Patrón Dietético	Distribución Nutricional	Beneficios cardiovasculares
Dieta Mediterránea 19 21 23 31, 34	<ul style="list-style-type: none"> Grasas: 35-45% kcal/d (principalmente monoinsaturadas, AOVE y nueces) CH: 35-45% kcal/d Proteínas: 15-18% kcal 	<ul style="list-style-type: none"> - Reducción de incidencia y mortalidad por ECV. - Reducción de PA (sistólica y diastólica) - Asociación inversa con mortalidad total - Mejoras en la dislipemia. - Reducción incidencia de DM tipo2.
Dieta DASH 20 22,26 35-37	<ul style="list-style-type: none"> Grasas: 27% kcal/d (gr. saturadas 6%) CH: 55% kcal/d Proteínas 18% kcal/d 	<ul style="list-style-type: none"> - Reducción de PA (sistólica y diastólica) - Reducción del IMC y del perímetro de cintura - Mejoras en el perfil metabólico. - Reducción incidencia de DM tipo2.
Dieta Vegetariana 38-40 41 42,43 44	<ul style="list-style-type: none"> - Reducción o restricción de alimentos animales - Alto consumo de alimentos basados en plantas - Grasas principalmente insaturadas. 	<ul style="list-style-type: none"> - Reducción de PA (sistólica y diastólica) - Disminución del peso corporal y del riesgo de obesidad - Reducción del riesgo de ECV - Disminución de la mortalidad por todas las causas - Reducción incidencia de DM tipo2
Dieta baja en CH Cetogénica 45-47 49,50 29,31	<ul style="list-style-type: none"> CH: <50% kcal/d (<10% kcal/d en dieta cetogénica. Alto consumo proteínas (20-30% kcal/d) Alto consumo en grasas (30-70% kcal/d) 	<ul style="list-style-type: none"> - Reducción de PA (sistólica y diastólica) - Disminución del peso corporal y del riesgo de obesidad - Reducción del riesgo de ECV - Disminución de la mortalidad por todas las causas - Reducción incidencia de DM tipo2

Conclusiones

1. Las enfermedades cardiovasculares son la primera causa de muerte en el mundo, y el factor más importante para prevenirlas es la dieta; pudiendo reducir hasta un tercio de dichas enfermedades.

2. Todos los patrones dietéticos estudiados tienen elementos en común: reducir el consumo de grasas saturadas, azúcares y carnes rojas y aumentar la ingesta de frutas, verduras y grasas insaturadas.

3. Cualquier patrón dietético adecuado junto con una restricción calórica pueden ayudarnos a reducir tanto el peso como el riesgo cardiovascular.

4. La dieta mediterránea sigue siendo el patrón con mayor evidencia sobre la reducción del riesgo cardiovascular y por tanto sobre la mortalidad cardiovascular.

5. La dieta DASH es una buena alternativa para pacientes hipertensos, ya que permite reducir considerablemente la tensión arterial, disminuyendo el sodio.

6. La dieta vegetariana ha demostrado multitud de beneficios cardiovasculares, siempre y cuando se suplemente adecuadamente para compensar los déficits nutricionales.

7. La dieta cetogénica a pesar de estar muy de moda, no cuenta con mucha evidencia sobre el beneficio cardiovascular; además se necesita una adecuada supervisión para su correcta realización.

Conflicto de intereses: Ninguno.

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ORIGINAL

Prevalence of Carpal Tunnel Syndrome(P-CTS) in Iran: An Updated Systematic Review

*Prevalencia del síndrome del túnel carpiano (P-CTS) en Irán:
una revisión sistemática actualizada*

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Abstract

Introduction: P-CTS depends on several factors, such as demographic changes. Regarding the changed lifestyle of the Iranian society and the economic and health consequences of the Carpal Tunnel Syndrome (CTS), the present study intended to investigate the P-CTS in the Iranian population.

Methods: The present systematic review study was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) steps. We systematically searched Scopus, Web of Sciences (ISI), PubMed, PEDro, and Science Direct databases and national databases (Magiran and SID) to identify relevant studies published from 2000 to 2020 using various combinations of the following keywords: carpal tunnel syndrome, wrist, median nerve, electrodiagnostic, and median nerve compression neuropathy. STROBE checklist was used to assess the quality of articles.

Results: 598 articles were initially identified, of which 16 (60% more than the previous meta-analysis) were evaluated with a total of 15325 subjects. The quality assessment of articles varied from 30 to 42 (all were excellent).

Conclusion: P-CTS among patients ranges from 18 to 26%. In the general population with general risk factors (i.e., diabetes, hand injuries, etc.) is 1.87-7%. In groups with a high frequency of repetitive movements of the wrist (e.g., carpenters, typists, those who use a wheelchair, computer users, employees), the prevalence is 10-15%.

Key words: Prevalence, Carpal Tunnel Syndrome, Systematic, Nerve Damage.

Resumen

Introducción: El síndrome del túnel carpiano (STC) depende de varios factores, como los cambios demográficos. En relación con el cambio en el estilo de vida de la sociedad iraní y las consecuencias económicas y sanitarias del STC, el presente estudio pretendía investigar el STC-P en la población iraní.

Métodos: El presente estudio de revisión sistemática se realizó siguiendo los pasos de los Elementos de Información Preferidos para Revisiones Sistemáticas y Meta-Análisis (PRISMA). Se realizaron búsquedas sistemáticas en las bases de datos Scopus, Web of Sciences (ISI), PubMed, PEDro y Science Direct, así como en las bases de datos nacionales (Magiran y SID), para identificar los estudios pertinentes publicados entre 2000 y 2020, utilizando varias combinaciones de las siguientes palabras clave: síndrome del túnel carpiano, muñeca, nervio mediano, electrodiagnóstico y neuropatía por compresión del nervio mediano. Se utilizó la lista de comprobación STROBE para evaluar la calidad de los artículos.

Resultados: Se identificaron inicialmente 598 artículos, de los cuales se evaluaron 16 (un 60% más que en el metanálisis anterior) con un total de 15325 sujetos. La evaluación de la calidad de los artículos varió de 30 a 42 (todos fueron excelentes).

Conclusiones: El STC-P entre los pacientes oscila entre el 18 y el 26%. En la población general con factores de riesgo generales (es decir, diabetes, lesiones de la mano lesiones en las manos, etc.) es del 1,87 al 7%. En grupos con una alta frecuencia de movimientos repetitivos de la muñeca (por ejemplo, carpinteros, mecanógrafos, quienes utilizan una silla de ruedas, usuarios de ordenadores, empleados), la prevalencia es del 10-15%.

Palabras clave: Prevalencia, Síndrome del Túnel Carpiano, Sistemática, Daño Nervioso.

Introduction

CTS is the most common peripheral nerve neuropathy caused by increased median nerve pressure in the wrist¹⁻³. Symptoms of CTS include pain, paresthesia, and sleep disturbances⁴⁻⁶. The most common cause of CTS is idiopathic, and its diagnosis is based on clinical symptoms, physical examination, and electrodiagnostic examination. Methods used to treat CTS include medication in mild to moderate cases and surgery in severe cases⁷⁻⁹.

It is more common in women than men (up to 15 times) and is more common among those aged 40 to 60 years (working age) compared to the general population (up to 10 times). P-CTS depends on the study population and type of the study¹⁰⁻¹². The most recent meta-analysis performed in Iran (in 2018) reported a prevalence of 17.53% for CTS, and its researchers recommended that by increasing the knowledge and awareness of people and general practitioners (GPs), the prevalence of this syndrome can be reduced in Iran¹³.

As this syndrome causes several social and occupational problems and carries a high economic burden for both patients and the society¹⁴⁻¹⁶, and regarding that various studies reported different prevalence rates for the CTS, particularly in Iran, the present systematic review study intended to investigate the P-CTS in Iran. Furthermore, the latest systematic review is conducted in 2018, and since then, several contributing factors have changed, including increased penetration of mobile phones, occupational accidents, neurological diseases, which probably have affected the P-CTS. Besides, several new studies are published since then, which indicates the importance of this syndrome. Hence, we decided to perform a new systematic review study with a wider perspective and by considering the limitations/weaknesses of previous studies, in order to investigate the P-CTS in Iran.

Method

The present systematic review study was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) steps in 2020¹⁷.

Search Strategy

We systematically searched Scopus, Web of Sciences (ISI), PubMed, PEDro, and Science Direct databases and national databases (Magiran and SID) to identify relevant studies published from 2000 to 2020 using various combinations of the following keywords: carpal tunnel syndrome, wrist, median nerve, electrodiagnostic, and median nerve compression neuropathy. The search was performed on 2020/11/20 by two independent researchers. And the third person confirmed the final result to increase the comprehensiveness of the search, references of identified articles were also evaluated.

Inclusion Criteria(IC) and Exclusion Criteria(EC)

IC were as follows: (1) Studies published from 2000 to the end of 2020; (2) studies on Iranians; (3) Articles published in English or Persian; (4) Having a descriptive cross-sectional design or longitudinal cohort studies that are suitable to estimate the incidence and P-CTS; and (5) studies that reported the sample size and P-CTS. EC also included (1) articles presented at conferences; (2) articles without full text; (3) studies that used an inappropriate method to measure the P-CTS; (4) articles with the inappropriate study population.

Study Selection

Titles, abstracts, and full papers were screened against inclusion and exclusion criteria. After removing the duplicates, eligible articles were selected.

Quality Assessment

After selecting the relevant articles concerning titles and content that met the inclusion criteria, the STROBE checklist (strengthening the reporting of observational studies in epidemiology) was used to assess the quality of articles. This STROBE consists of 44 sections on text and methodology of the study, including the objectives of the study, determining the appropriate sample size, type of study, sampling method, study population, data, tests performed on data collection tool(s), how variables are defined, methodology, sample evaluation, statistical tests, study objectives, and an appropriate description of findings based on the objectives of the study. The total score of STROBE ranges from zero to 44. Based on the results of the quality assessment, articles were divided into three categories: high quality (less than 15.5), average quality (15.5-29.5), and high quality³⁰⁻⁴⁴. Articles with a score of less than 15.5 were excluded¹⁸.

Data Extraction

An author developed form was used to collect data from each article, which included first author name, publication year, sample size (separated by male and female), target population, the criteria for estimating the P-CTS, and the P-CTS. All data were recorded using Microsoft Excel.

Results

In total, 598 articles were identified, of which 119 were excluded after limiting the search strategy. Titles and abstracts of these 479 articles were reviewed, which resulted in the exclusion of 189 articles. Afterward, the full text of the remaining 290 articles was evaluated against inclusion and exclusion criteria, which resulted in the exclusion of 274 articles. The quality assessment score of the remaining 16 articles was above 15.5, all of which were entered into this study. The quality assessment of articles indicated that all of them have an excellent level of quality, and their score ranged from 30 to 42 (**Table I**).

Table 1: Details of selected studies for regular and meta-analysis.

Author (Year)	Sample size	Objective	Including and Excluding Criteria	Criteria used for diagnosis	Prevalence		Conclusion
					Male	Female	
Yazdanpanah (2004) ¹⁹	N=42	P-CTS in Carpenters	Inclusion criteria: Satisfaction with the study, carpentry Exclusion criteria: Having diseases such as diabetes, thyroid disorders, rheumatism	Clinical symptoms and electrodiagnosis	15/80	-	Carpentry is a job that leads to vibrational movements in the upper limbs, and these movements lead to an increase in the P-CTS in carpenters
Bahrami (2005) ²⁰	N=100	Prevalence and severity of CTS during pregnancy	Inclusion criteria: pregnancy, age >18 year Exclusion criteria: diabetes, thyroid disorders	Clinical symptoms and electrodiagnosis	26	-	Pregnancy and stress on the spine increase the incidence of CTS in pregnant women
Mehdinasab (2008) ²¹	N=33	P-CTS among typewriter	Inclusion criteria: - Exclusion criteria: diabetes, thyroid disorders, rheumatism, Wrist fracture	Clinical symptoms (Pain, numbness of the finger, paraesthesia of the fingers)	4.2%		More than 12 months of work experience, female gender, increasing age, increasing work experience and body mass index above 30 lead to an increase in the severity of CTS symptoms.
Choobineh (2009) ²²	N=305	Epidemiological study of CTS	Inclusion criteria: Age >18 years Exclusion criteria: Dissatisfaction with participating in this study	Clinical symptoms electrodiagnosis	74%		Occupations such as tailoring, clerical work, labor, carpet weaving, and previous wrist injuries are among the risk factors for CTS among non-governmental occupations.
Rayegani (2010) ²³	N=1000	Frequency of CTS and its related risk factors in patients upper extremity pain	Inclusion criteria: Upper limb pain Exclusion criteria: -	Clinical symptoms – electrodiagnosis – Boston Questionnaire	25%		Body mass index above 25, wrist fractures, diabetes mellitus and menopause were risk factors for exacerbating carpal tunnel syndrome.
Ghasemi (2012) ²⁴	N=906	CTS: the role of occupational factors among 906 worker	Inclusion criteria: Age over 18, work experience more than two years, working hours more than 40 hours per week Exclusion criteria: rheumatoid arthritis, diabetes mellitus, cervical radiculopathy, hypothyroidism, thoracic outlet syndrome, trauma to the upper limbs and medically diagnosed CTS	Clinical symptoms Tinel test Phalen's test	14	8/9%	Male gender, high body mass index and wrist fractures are risk factors for CTS.
Alizadeh (2012) ²⁵	N=88	Wrist function, range of motion and pain between sports and non sports wheelchair-dependent persons with CTS	Inclusion criteria: Wheelchairs Professional Basketball Players Exclusion criteria: Dissatisfaction with participating in this study	Clinical symptoms – electrodiagnosis	17/14% Athlete 15/15% Non-athlete		The most important cause of CTS is repetitive wrist movements.
Haghighat (2012) ²⁶	N=240	Prevalence of clinical findings of CTS in Isfahanian dentists	Inclusion criteria: - Exclusion criteria: diabetics, rheumatoid arthritis, thyroid gland disease, and wrist fractures	Clinical symptoms Phalen and Tinel TEST	16/2	17/9	Increasing working hours per week as well as aging are risk factors for CTS.
Khosravi (2012) ²⁷	N=100	The prevalence and severity of CTS during pregnancy	Inclusion criteria: pregnancy without symptoms of CTS before pregnancy Exclusion criteria: history of fracture or trauma to the hand, hypothyroidism, diabetes, or diagnosed neuropathy	Clinical symptoms – electrodiagnosis	19		The P-CTS in pregnant women is relatively high, increasing gestational age leads to the disappearance of symptoms, so it is better for women with CTS to be diagnosed in the first months

Author (Year)	Sample size	Objective	Including and Excluding Criteria	Criteria used for diagnosis	Prevalence		Conclusion
					Male	Female	
Yazdanpanah (2012) ²⁶	N=4164	Prevalence and Severity of CTS in Women	Inclusion criteria: - Exclusion criteria: DM, HTN, amyloidosis, and RD positive family history of neuropathy, previous wrist fracture, pre-pregnancy CTS and CT surgery	Clinical symptoms – electrodiagnosis Tinel's and Phalen's tests	4/2%		The severity of CTS in Iranian pregnant women is mild, but preventive measures should be considered for pregnant women.
Yazdanpanah (2015) ²⁹	N=105	Incidence of Recurrent and Persistent CTS following Open Transverse Carpal Ligament Release	Inclusion criteria: open surgical release of the median nerve	Clinical symptoms – electrodiagnosis MRI	12%		Recurrence of CTS follows high transverse surgery and it is recommended to make accurate diagnoses before surgery.
Karimi (2017) ³⁰	N=7560	P-CTS	Inclusion criteria: Neurological diseases AGE >18 years Exclusion criteria: Wrist involvement other than carpal tunnel syndrome and skin and musculoskeletal involvement	Clinical symptoms – electrodiagnosis MRI	2/23	1/82	Diabetes mellitus Hypothyroidism, anterior fracture of the dentin and rheumatoid arthritis are the most important risk factors associated with CTS.
Mohammadi (2019) ³¹	N=50	enefits of Breast-feeding in the Natural Course of CTS	Inclusion criteria: AGE >15 years - bilateral paresthesia of hands Exclusion criteria: DM, HTN, amyloidosis and RD, positive family history of neuropathy, previous wrist fracture, pre-pregnancy CTS and carpal tunnel surgery	electrodiagnosis	23		Hormonal changes as well as wrist postures while breastfeeding and repetitive wrist movements during breastfeeding increase the rate of CTS in lactating women.
Roshandel (2019) ³²	N=109	P-CTS among Male Hairdressers	Inclusion criteria: symptoms of carpal tunnel syndrome Exclusion criteria: diabetes mellitus, hypothyroidism, amyloidosis, and rheumatoid disease	electrodiagnosis	20/18%		Hairdressing is one of the most common types of CTS; This syndrome manifests itself in hairdressers with mild symptoms and severe symptoms are rarely seen in them.
Pirami (2019) ³³	N=363	P-CTS symptoms in computer users	Inclusion criteria: work with computer Exclusion criteria: Diabetes, rheumatoid arthritis, thyroid disorder or wrist trauma and fracture, neck, shoulder or diffuse hand pain	Electrodiagnosis Boston Questionnaire	14.05% conflict in one hand 85.95% of the conflict in both hands		Long-term computer work, female gender, and body mass index above 25 are risk factors for CTS.
Khanbabayi Gol (2020) ³⁴	N=160	CTS in Women with Breast Cancer	Inclusion criteria: Complete treatment of breast cancer and at least 6 months after it, developing lymphedema after breast surgery or after receiving chemotherapy and radiotherapy Exclusion criteria: Previous history of CTS, history of shoulder surgery and shoulder nerve surgery, history of shoulder and wrist trauma, use of corticosteroids in the past 6 months, metastatic cancers, nervous system and cervical disc problems.	Electrodiagnosis Boston Questionnaire electrodiagnosis	20/62%		Old age, lymphedema, history of radiotherapy, history of surgery, lymph node dissection, and a history of diabetes mellitus are risk factors for CTS in women with breast cancer.

Of 16 eligible articles, 16 evidence related to the P-CTS were found in Iran, with a total of 15325 subjects. The lowest and highest prevalence rates were 1.82% and 74%, respectively (Table I). Since the identified articles had different populations and had different methodologies to measure the CTS, including clinical examinations, electrodiagnosis, Boston questionnaire, and Tinel and Phalen tests, which were performed by various individuals, it was not possible to conduct a meta-analysis. Also, various studies reported contradicting results, which scientifically can not be synthesized. Hence, it is not possible to provide an overall prevalence. As a result, in this study, a prevalence rate is provided.

Discussion

This systematic review intended to investigate the P-CTS in Iran. In this study, different populations such as athletes, patients, and workers were evaluated, which can be used to justify the observed changes in the findings of the present study. According to the findings, the P-CTS in patients with neurological damages ranges from 18 to 26%. On the other hand, in the general population with general risk factors (diabetes, hand injuries, etc.), the prevalence of this syndrome is 1.82-7%. In groups with a high frequency of repetitive movements of the wrist (e.g. carpenters, typists, those who use a wheelchair,

computer users, employees), the prevalence is 10-15%. Finally, it can be argued that the more severe the damage and pressure to the nerve in the wrist, the higher will be the risk of CTS.

A meta-analysis study by Barcenila et al³⁵. on 14 English-language articles reported a statistically significant association between CTS and hand force and wrist power, vibration tools, and rotating the wrist. Also, it was mentioned that different diagnostic methods used by various studies had a significant effect on the estimated P-CTS. Unfortunately, because the included articles did not evaluate the impact of rotational and repeated hand movements, we could not investigate this issue in the present study. Nevertheless, there is no doubt that these movements contribute to CTS, which can be used to justify the high P-CTS in the present study.

Various studies have used different methods to evaluate the CTS³⁶⁻⁴⁰. The most common methods were physical examinations and electrodiagnosis. In two articles, author-developed tests and questionnaires were used to evaluate the CTS. This study demonstrated that the overall P-CTS is relatively high in Iran, and its rate varies greatly according to the target population, diagnosis method, and gender. Therefore, its prevalence should be investigated according to different target groups. Based on the findings of the present systematic review study, the authors suggest investigating the P-CTS and its risk factors in a target population using similar diagnostic tools and by considering important contributing variables, such as occupation, age, body mass index (BMI), work experience, gender, etc. in future studies. Also, based on the findings, it can be argued that various criteria are used to diagnose CTS, which each has its sensitivity and

specificity. It also seems that most patients are diagnosed in specialized and subspecialty healthcare centers. Therefore, if a patient with CTS symptoms is referred to a GP and the disease is ignored (i.e., not referring to a neurologist), the probability of disability will increase significantly. Therefore, it is suggested that GPs gain a deeper knowledge about the clinical and diagnostic aspects of the disease and how to manage it.

Limitations

One of the limitations of the present research is differences in study populations. The importance of this limitation roots in the fact that probably factors such as occupation, BMI, age, work experience, etc. affect the prevalence of the disease.

Suggestion

It is suggested that, due to the increasing P-CTS over time, a series of interventions be developed to increase the awareness of high-risk populations about the CTS.

Conclusion

The P-CTS among patients ranges from 18 to 26%. In the general population with general risk factors (i.e. diabetes, hand injuries, etc.) is 1.87-7%. In groups with a high frequency of repetitive movements of the wrist (e.g., carpenters, typists, those who use a wheelchair, computer users, employees), the prevalence is 10-15%.

Conflicts of interest

The authors have no potential conflicts of interest to report in connection with this article.

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CASE REPORT

Budd-Chiari Syndrome: An Unexpected Diagnosis in a Clinical Practice in Somalia

Síndrome de Budd-Chiari: Un diagnóstico inesperado en la práctica clínica en Somalia

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Abstract

Although hepatic vascular diseases are relatively uncommon in clinical practice and require accurate diagnosis and treatment, Budd-Chiari syndrome (BCS) is a group of disorders described by hepatic venous outflow obstruction, which can be thrombotic or non-thrombotic. It occurs at any level of hepatic veins or hepatic portion of the inferior vena cava (IVC) to the right atrium as defined by the European Association for the Study of the Liver (EASL) guidelines. We report a 55-year-old male patient with a history of diabetes mellitus who developed a Budd-Chiari Syndrome that has the classical triad of BCS (Abdominal pain, Ascites and hepatomegaly). The investigations showed an alteration of liver function tests and imaging characteristics of sub-acute Budd-Chiari syndrome. We could identify the causal factors of BCS in this case. Although many cases have been reported in the literature, none is from Somalia or east African countries. The diagnosis could be reached with abdominal ultrasound, but because of limited clinical experience in diagnosis imaging, many cases may be misdiagnosed. We recommend our physician and radiologist to keep this diagnosis in their mind and diagnose, so the patients could be managed properly.

Key words: Budd-Chiari Syndrome, Abdominal Pain, Ascites, Hepatomegaly.

Resumen

Aunque las enfermedades vasculares hepáticas son relativamente infrecuentes en la práctica clínica y requieren un diagnóstico y tratamiento precisos, el síndrome de Budd-Chiari (SCB) es un grupo de trastornos descritos por la obstrucción del flujo de salida venoso hepático, que puede ser trombótico o no trombótico. Se produce a cualquier nivel de las venas hepáticas o de la porción hepática de la vena cava inferior (VCI) hasta la aurícula derecha, según la definición de las directrices de la Asociación Europea para el Estudio del Hígado (EASL). Informamos de un paciente varón de 55 años con antecedentes de diabetes mellitus que desarrolló un síndrome de Budd-Chiari que presenta la tríada clásica del SCB (dolor abdominal, ascitis y hepatomegalia). Las investigaciones mostraron una alteración de las pruebas de función hepática y características de imagen del síndrome de Budd-Chiari subagudo. Pudimos identificar los factores causales del SCB en este caso. Aunque se han descrito muchos casos en la literatura, ninguno procede de Somalia o de países del este de África. Se pudo llegar al diagnóstico con la ecografía abdominal, pero debido a la limitada experiencia clínica en el diagnóstico por imagen, muchos casos pueden ser diagnosticados erróneamente. Recomendamos a nuestros médicos y radiólogos que tengan presente este diagnóstico y lo diagnostiquen, para que los pacientes puedan ser tratados adecuadamente.

Palabras clave: Síndrome de Budd-Chiari, Dolor abdominal, Ascitis, Hepatomegalia.

Introduction

A British internist George Budd first described Budd-Chiari Syndrome (BCS) in 1845, and reported three cases of hepatic vein thrombosis due to abscess-induced phlebitis, and then an Austrian pathologist Hans Chiari expanded it by presenting 13 cases and described the first pathological features of liver with "obliterating endophlebitis" of the hepatic veins¹.

BCS is an uncommon and rare vascular disorder characterised by hepatic venous outflow obstruction, which can be either thrombotic or non-thrombotic and it occurs at any level hepatic veins or hepatic portion of the inferior vena cava (IVC) to the right atrium as defined EASL guidelines². This excludes the absence of right sided heart failure, pericarditis, or sinusoidal obstruction

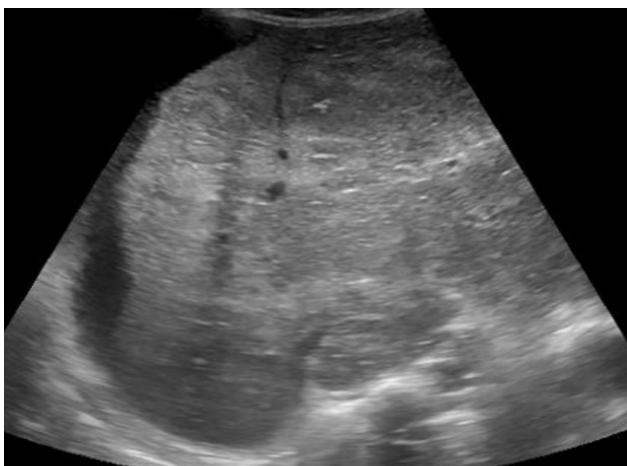
syndrome³. The BCS can lead to acute liver failure, liver cirrhosis, and even hepatocellular carcinoma⁴.

The BCS can be classified according to aetiological factors into primary and secondary. Primary BCS is a flow obstruction due to an endoluminal lesion or primary venous process, such as thrombosis or phlebitis. This primary BCS obstruction can range from the small hepatic veins to the orifice of the IVC into the right atrium. The most common causative factors of BCS that have been identified are haematologic or prothrombotic state that is approximately estimated around 75% of patients, so haematological disorders that are associated to BCS include; polycythaemia Vera, essential thrombocythemia and myelofibrosis. Prothrombotic conditions that associated to BCS include; paroxysmal nocturnal haemoglobinuria, antiphospholipid syndrome and inherited deficiencies of protein C, protein S, and antithrombin III. Secondary BCS is when flow is obstructed due to compression or invasion of lesion outside the hepatic venous outflow tract such as benign or malignant diseases (e.g. abscesses, hepatocellular carcinomas, and renal cell carcinomas, or secondary to cardiac or pericardial diseases) are more linked to BCS while less common causes that associated with BCS are inflammatory bowel disease, aspergillosis and Behcet's syndrome^{4,5}.

BCS is diagnosed clinically and confirmed by investigation. Abnormal liver function tests are a trademark, however they can also be normal. Serum aminotransferase levels may be five times normal in acute and fulminant BCS. Radiological imaging confirms a BCS diagnosis. Hepatomegaly, limited liver vein visibility, and compressed IVC are all shown on abdominal ultrasonography. Intrahepatic collaterals, splenomegaly, and ascites indicate chronic BCS⁵.

The BCS management focuses on controlling of portal hypertension and ascites with systemic anticoagulation to prevent progressive extension of the venous thrombosis⁶.

Figure 1A: Liver Ultrasonography revealed enlarged liver with heterogeneous parenchyma and no definite focal lesion. Hepatic veins were not visualized. Marked ascites noted perihepatic area.



We present a case of BCS in an adult male patient who came to internal medicine clinic with abdominal pain and distension.

Case

A 55-year-old male patient from Mogadishu, Somalia, presented to us with a complaint of a two-month history of gradually progressive abdominal distension. He is a known case of diabetes mellitus and takes metformin 850mg tablet twice a day and Gliclazide 60mg tablet once per day. The abdominal distension is associated with nausea and loss of appetite. Complete blood count revealed haemoglobin 15g/dL, leukocytes $8.3 \times 1000/\text{mm}^3$, and platelets $429 \times 1000/\text{mm}^3$. Liver biochemistry showed a total bilirubin of 1.65mg/dL, direct bilirubin 0.89mg/dl, aspartate transaminase 76 IU/L, alanine transaminase 83 IU/L, alkaline phosphatase 249 IU/L, gamma glutamyl transferase 381 IU/L and albumin 5 g/DL. The International normalised ratio (INR) was 1.25. Ascitic tap showed Serum Ascites Albumin Gradient (SAAG) >1.1 .

Liver sonography revealed enlarged liver with heterogeneous parenchyma and no definite focal lesion. Hepatic veins were not visualized. Marked ascites were noted perihepatic area (**Figure 1A**). Further imaging with abdominal CT without (**Figure 1B**) and with contrast (**Figure 2**) Showed a Mottled appearance of peripheral hypodensity in the liver parenchyma. Hepatic veins do not opacify. Mildly enlarged Caudate lobes with normal enhancement. Portal veins opacity normally (**Figure 3**). Upper gastrointestinal endoscopy showed small oesophageal and gastric varices (**Figure 4**). Therefore, based on the clinical and imaging finding, the patient was diagnosed with subacute form Budd-Chiari syndrome. Treatment with diuretics and anticoagulant was initiated.

Figure 1B: Unenhanced Axial CT scan shows slightly heterogeneous liver parenchymal appearance, enlarged caudate lobe with Massive Ascites.



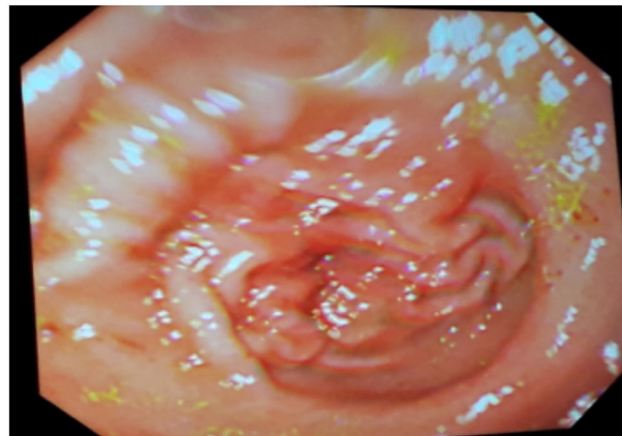
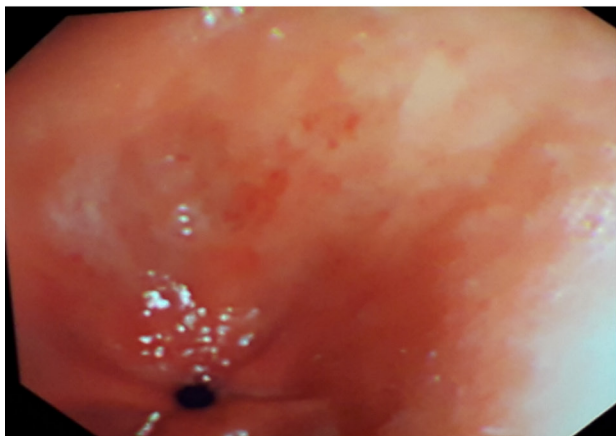
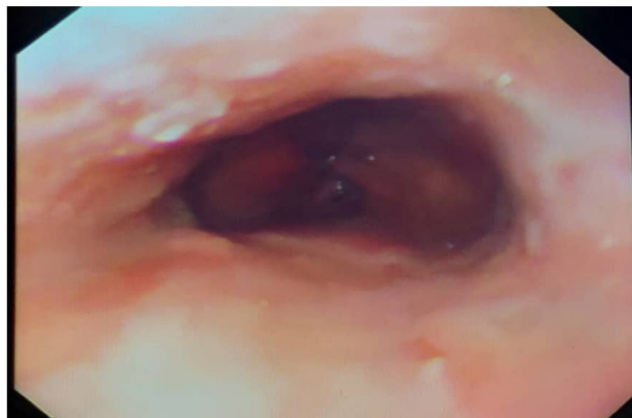
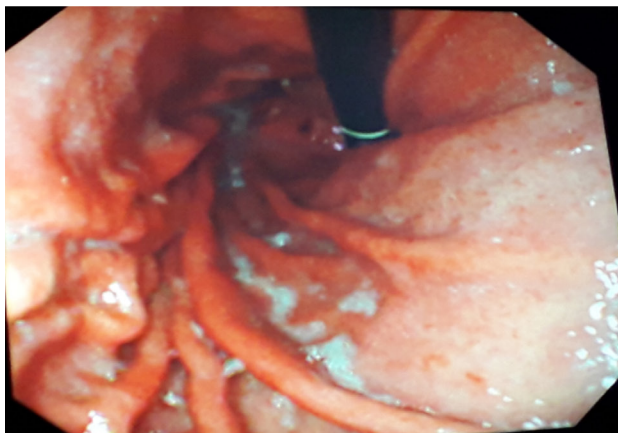
Figure 2: Contrast-enhanced Axial CT scan Shows Mottled appearance peripheral hypodensity in the liver parenchyma(yellow arrow). Hepatic veins do not opacity (blue arrow). Mildly enlarged caudate lobes with normal enhancement (red arrow). Portal veins opacity normally (thick black arrow head).



Figure 3: Contrast-enhanced Axial and Coronal CT scans showed no enhancement branch of hepatic veins draining IVC (Red arrow) corresponding to occlusion due to thrombosis (Black arrow).



Figure 4: Upper gastrointestinal endoscopy showed small oesophageal and gastric varices.



Discussion

Budd-Chiari syndrome is a rare disease of the liver, with its nature is heterogenous that characterised by occlusion of hepatic venous¹. Reporting such as this case in Somalia is difficult in our context due to misdiagnosis or a low index of suspicion. BCS is usually diagnosed as clinically and radiologically. We report the first case in the country that had abdominal pain, ascites and with the presence of hepatomegaly with imaging studies revealed the presence hepatic venous thrombosis so the diagnosis was most suggestive BCS.

Clinically, the BCS most often appears with a triad features that are abdominal pain, Hepatomegaly and ascites, while laboratory analysis of BCS are included liver function test such transaminase, bilirubin and alkaline phosphatase, Gama glutamyl transferase, albumin, coagulation test and platelet count. The ultrasound is first useful choice investigation while the Computer tomography and magnetic resonance imaging studies are the second choice of the investigation, so the combination of these imaging modalities, clinical information and laboratory

should suffice to diagnosis of BCS in the clinical practices⁶. Portal veins opacity normally with exclusion of the presence of a tumour, abscess or a cyst that originated outside the veins that may result of obstruction to the hepatic outflow via compression or invasion which is secondary BCS and the finding of gastrointestinal endoscopy that showed small oesophageal varices in this would suggest that our patient had a primary type BCS of a subacute form.

The Treatment of BCS can be divided into medical, radiological and surgical procedures; the goals of treatment are to prevent thrombus propagation, restore the flow in clogged veins, decongest the liver, and treat and prevent complications related to fluid retention, malnutrition and portal hypertension⁶.

Conclusion

BCS is a rare disorder in our clinical practice that requires accurate diagnosis and immediate therapy. Diagnosing such a rare case requires high suspicion index and highly skilled radiologists, especially in low resource countries

like Somalia, where communicable disease dominates. Early detection of symptoms helps in early diagnosis and management of the disease.

Ethical Approval

In our institution, Ethical approval is waived from case reports.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Provenance and peer review

Not commissioned, externally peer-reviewed

Conflict of Interest

Authors declare no conflict of interest.

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None

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