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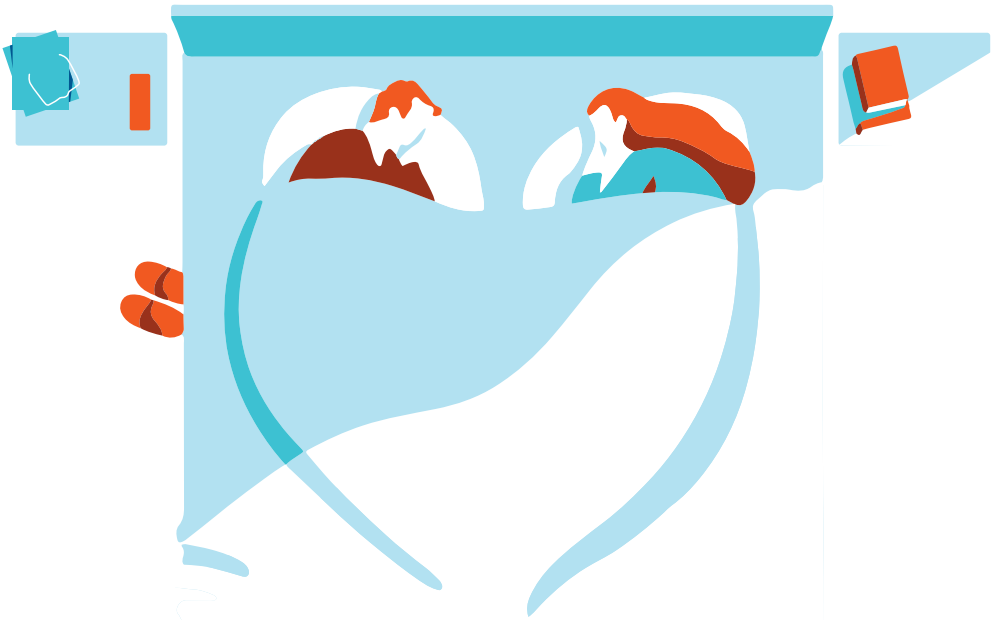

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EDITORIAL

Alimentación saludable, medioambiente y sostenibilidad

Healthy eating, environment and sustainability

Dr. Giuseppe Russolillo Femenías

Presidente de la Internarional Confederation of Dietetic Associations. Escuela Universitaria ADEMA

La tendencia actual del cuidado de la salud, según la Organización Mundial de la Salud (OMS), se enfoca hacia el alcance del mayor potencial posible de salud a lo largo de la vida de la persona, dando prioridad a la prevención y promoción frente a la curación. Es por ello por lo que la meta principal de las políticas de salud debería encaminarse a disminuir la incidencia de las principales enfermedades y lesiones. Una importante estrategia para alcanzar dicha meta consiste en focalizar los esfuerzos en la mejora del sistema de Atención Primaria de Salud.

Actualmente, la etiología de muchas enfermedades crónicas está más clara y las intervenciones para disminuir el riesgo de padecerlas ha mostrado su eficacia. Así, en la mayoría de los países, los Sistemas Nacionales de Salud incluyen la figura del dietista-nutricionista como un profesional a cargo del manejo de los aspectos dietético-nutricionales de la población, para promover la salud y prevenir las enfermedades.

Asimismo, existe suficiente evidencia epidemiológica para poder determinar, por un lado, los factores de riesgo de las enfermedades más prevalentes, y por otro lado los componentes dietéticos que incrementan la probabilidad de padecer dichas enfermedades. Según la Organización Mundial de la Salud (OMS), las enfermedades más comunes relacionadas con la nutrición, tanto en países desarrollados como en países en vías de desarrollo, son la obesidad, la diabetes, las enfermedades cardiovasculares, el cáncer, la osteoporosis y las enfermedades dentales.

Los diez riesgos que más perjudican a la salud, según la OMS son:

1. Las prácticas sexuales sin protección,
2. la hipertensión,
3. el tabaco,
4. el alcohol,
5. las deficiencias en agua y los saneamientos,
6. el colesterol elevado,
7. los humos de combustibles sólidos en ambientes interiores,
8. la deficiencia de hierro,
9. la obesidad y
10. el sobrepeso.

Estos factores causan el 40% de los 56 millones de fallecimientos que se registran cada año en el mundo, según la OMS. De las diez causas declaradas por la OMS, seis están directamente relacionadas con la nutrición.

Según la OMS, las enfermedades más comunes relacionadas con la nutrición, tanto en países desarrollados como en países en vías de desarrollo, son: la obesidad, la diabetes, las enfermedades cardiovasculares, el cáncer, la osteoporosis y las enfermedades dentales.

Además, la OMS advierte que un bajo consumo de frutas y hortalizas causa más de 2,7 millones de muertes al año, un 30% de las cardiopatías isquémicas, un 20% de los cánceres gastrointestinales y un 10% de las enfermedades cerebrovasculares.

La enfermedad cardiovascular, el cáncer y la diabetes tipo 2, claramente relacionadas con la alimentación, son responsables de 2 de cada 3 muertes en Estados Unidos, según las asociaciones americanas del cáncer, de la diabetes y del corazón.

En Europa, la mejora en la dieta puede ser el mayor factor modificable para reducir las enfermedades en economías desarrolladas, así como las enfermedades cardiovasculares y los cánceres son causantes de aproximadamente dos tercios de todas las muertes.

En España, cerca del 87,4% de todas las muertes están causadas por enfermedades no trasmisibles. Entre las principales 5 enfermedades no trasmisibles, 3 de ellas están directamente relacionadas con la alimentación: enfermedades cardiovasculares, cáncer, enfermedades respiratorias, diabetes y otras.

Por consiguiente, la alimentación es uno de los factores más determinantes de la promoción de la salud y de la prevención de gran parte de las enfermedades más prevalentes.

En los últimos años se ha puesto de manifiesto la necesidad de hacer compatible una alimentación sana con una alimentación respetuosa con el medio ambiente. De hecho, el cuidado de la salud cada vez se vincula más al cuidado del planeta. Muchos ambientalistas sostienen que si el planeta enferma, quienes habitan en él también.

En 2019, el programa de las Naciones Unidas hizo una llamada para revertir el cambio climático, describiendo las dietas basadas en plantas como una gran oportunidad para mitigar y adaptarse al cambio climático, e incluyendo una recomendación de política para reducir el consumo de carne.

La *Food and Agriculture Organization of the United Nations* publicó en 2019 los principios que deberían guiar la llamada "Dieta Saludable y Sostenible". En este documento se enfatiza que la transición nutricional que viven los países industrializados, determinados en gran medida, por afluencia de población a zonas urbanizadas, aumenta la demanda de carnes, pescados, lácteos, huevos, azúcares y grasas, y con ellos, la presión sobre el medioambiente.

Diversos estudios basados en modelos teóricos sugirieron que las dietas más sostenibles estarían basadas en plantas con reducciones en el consumo de carne, en particular, la de rumiantes. Además, uno de ellos concluyó que proporcionar consejos más claros sobre la limitación del consumo de alimentos de origen animal, en particular carne de vacuno y lácteos, tendría el mayor potencial sobre la sostenibilidad de las guías alimentarias.

Estas estimaciones teóricas son acordes con los resultados de una revisión robusta que incluyó 23 estudios y que fue publicada en 2016, que sugirió que había pruebas consistentes para señalar que un patrón dietético más bajo en energía total, rico en alimentos de origen vegetal y bajo en alimentos de origen animal, especialmente bajo en carnes rojas, se asociaría con un menor impacto en el medio ambiente.

Por otra parte, y como apuntan algunos primeros estudios, en importante destacar que el consumo de carnes producidas por métodos extensivos y tradicionales, basados en economía circular, juega un papel relevante en el mantenimiento de la biodiversidad en zonas, muchas veces no cultivables, y que se asocia con la economía de las familias, la resiliencia y el tejido productivo y social de los entornos rurales.

En la actualidad, los datos científicos disponibles parecen apuntar de forma unánime a que una reducción del consumo de carnes, en particular de carnes rojas y procesadas, podría tener un impacto positivo para el planeta.

¿Cómo implementar estas recomendaciones en mi estilo de vida y de alimentación?

Según la Academia Española de Nutrición y Dietética, a falta en nuestro país de unas guías de alimentación saludable y sostenibles basadas en la evidencia y dirigidas a la población española, se recomienda:

1. Aumentar el consumo de alimentos de origen vegetal como frutas y hortalizas, legumbres, cereales de grano entero y sus derivados como el pan, y el de frutos secos y semillas oleaginosas en detrimento del consumo de alimentos de origen animal como carnes, pescados, huevos y quesos, y de forma particular, reducir el consumo de carnes rojas y procesadas.
2. Si se eligen alimentos de origen animal dar preferencia al consumo de huevos, quesos, pescados y carnes de aves y conejo con una frecuencia de consumo semanal de 2-3 veces de carnes, y limitar el de carnes rojas (ternera, cordero, cerdo, caballo) y de carnes procesadas (salazón, curado, fermentación o ahumado) a no más de 3 veces al mes.
4. Consumir al menos 5 raciones entre frutas y hortalizas al día.
5. Consumir al menos 3 ó 4 raciones de legumbres a la semana.
6. Elegir cereales integrales procedentes de grano entero.
7. Evitar especialmente los productos alimenticios ultraprocesados, de elevado contenido calórico, ricos en azúcares añadidos, sal y grasas saturadas como son la comida rápida, alimentos precocinados, dulces, pastelería, confitería, bollería industrial, snacks de aperitivo fritos y salados, salsas comerciales y bebidas refrescantes con azúcar o edulcoradas.
8. Llevar una vida mucho más activa y reducir el sedentarismo llevando a cabo actividades de ejercicio físico con mayor frecuencia y de intensidad moderada, en coherencia con cada una de las etapas de la vida donde se puede encontrar la población (infancia, adolescencia, adultos y mayores).
9. Apostar por el consumo de alimentos del entorno geográfico cercano y de temporada, contribuyendo así a promover la economía local, y a ser posible producidos de forma respetuosa con el medio ambiente y protegiendo el bienestar animal, particularmente en el caso de los huevos, quesos, pescados y carnes, eligiendo aquellos que se hayan producido de forma sostenible con métodos extensivos y tradicionales.

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ORIGINAL

Virulence characters and oligotyping of *Pseudomonas aeruginosa* isolated from meat and assessment of the antimicrobial effects of *Zataria multiflora* against isolates

Caracteres de virulencia y oligotípicos de Pseudomonas aeruginosa aislada de la carne y evaluación de los efectos antimicrobianos de Zataria multiflora contra los aislados

Mohammadhosseini Sakhaei Shahreza[1], Nastaran Ghaderi Dehkordi[1], Maadh Fawzi Nassar[2], Raed Muslim Muhibes Al-Saedi[3]

1. Doctor Veterinary Medicine, Faculty of Veterinary Medicine, Shahrekord Branch, Islamic Azad University, Shahrekord, Iran
2. Department of Chemistry, Faculty of Science, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia
3. Lecturer, Ph.D Organic Chemistry, Department of Biochemistry, Medical College, Missan University, Iraq

Corresponding author
Raed Muslim Muhibes Al-Saedi
E-mail: Raed_muslim7@gmail.com

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Abstract

Background: *Pseudomonas aeruginosa* is considered opportunistic pathogen responsible for some cases of food spoilage and probable foodborne diseases. The present survey was done to assess the prevalence, virulence characters, and oligotyping of *P. aeruginosa* strains isolated from meat samples and evaluate the antimicrobial effects of *Zataria multiflora* against isolates.
Methods: Two-hundred and seventy raw meat samples were collected and presence of *P. aeruginosa* was assessed using the culture. Isolates were subjected to sequencing and oligotyping and also PCR procedure to obtained the virulence characters. *Z. multiflora* aerial parts were used to prepare essential oil. Gas chromatography was used to determine chemical components. Disk diffusion was used to assess the antimicrobial effects of *Z. multiflora*. Minimum Inhibitory Concentration and Minimum Bacterial Concentration of *Z. multiflora* was also assessed.
Results: Twelve out of 270 (4.44%) meat samples were contaminated with *P. aeruginosa*. Raw bovine meat had the highest *P. aeruginosa* prevalence (7.14%). ExoS (41.66%) was the most commonly detected virulence factors, while *algD* was the rarest (8.33%). Four oligotypes were detected in *P. aeruginosa* isolates. Oligo_7 (33.33%) had the highest distribution. Thymol (22.75%), carvacrol (15.81%), caryophyllene oxide (8.84%), and a-Pinene (7.73%) were the most commonly identified phytochemical compounds in the *Z. multiflora* essential oil. The dimeter of the growth inhibition zone of *P. aeruginosa* isolates treated with *Z. multiflora* (1%) essential oil was statistically higher than penicillin, gentamicin, ampicillin, and tetracycline ($P< 0.05$) and insignificantly lower than azithromycin ($P> 0.05$). The MIC and MBC of *P. aeruginosa* isolates treated with *Z. multiflora* essential oil were 1 and 2 mg/ml, respectively.
Conclusion: Role of meat as a reservoir for transmission of P. aeruginosa strains was determined in this survey. According to the high antimicrobial effects of *Z. multiflora* and its edible nature, its application as an edible film to extend the shelf-life of different meat-based products should consider in further researches.

Key words: *Pseudomonas aeruginosa*, virulence factors, oligotypes, raw meat, *Zataria multiflora*, antimicrobial effects.

Resumen

Antecedentes: *Pseudomonas aeruginosa* se considera un patógeno oportunista responsable de algunos casos de deterioro de los alimentos y de probables enfermedades de transmisión alimentaria. El presente estudio se realizó para evaluar la prevalencia, los caracteres de virulencia y la oligotípica de las cepas de *P. aeruginosa* aisladas de muestras de carne y evaluar los efectos antimicrobianos de *Zataria multiflora* contra los aislados.
Métodos: Se recogieron doscientas setenta muestras de carne cruda y se evaluó la presencia de *P. aeruginosa* mediante el cultivo. Los aislados fueron sometidos a secuenciación y oligotípica y también a un procedimiento de PCR para obtener los caracteres de virulencia. Las partes aéreas de *Z. multiflora* se utilizaron para preparar el aceite esencial. Se utilizó la cromatografía de gases para determinar los componentes químicos. Se utilizó la difusión en disco para evaluar los efectos antimicrobianos de *Z. multiflora*. También se evaluó la concentración inhibitoria mínima y la concentración bacteriana mínima de *Z. multiflora*.
Resultados: Doce de 270 (4,44%) muestras de carne estaban contaminadas con *P. aeruginosa*. La carne bovina cruda presentó la mayor prevalencia de *P. aeruginosa* (7,14%). ExoS (41,66%) fue el factor de virulencia más comúnmente detectado, mientras que algD fue el más raro (8,33%). Se detectaron cuatro oligotipos en los aislados de *P. aeruginosa*. El oligo_7 (33,33%) tuvo la mayor distribución. El timol (22,75%), el carvacrol (15,81%), el óxido de cariofileno (8,84%) y el a-pineno (7,73%) fueron los compuestos fitoquímicos más identificados en el aceite esencial de *Z. multiflora*. El diámetro de la zona de inhibición del crecimiento de los aislados de *P. aeruginosa* tratados con el aceite esencial de *Z. multiflora* (1%) fue estadísticamente superior al de la penicilina, la gentamicina, la ampicilina y la tetraciclina ($P< 0,05$) e insignificantemente inferior al de la azitromicina ($P> 0,05$). La CIM y la CBM de los aislados de *P. aeruginosa* tratados con aceite esencial de *Z. multiflora* fueron de 1 y 2 mg/ml, respectivamente.
Conclusiones: En este estudio se determinó el papel de la carne como reservorio para la transmisión de cepas de *P. aeruginosa*. Debido a los elevados efectos antimicrobianos de *Z. multiflora* y a su naturaleza comestible, su aplicación como película comestible para prolongar la vida útil de diferentes productos cárnicos debería considerarse en futuras investigaciones.

Palabras clave: *Pseudomonas aeruginosa*, factores de virulencia, oligotipos, carne cruda, *Zataria multiflora*, efectos antimicrobianos.

Introduction

Pseudomonas aeruginosa (*P. aeruginosa*) is an unscrupulous bacterium related to both humans and animals. The bacterium is a causative agents in different infectious diseases, such as respiratory tract, urinary tract, gastric tract, burn and wound, bone and joint, and soft tissue infections, and bacteremia in hospitalized patients[1].

The bacterium has some responsibilities in the procedure of food spoilage and contamination, especially in meat samples. This procedure caused several bad effects on flavor, odor, and color of meat and derived products. In keeping with this, there is no available data about the foodborne aspects of the *P. aeruginosa*. However, consumption of food contained the bacterium may be result in gastrointestinal disorders[2].

P. aeruginosa has so many virulence factors with important responsibilities in the pathogenesis of infections. Among them, exoenzymes (*exoS*), elastase gene (*las*), and alginate-encoded genes (*algD* and *algU*) are considered important factors in adhesion and invasion[3].

Taxonomic classification of *P. aeruginosa* strains has so many advantageous in epidemiological studies. Oligotyping, which decays a given taxon, or 97% operational taxonomic units (OUT), into high-resolution units ('oligotypes') by only using the most information-rich nucleotide positions identified by Shannon entropy calculations is one of the best techniques for taxonomic classification[4]. Application of this technique as an analytical tool for studies of microbial ecology have provided the possibility for in-depth researches of microbial diversity in food and food-related environments[5].

P. aeruginosa has an emergence of antibiotic resistance[6]. Thus, scientists attracted to the synthesis of novel antimicrobial agents based on plant materials and essential oils. *Zataria multiflora* (*Z. multiflora*) is a medicinal plant belonging to the Laminaceae family. It grows in Iran, Pakistan and Afghanistan and is known as Shirazi Avishan. This plant is known as potential edible antimicrobial agents. It application as an edible film for improve the shelf-life of different types of foods has been reported previously[7].

Rendering the high importance of *P. aeruginosa* the present survey was done to assess the virulence characters and oligotyping of *P. aeruginosa* strains isolated from meat and evaluation of the antimicrobial effects of *Z. multiflora* against isolates.

Materials and methods

Plant materials

Aerial parts of the *Z. multiflora* were collected from Isfahan province. Plants were confirmed by an expert professor of the field of medicinal plants. The aerial parts of plant were dried in shade at room temperature. They were then ground. The essential oil was obtained by hydro-distilling of ground material with boiling water up to 4 h utilizing a Clevenger-type apparatus. The extracted oils were dried over anhydrous sodium sulfate followed by filtering and stored at 4ºC in sealed glass vials for further use.

Gas Chromatography-Mass Spectrometry (GC-MS)

The GC/MS analyses were done using Hewlett–Packard 6890N gas chromatograph equipped with a column HP-5MS (30 m length, 0.25 mm diameter., and 0.25 lm film thickness) coupled with a Hewlett–Packard 5973N mass spectrometer. The column temperature was programmed at 50ºC, holding for 6 min, with 3ºC increases per min to reach to a final the temperature of 240ºC, followed by a temperature enhancement of 15ºC per min up to 300ºC and holding for 3 min. Injector port temperature was 290ºC and helium used as carrier gas at a flow rate 1.5 ml/min. Ionization voltage of mass spectrometer in the EI-mode was equal to 70 eV and ionization source temperature was 250ºC. The individual compounds were identified and confirmed thereafter of Kovats or retention indices calculation of components relative to their retention times of a series of n-alkanes and comparing them and their mass spectra with those of authentic samples or with available library data of the GC/MS system (WILEY 2001 data software) and Adams libraries spectra[8].

Meat samples

A total of 270 raw bovine (n= 70), ovine (n= 70), caprine (n= 50), and camel (n= 80) meat samples were collected from Isfahan province (25 g each in a sterile plastic bag). Samples were transferred to laboratory in 4ºC. For unique conditions, the thigh muscle was used for sampling.

P. aeruginosa isolation and identification

Twenty-five grams of meat samples were put in sterile Stomacher bags contained 225 ml peptone water (Oxoid, Basingstoke, UK). The bags underwent maceration within the stomacher (Seward 400 circulator) for 4 min at 260 beats per min. A total of 100 µl homogenate samples were placed on CN Selective Agar (Oxoid SR 102E, UK) supplemented with Pseudomonas Agar base (Oxoid, UK). Media were incubated at 37ºC for 24 h in aerobic conditions. Pseudomonas were identified by microscopic morphology, catalase, oxidase and urease activity, casein and starch hydrolysis, citrate and indole utilization, and Methyl Red-Voges Proskauer and gelatin liquefaction tests, using standard microbial techniques. Additionally, API 20NE strips (BioMeriouxVitek, Inc., MO, USA) system was used to identify the *P. aeruginosa*.

DNA extraction and PCR examination of virulence factors

DNA was extracted from the bacterial colonies using the cinnamene DNA extraction kit (Cinnagen, Iran)

Table I: PCR used to detect virulence factors[17,18].

Targeted genes	Primer sequence (5'-3')	PCR product (bp)	PCR programs	PCR volume (50µL)
algD	F:AAGGCGGAAATGCCATCTCC R: AGGGAAGTTCCGGGCGTTTG	275	**1 cycle:** 2 min: 95^{0C} **30 cycles:** 30s: 94^{0C} 30s: 58^{0C} 60s: 72^{0C} **1 cycle:** 7 min: 72^{0C}	10X PCR buffer: 5 µL $Mgcl_2$: 1.5 mM dNTP: 200 µM Primer F: 0.5 µM Primer R: 0.5 µM Taq DNA polymerase: 1.25 U DNA: 2.5 µL
algU	F: CGCGAACCGCACCATCGCTC R: GCCGCACGTCACGAGC	410		
lasB	F: ACACAATACATATCAACTTCGC R: AGTGTGTTTAGAATGGTGATC	284	**1 cycle**: 3 min: 94^{0C} **30 cycles:** 30 s: 94^{0C} 60 s: 55^{0C} 90 s: 72^{0C} **1 cycle:** 5 min: 72^{0C}	10X PCR buffer: 5 µL $Mgcl_2$: 1.5 mM dNTP: 200 µM Primer F: 0.5 µM Primer R: 0.5 µM Taq DNA polymerase: 1.25 U DNA: 2.5 µL
exoS	F: GTGTGCTTTATGCCATGAG R: GGTTTCCTTTTCCAGGTC			

according to method described by instruction[9,10]. Quality and quantity of extracted DNA were then checked[11-13]. **Table I** shows the PCR conditions met to detect virulence factors. A thermocycler (Eppendorf, Germany) was used in all PCR reactions. Electrophoresis was done according to previous researches[14-16].

Oligotypes detection

At first sequencing of isolates was done according to method described by Stellato et al. (2017)[19]. For oligotyping, 308 and 842 quality-controlled V1-V3 reads from bacteria isolates were used. Raw reads were quality-filtered as follows: reads were trimmed at the first ambiguous base or when the average quality score dropped below 25 within a 50-bp-long window, and reads shorter than 500 bp and with >1 primer mismatch were discarded. The PyNAST algorithm aligned the high-quality 454 reads against the GreenGenes multiple sequence alignment template and alignment was further trimmed to equal length by using the o-smart-trim script included in the oligotyping package v. 1.0. Global Assignment of Sequence Taxonomy (GAST) algorithm was used to identify "Pseudomonas." Following the initial entropy analysis oligotyping was performed using version 2.1 of the oligotyping pipeline1 using a total of 14 positions with high entropy, chosen to compute the oligotypes (-C option). After removal of oligotypes that did not meet these criteria, the analysis retained 299,055 reads (88.765% of the original reads). Oligotyping analysis identified 15 Pseudomonas oligotypes, representative sequences of which had at least one perfect match (100% sequence identity over 100% of query alignment) to rRNA gene entries in NCBI non-redundant (nr) database.

Antimicrobial effects of Z. multiflora

The simple disk diffusion method was used to assess the antimicrobial effects of *Z. multiflora* against *P. aeruginosa* isolates. For this purpose, isolated bacteria were cultured on Muller Hinton agar media. A total of 1000 µl of 1% *Z. multiflora* essential oil were poured into the blank disk and located at the surface of each media. For comparison, tetracycline (30 µg/disk), penicillin (10 µg/disk), gentamicin (10 µg/disk), azithromycin (15 µg/disk), and ampicillin (10 µg/disk) (Oxoid, UK) antibiotic disks were accompanies. All guidelines were performed according to the Clinical and laboratory standard institute (CLSI)[20-22]. The Minimum Inhibitory Concentration (MIC) and Minimum Bacterial Concentration (MBC) of *Z. multiflora* essential oil were also assessed. For this purpose, 0.5, 1, 2, and 4 mg/ml concentrations of *Z. multiflora* essential oil were prepared and the MIC and MBC values were determined using the previously described method[23].

Data analysis

Data analysis was performed by SPSS Statistics 21.0 (SPSS Inc., Chicago, IL, USA). Chi-square and Fisher's exact two-tailed tests were performed to assess any significant relationship[24,25]. Besides, p-value < 0.05 was considered statistically significant[26,27].

Results

P. aeruginosa distribution

Table II shows the *P. aeruginosa* distribution amongst examined meat samples. Total contamination rate of meat samples with the *P. aeruginosa* was 4.44% (12/270). Raw bovine meat harbored the highest prevalence of contamination with *P. aeruginosa* (7.14%), while raw camel meat harbored the lowest (1.25%). Statistically significant differences were observed between type of samples and *P. aeruginosa* distribution (P< 0.05).

Table II: *P. aeruginosa* distribution amongst examined meat samples.

Meat samples	N. collected	N. positive for P. aeruginosa (%)
Bovine	70	5 (7.14)
Ovine	70	3 (4.28)
Caprine	50	3 (6)
Camel	80	1 (1.25)
Total	270	12 (4.44)

P. aeruginosa virulence characters

Figure 1 shows the PCR electrophoresis of the virulence factors of *P. aeruginosa* isolates.

Figure 1: PCR gel electrophoresis of the virulence factors.

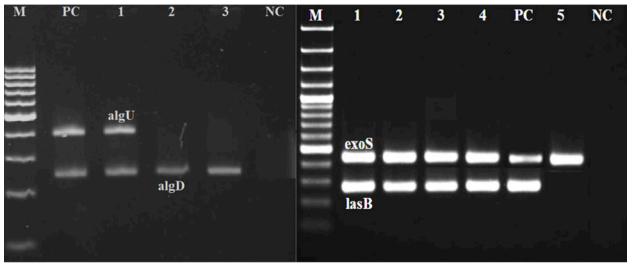


Table III shows the virulence factors distribution amongst the *P. aeruginosa* isolates of meat samples. *ExoS* (41.66%) was the most commonly detected virulence factors, while *algD* was the rarest (8.33%). *P. aeruginosa* isolates of raw bovine meat harbored the highest and most diverse profile of virulence factors. Statistically significant differences were observed between type of samples and *P. aeruginosa* virulence factors distribution ($P< 0.05$).

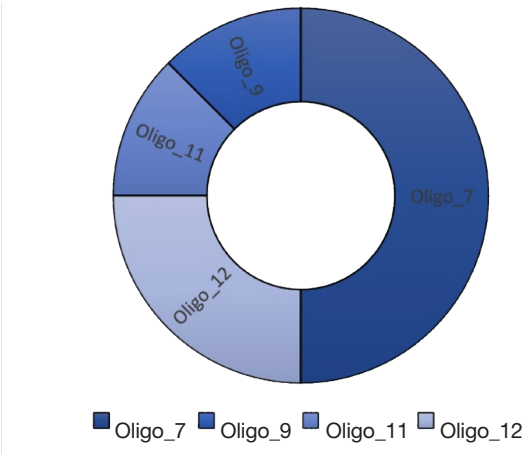
Table III: Virulence factors distribution amongst the *P. aeruginosa* isolates.

Meat	N. positive	N. isolates harbored each virulence factors samples (%)			
		algD	***algU***	***lasB***	***exoS***
Bovine	5	2 (40)	1 (20)	2 (40)	2 (40)
Ovine	3	1 (33.33)	-	1 (33.33)	1 (33.33)
Caprine	3	-	-	1 (33.33)	1 (33.33)
Camel	1	-	-	-	1 (100)
Total	12	3 (25)	1 (8.33)	4 (33.33)	5 (41.66)

P. aeruginosa oligotypes

Figure 2 shows the oligotypes abundance amongst the *P. aeruginosa* strains isolated from different meat samples. Four different oligotypes were identified amongst the isolates. Our findings showed that the Oligo_7, Oligo_9, Oligo_11, and Oligo_12 types were detected in 33.33%, 8.33%, 8.33%, and 16.66% of isolates.

Figure 2: Oligotypes abundance amongst the *P. aeruginosa* strains isolated from different meat samples.



Z. multiflora phytochemical analysis

Table IV shows the GC-MS analysis of the phytochemical compounds of the *Z. multiflora* essential oil. A total of 13 phytochemical compounds were detected in *Z. multiflora* essential oil (93.81%). Thymol (22.75%), carvacrol (15.81%), caryophyllene oxide (8.84%), a-Pinene (7.73%), a-Terpineol (7.19%), and linalool (7.09%) were the most commonly identified phytochemical compounds in the *Z. multiflora* essential oil.

Table IV: GC-MS analysis of the phytochemical compounds of the *Z. multiflora* essential oil.

No	Chemical compounds	Frequency (%)
1	p-Cymene	4.39
2	Cis-Sabinene hydrate	1.12
3	Borneol	2.71
4	Thymol	22.75
5	Carvacrol	15.81
6	a-Pinene	7.73
7	b-Myrcene	1.92
8	a-Phellandrene	5.37
9	a-Terpineol	7.19
10	Eugenol	2.28
11	Spathlenol	6.61
12	Linalool	7.09
13	Caryophyllene oxide	8.84
	Total	93.81

Antimicrobial effects of Z. multiflora

Table V shows the growth inhibition zone of *P. aeruginosa* isolates. The diameter of the growth inhibition zones had the ranges between 14.55±1.17 to 5.92±0.40 mm. The dimeter of the growth inhibition zone of *P. aeruginosa* isolates treated with *Z. multiflora* (1%) essential oil was 13.00±1.08 mm. The dimeter of the growth inhibition zone of *P. aeruginosa* isolates treated with *Z. multiflora* (1%) essential oil was statistically higher than penicillin, gentamicin, ampicillin, and tetracycline ($P< 0.05$) and insignificantly lower than azithromycin ($P> 0.05$).

Table V: Growth inhibition zone of *P. aeruginosa* isolates.

Tested antimicrobial agents	Diameter of the growth inhibition zone of ***P. aeruginosa*** isolates (mm)
Z. multiflora (1%)	13.00±1.08^{a*}
Tetracycline	6.28±0.41^{c}
Penicillin	6.88±0.27^{c}
Gentamicin	5.92±0.40^{c}
Azithromycin	14.55±1.17^{a}
Ampicillin	8.33±0.71^{b}

Table VI shows the MIC and MBC of *P. aeruginosa* isolates treated with *Z. multiflora* (1%) essential oil. The MIC and MBC of *P. aeruginosa* isolates treated with *Z. multiflora* essential oil were 1 and 2 mg/ml, respectively.

Table VI: MIC values of *Z. multiflora* against *P. aeruginosa* isolates.

Treatment	MIC (mg/ml)	MBC (mg/ml)
Z. multiflora	1	2

Discussion

Scarce data are available about the isolation of *P. aeruginosa* from meat samples. In this survey, total prevalence of *P. aeruginosa* amongst the examined raw bovine, ovine, caprine and camel meat samples was 7.14%, 4.28%, 6% and 1.25%. from surveys conducted in this field previously, majority of them assess the *P. aeruginosa* distribution amongst fish and meat products[28,29]. Previous survey in west Africa[30] showed that the prevalence of *P. aeruginosa* amongst the bovine meat samples was 53.04%. in previous researches presence of *P. aeruginosa* strains was reported from chicken meat (46.70%)[31], camel meat (80.00%)[32], and retail meat (3.00%)[33]. Differences in prevalence maybe due to differences in the hygienic conditions of slaughterhouses in different countries.

P. aeruginosa isolates harbored several virulence factors, including *exoS, lasB, algD*, and *algU*. It may show their virulent nature. These genes are mainly responsible for the adhesion and invasion of bacteria into the host cells. In keeping with this, consuming meat containing virulent *P. aeruginosa* strains may cause severe food-borne infection. However, there were no previously published data about the distribution of *P. aeruginosa* virulence factors amongst food samples. Oligotyping of strains (Oligo_7, Oligo_9, Oligo_11, and Oligo_12) showed similar taxonomy of our isolates with those of Pseudomonas sp. isolated from meat, dairy samples and environment[19]. This finding may show their similar source of contamination of isolated *P. aeruginosa* strains.

Z. multiflora medicinal plant had the boost antimicrobial effects against *P. aeruginosa* strains. This matter maybe partly due to the antimicrobial compounds found in the pants, such as thymol (22.75%), carvacrol (15.81%), caryophyllene oxide (8.84%), a-Pinene (7.73%), a-Terpineol (7.19%), and linalool (7.09%). All of these phytochemical components were found in other surveys as antimicrobial agents of the *Z. multiflora* essential oil[34,35]. As showed the *Z. multiflora* had higher antimicrobial effects against *P. aeruginosa* strains than other antimicrobial agents (except vancomycin). In the authors opinions, its antimicrobial effects should be higher that those reported in this study. It is because of the hard and strict lipopolysaccharide wall of the *P. aeruginosa* strains as a Gram-negative bacteria.

Conclusion

Findings of this paper showed that raw meat may consider as a reservoir of virulent and resistant *P. aeruginosa*. Additionally, isolates were mainly susceptible toward *Z. multiflora* essential oil. This matter may pose the application of *Z. multiflora* essential oil as an edible antimicrobial compound to extend the shelf life of foods, especially meat samples and derived products in the food industry. Role of food as a vector for transmission of *P. aeruginosa* should consider in further studies.

Conflict of interest

Authors do not have any conflict of interest to declare.

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ORIGINAL

Efectos del ejercicio y condición física sobre la atención en población escolar juvenil: una prueba piloto

Effects of exercise and physical condition on attention in a young school population: a pilot test

Antoni Nicolau Miralles[1], Pablo Nieto Alfonso[2], Bartolomé Pizá-Mir[1]

1. i-DEA. Investigación didáctica y Estudios curriculares avanzados. Universidad Pontificia Comillas. España
2. Hospital Son Llàtzer. IB-Salut. Servei de Salut de les Illes Balears. España

Corresponding author
Bartolomé Pizà-Mir
E-mail: bpiza@comillas.edu

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Resumen

Introducción: El TDAH es un trastorno sobre la atención que puede relacionarse con el rendimiento físico y la actividad física.
Material y métodos: Se presenta una evaluación antropométrica y de condición física básica y comparándola con la prueba del Trail Marking Test para evaluar la capacidad atencional, y evaluar si el ejercicio físico contribuye a la mejora de las capacidades atencionales.
Resultados: Existen diferencias significativas y más acentuadas en la mejora de variables atencionales en aquellos sujetos con sobrepeso y TDAH.
Conclusiones: El ejercicio físico, incluso a baja intensidad produce una mejora atencional.

Palabras clave: Atención, condición física, sobrepeso, TDAH.

Abstract

Introduction: ADHD is an attention disorder that can be related to physical performance and physical activity.
Material and methods: An anthropometric and basic physical condition assessment is presented, comparing it with the Trail Marking Test to assess attentional capacity, and to assess whether physical exercise contributes to the improvement of attentional capacities.
Results: There are significant and more accentuated differences in the improvement of attentional variables in those subjects with overweight and ADHD.
Conclusions: Physical exercise, even at low intensity, produces an attentional improvement.

Key words: ADHD, Attention, overweight, physical condition.

Introducción

El Trastorno por Déficit de Atención e Hiperactividad (TDAH) se define como un trastorno neurobiológico o trastorno del neurodesarrollo en el que se ven implicados diversos genes responsables de la transmisión de serotonina y del control o regulación de la norepinefrina y de la dopamina[1]. Suele presentarse en la infancia y no solamente afecta a la persona que lo padece, sino también a su entorno[2].

Entre los síntomas más comunes del TDAH encontramos la falta de capacidad atencional y la hiperactividad, sin embargo, otros autores agregan otras manifestaciones como trastornos de la conducta, insomnio[3], agresividad, impulsividad o falta de autocontrol, ansiedad o depresión, escasa coordinación motriz, dificultad de aprendizaje y dificultad a la hora de respetar las reglas[4,5].

Autores como Putnam y Copans6 afirman que la probabilidad de verse afectados por el TDAH aumenta y está relacionada con una escasa práctica de ejercicio físico. Además, Pontifex et al[7] afirman que, a las personas que sufren dicha patología, el ejercicio físico puede aportarles beneficios muy positivos en su comportamiento, en su función neurocognitiva y, por lo tanto, en su desarrollo, progreso y vida académica. McKune, Pautz y Lombard[8] también quisieron realizar un estudio con el objetivo de evaluar la influencia del ejercicio físico en el comportamiento de los alumnos con TDAH. Lo llevaron a cabo dividiendo en dos un grupo de 19 niños y niñas de entre 5 y 13 años, donde uno de ellos fue sometido a un programa de intervención basado en sesiones de 60 minutos de ejercicio físico. Los resultados demostraron una cierta mejoría en el comportamiento del grupo sometido a la intervención físico-deportiva.

El objetivo del estudio es comparar el desempeño en pruebas atencionales con las medidas antropométricas en sujetos con TDAH y sin el trastorno.

Materiales y métodos

El estudio piloto se llevó a cabo con 47 alumnos (53.2% de mujeres y 46.8% varones) de los cuales un 10% tenía un diagnóstico de TDAH.

Los criterios de inclusión fueron

- Pertenecer a población escolar infantil (quinto curso) y primaria (cuarto curso).
- Aceptar participar en el estudio por parte de los representantes legales.

Las pruebas que se llevaron a cabo fueron de tipo antropométrico (ver **tabla I**) así como la prueba del Trail Marking Test (TMT) para valorar la capacidad atencional de los sujetos.

La prueba del TMT consta de dos partes: en la primera, el sujeto debe conectar en orden secuencial los números del 1 al 25; en la segunda parte, los puntos van del 1 al 13 e incluyen letras de la A a la L. Al igual que en la primera parte, el sujeto debe conectar los puntos en orden alternando letras y números, como en 1-A-2-B- 3-C..., en el menor tiempo posible y sin levantar el bolígrafo del papel. La primera parte se utiliza principalmente para examinar la velocidad de procesamiento cognitivo mientras que la segunda parte de la prueba, en la que el sujeto alterna entre números y letras, se utiliza para examinar el funcionamiento ejecutivo[9].

La metodología se basó en una fase de evaluación inicial de la atención (pre-test) y una fase posterior (una semana más tarde) con la misma prueba atencional (post-test). Dicha intervención buscó aumentar la frecuencia cardiaca de los alumnos con juegos aeróbicos y anaeróbicos realizados durante una sesión de educación física con una duración de 20 minutos y evaluar si mejoraba la capacidad atencional de los sujetos.

Análisis estadístico

Se ha llevado a cabo un análisis descriptivo de las frecuencias y distribución de las diferentes variables y entre diferentes grupos (según sexo, presencia/ausencia de TDAH y según IMC), midiendo la media y la desviación típica, así como un análisis de componentes principales entre las variables BAI, tiempos en la prueba de atención (pre-test y post-test) y las pruebas sobre condición física.

El análisis estadístico se realizó con el software XLSTAT.

Resultados y discusión

A continuación se muestran los resultados de los diferentes índices y variables antropométricas (**tabla II**), las variables sobre la condición física (**tabla III**), así como la prueba sobre capacidad atencional (**tabla IV**).

Los resultados muestran que existe una homogeneidad entre ambos sexos, tanto en la condición de normopeso como en aquellos individuos sin TDAH, mientras que los sujetos con sobrepeso y/o TDAH mostraron una variabilidad mayor en cuanto a las pruebas analizadas como se refleja en el análisis de componentes principales de la **figura 1**, en el que se aprecian dos grupos diferenciados, uno homogéneo con los sujetos con normopeso y sin TDAH, mientras que los sujetos con sobrepeso o con TDAH presentan una distribución heterogénea.

Tabla I: Índices antropométricos.

Masa corporal y Altura	Balanza: modelo SECA 700 con divisiones de 50 gramos, con una vara de medir telescópica SECA 220 con división milimétrica y un intervalo de 60-200 cm.
Circunferencia abdominal	Cinta métrica modelo SECA 20, con un intervalo de 1-200 cm y división milimétrica
Índice de Masa Corporal (IMC)	IMC= masa/altura^2
Clínica Universidad de Navarra Body Adiposity Estimator[10]	-44.988 + (0.503 x edad) + (10.689 x sexo) + (3.172 x IMC) - (0.026 x IMC^2) + (0.181 x IMC x sexo) - (0.02 x IMC x edad) - (0.005 x IMC^2 x sexo) + (0.00021 x IMC^2 x edad)
Equation Córdoba for Estimation of Body Fat[11]	-97.102 + 0.123 (edad) + 11.9 (sexo) + 35.959 (LnIMC)
Deurenberg (Fat mass index)[12]	Fat mass %= 1.2 x (IMC) + 0.23 x (edad) - 10.8 x (sexo) - 5.4
Normalized weight-ajusted index (NWAI)[13]	MWAI= (masa/10) - (10 x altura) + 10] weight is expressed in kg and height in meters.
Body Adiposity Index (BAI)[14]	BAI = ((diámetro cintura)/((altura)1.5)-18)
Body roudness index (BRI)[15]	BRI = 364.2-365.5x√1-[(diámetro cintura/(2π)2)/(0.5 x masa)2]
Body Surface Index (BSI)[16] y Body Surface Area (BSA)	BSA = masa^{0,425} x altura^{0,725} x 0,007184 ; BSI = masa/√ BSA

Tabla II: Valores de índices antropométricos.

	IMC	CUN-BAE	ECORE-BF	Deuremberg (FMI)	NWAI	BAI	BSA	BSI
Masculino	18,07±3,55	17,73±7,29	19,37±6,76	18,36±4,26	13,33±0,69	21,2±3,65	1,15±0,11	32,11±5,01
Femenino	17,83±3,08	17,29±6,31	19,03±5,82	18,07±3,69	13,27±0,66	20,63±3,19	1,14±0,11	31,7±4,65
TDAH_Masc	20,51±0,11	22,73±11,94	23,99±10,92	21,28±7,08	13,66±1,3	25,28±5,44	1,18±0,2	34,74±9,17
TDAH_Fem	19,72±0,11	20,98±11,94	22,3±10,92	20,34±7,08	13,5±1,3	22,38±5,44	1,15±0,2	33,49±9,17
NoTDAH_Masc	16,96±0,44	16,58±7,03	18,03±6,78	17,2±4,95	12,62±2,93	19,67±4,76	1,09±0,26	30,32±7,58
NoTDAH_Fem	17,66±0,11	16,95±5,95	18,73±5,51	17,86±3,47	13,24±0,62	20,47±3,07	1,14±0,1	31,53±4,39
Sobrep_Masc	23,23±0,71	28,21±1,3	28,99±1,11	24,54±0,85	14,24±0,21	26,4±1,88	1,27±0,04	38,86±1,26
Sobrep_Fem	22,68±1,28	27,18±2,4	28,1±2,06	23,88±1,54	14,25±0,1	25,06±2,38	1,28±0,02	38,72±0,81
Normop_Masc	16,01±1,38	13,52±3,05	15,52±3,03	15,89±1,65	12,96±0,41	19,11±1,21	1,1±0,08	29,41±2,8
Normop_Fem	16,22±1,13	13,99±2,49	16,01±2,44	16,13±1,36	12,94±0,36	19,16±1,71	1,09±0,08	29,36±2,41

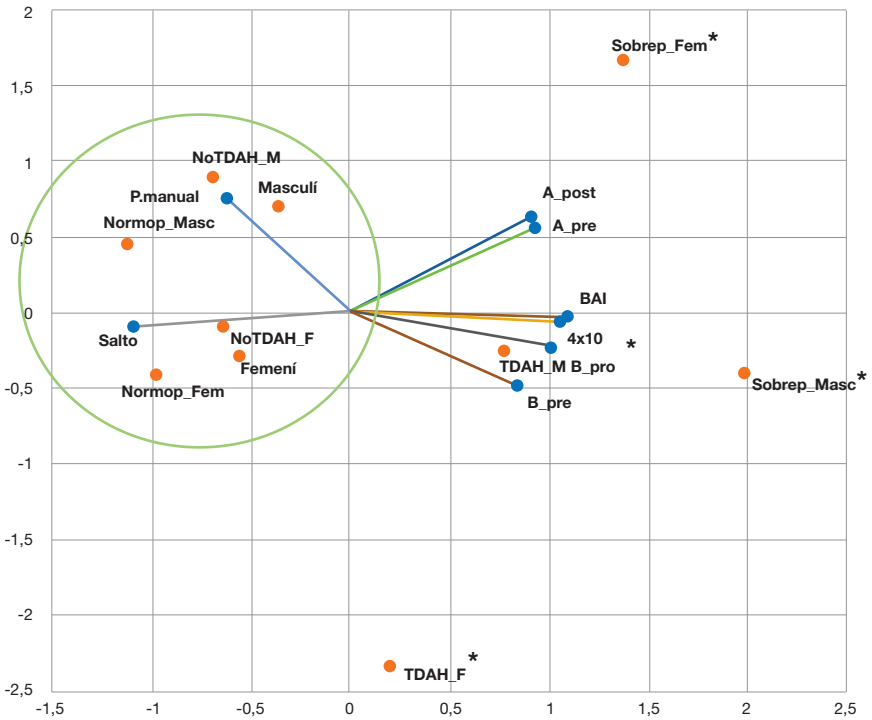
Tabla III: Pruebas de valoración de condición física básica.

	Salto de longitud (m)	Velocidad (4x10) (s)	Fuerza de Prensión manual (N)
Masculino	1,12±0,29	13,22±1,39	14,58±3,79
Femenino	1,16±0,18	13,38±1,27	13,05±3,2
TDAH_Masc	0,95±11,53	14,53±0,37	11,23±1,46
TDAH_Fem	1,08±11,53	14,01±0,37	11,65±1,46
NoTDAH_Masc	1,1±13,49	12,37±0,35	14,88±3,04
NoTDAH_Fem	1,16±5,3	13,32±0,17	13,18±1,27
Sobrep_Masc	0,84±0,13	14,96±0,45	9,4±3,13
Sobrep_Fem	0,91±0,11	15,14±0,34	15,02±2,33
Normop_Masc	1,23±0,25	12,53±0,93	14,87±4,09
Normop_Fem	1,24±0,12	12,76±0,78	12,71±3,24

Tabla IV: Valores de la prueba atencional TMT.

	A (pre-test) (s)	A (post-test) (s)	B (pre-test) (s)	B (post-test) (s)
Masculino	84,62±38,55	57,43±25,79	202,67±58,17	158,22±60,91
Femenino	63,74±33,09	46,69±21,49	197,21±57,21	153,61±72,73
TDAH_Masc	95±1,56	63,33±3,54	225±24,75	168,9±34,65
TDAH_Fem	50,9±1,56	36,2±3,54	279,5±24,75	217,5±34,65
NoTDAH_Masc	80,79±37,85	55,02±25,1	190,92±68,1	152,14±58,56
NoTDAH_Fem	64,9±34,38	47,65±22,22	189,73±53,41	147,8±72,89
Sobrep_Masc	131±9,77	82±14,81	244±30,73	292±20,94
Sobrep_Fem	126,16±38,23	91,83±17,48	248,16±48,40	217±72,65
Normop_Masc	68±32,46	43,67±12,72	184,47±57,05	134,71±55,4

Figura 1: Análisis de componentes principales sobre los diferentes grupos según índice BAI, pruebas de condición física y prueba atencional (con asterisco se marcan los grupos heterogéneos).



Tras la realización de la revisión bibliográfica, se puede observar que estudios como el de Gapin y Etnier[17], el de Chang, Liu, Yu y Lee[18] , el de Pontifex et al.[7], el de Hillman et al.[19] y el de Ma[20] coinciden en que la actividad física puede mejorar la función cognitiva y ejecutiva de los alumnos con TDAH. Lo demuestran evaluando aspectos como el control inhibitorio, la velocidad de procesamiento, la memoria y la capacidad atencional de los alumnos tras realizar una o varias sesiones de ejercicio físico. Aunque otros estudios como el de Verret, Guay, Berthiaume, Gardiner y Béliveau[21], el de Smith et al.[22] y el de Ziereis y Jansen[23] demuestran que el ejercicio físico también puede aportar beneficios a nivel cognitivo y ejecutivo aplicando un programa de intervención más prolongado en el tiempo.

Por lo que hace al comportamiento de los alumnos con TDAH, varios autores defienden la influencia del ejercicio físico sobre su estado de ánimo, llegando a regular los síntomas relacionados con la ansiedad y la depresión[24]. Otros estudios entienden el ejercicio físico como una herramienta útil para mejorar las habilidades sociales de los alumnos que padecen el trastorno, hasta el punto de ayudarles a solucionar sus problemas sociales[25]. o hasta el punto de regular sus comportamientos negativos[26].

Entendiendo que según Khalife et al.[27] el ejercicio físico requiere poseer o adquirir determinadas capacidades que pueden resultar de mayor dificultad para el alumnado con TDAH (concentración, percepción y autocontrol), Kim, Mutyala, Agiovlasitis y Fernhall[28] demostraron con su estudio que el resto de la sociedad realiza más ejercicio que este tipo de alumnos, factor que, según Khalife et al.[27], puede ser una de las causas del factor de riesgo de obesidad que sufren estos alumnos, concluyendo que esta inactividad física podría relacionarse con los síntomas del trastorno.

Por su parte, Harvey et al.[4] demostró que los alumnos con TDAH, además de realizar menos ejercicio, lo hacían con menos éxito que el resto. Como consecuencia, esta situación podría influir de manera directa en este tipo de alumnado, hasta el punto de despertar en ellos, según Harvey et al.[4] y Williams et al.[29], el temor a un posible rechazo por parte de sus compañeros y la aceptación social está relacionada con el éxito deportivo.

Conclusiones

Existen diferencias entre ambos sexos en cómo el ejercicio físico afecta a las capacidades cognitivas tanto de velocidad como de procesamiento, al mismo tiempo la condición física también influye en las capacidades cognitivas, siendo los sujetos con sobrepeso aquellos que presentan unas mejoras respecto al grupo control.

Conflicto de intereses

Los autores declaran no tener ningún conflicto de intereses.

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ORIGINAL

Palpebral fissure widening after different types of strabismus surgery

Ensanchamiento de la fisura palpebral después de diferentes tipos de cirugía de estrabismo

Abdolreza Medghalchi[1], Mitra Akbari[1], Reza Soltani Moghadam[1], Yousef Alizadeh[1], Ehsan Kazemnejad[1], Seyedeh Fatemeh Mirjani[2], Farhad Atakpour[1]

1. Eye Research Center, Department of Eye, Amiralmomenin Hospital, School of Medicine, Guilan University of Medical Science, Rasht, Iran 2. TIP Department, Medical Faculty, Izmir University of Economics, Izmir, Turkey

Corresponding author
Mitra Akbari
E-mail: mitra.akbarimed20@gmail.com

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Abstract

Objectives: Strabismus surgery may be associated with postsurgical complications such as palpebral fissure widening. For a better understanding of this finding, we studied the surgical outcome of patients undergoing strabismus surgery at our center and its effect on palpebral fissure alterations.

Methods: In this cross-sectional study, 58 patients who underwent strabismus surgery at Amir–Almomenin Hospital, Rasht, Iran during March 2015-2016 were investigated for the changes in eye deviation and palpebral fissure height (PFH) 1 and 3 month(s) after surgery compared with the pre-surgical status. Also, their corneal light reflex of upper eyelid margin to reflex distance (UMRD) and lower eyelid margin to reflex distance (LMRD) was clinically evaluated.

Results: Evaluation of 97 eyes of 58 patients (47 left and 50 right eyes; 63.8% women; mean age of 19.7±13.8 years) undergoing strabismus surgery showed significant changes in deviation, PFH, and LMRD, 1 and 3 month(s) after surgery compared with the pre-surgical status with significant differences based on the type of surgery. Correction of deviation had a significant effect on PFH change (3 months after surgery compared with baseline) in medial and lateral rectus recession techniques (P<0.001).

Conclusion: The results of this study showed significant effect of medial and lateral rectus recession on PFH, UMRD, and LMRD, which emphasizes on the need to inform patients about the possibility of such changes after surgery and search for intra-operative strategies to reduce such changes.

Key words: Strabismus, eyelids, palpebral fissure, medial rectus, lateral rectus.

Resumen

Objetivos: La cirugía de estrabismo puede estar asociada a complicaciones postquirúrgicas como el ensanchamiento de la fisura palpebral. Para una mejor comprensión de este hallazgo, estudiamos el resultado quirúrgico de los pacientes sometidos a cirugía de estrabismo en nuestro centro y su efecto sobre las alteraciones de la fisura palpebral.

Métodos: En este estudio transversal, se investigaron los cambios en la desviación ocular y la altura de la fisura palpebral (PFH) de 58 pacientes que se sometieron a cirugía de estrabismo en el Hospital Amir-Almomenin, Rasht, Irán, durante marzo de 2015-2016, en comparación con el estado prequirúrgico. Además, se evaluó clínicamente su reflejo luminoso corneal del margen del párpado superior a la distancia del reflejo (UMRD) y del margen del párpado inferior a la distancia del reflejo (LMRD).

Resultados: La evaluación de 97 ojos de 58 pacientes (47 ojos izquierdos y 50 ojos derechos; 63,8% mujeres; edad media de 19,7±13,8 años) sometidos a cirugía de estrabismo mostró cambios significativos en la desviación, la PFH y la LMRD, 1 y 3 meses después de la cirugía en comparación con el estado prequirúrgico, con diferencias significativas en función del tipo de cirugía. La corrección de la desviación tuvo un efecto significativo en el cambio de la PFH (3 meses después de la cirugía en comparación con el estado inicial) en las técnicas de recesión del recto medial y lateral (P<0,001).

Conclusión: Los resultados de este estudio mostraron un efecto significativo de la recesión del recto medial y lateral sobre la PFH, la UMRD y la LMRD, lo que enfatiza en la necesidad de informar a los pacientes sobre la posibilidad de que se produzcan dichos cambios tras la cirugía y buscar estrategias intraoperatorias para reducirlos.

Palabras clave: Estrabismo, párpados, fisura palpebral, recto medial, recto lateral.

Introduction

Strabismus is a common visual disorder, which typically starts at early childhood, mainly by a genetic, structural, or developmental disorder. It involves the extraocular muscles[1], and can cause diplopia, stereopsis, and asthenopia, or result in amblyopia[2].Different prevalence rates of strabismus (0.3-4.4%) and its subtypes, namely esotropia, exotropia, and hypertropia, have been reported in different ethnicities, highest in European countries[3,4].In Asian children, a prevalence of 3.5% is reported for strabismus[5],and in most cities of Iran, the prevalence of strabismus is reported at about 2%[6,7].

Considering the treatment of strabismus, some conservative treatments, like prisms, occlusion, and orthoptic exercises, have been suggested to help realign the visual axes[8].However, surgical correction seems to be the only curative treatment of strabismus, which aims to recover binocular vision, promote fusion of eye's images, and restore normal eye contact, while the cosmetic improvement can also have positive psychological impact[9,10].Strabismus surgery can be performed by different techniques including muscle recession and resection, selected by the surgeon based on the type and severity of the patients' strabismus[10]. Beside the debate on the surgical technique with the best surgical success on correction of eye's deviation[11,12], postoperative complications are the important aspects in strabismus surgery, during which the change in the position of adjacent structures, such as palpebral fissure widening, can cause negative esthetic outcomes, eye dryness, ptosis, and further problems for the patient[13,14].

Vertical widening of the palpebral fissure is reported by some researchers after surgical correction of horizontal strabismus by recession of lateral rectus muscle[15,16],while muscle resection is reported to cause narrowing of the palpebral fissure[17]. As suggested, transposition of horizontal rectus muscle to posterior position during strabismus surgery can change the orbital globe's position and increase the palpebral fissure height (PFH)[18]. Accordingly, researchers have been looking for surgical techniques to reduce these complications, suggesting intermuscular septum dissection in lateral rectus muscle recession[19,20].

Because of the fact that few studies have investigated the change in PFH and the negative effects of these complications on patients, we aimed to study the surgical outcome of all patients undergoing strabismus surgery at our center and the effect of muscle recession and resection on palpebral fissure widening in order to identify the change in PFH after different surgical techniques and investigate the possible cause underlying this change.

Methods

Study design

In this cross-sectional study, patients who underwent strabismus surgery at Amir–al–Momenin Hospital, Rasht, Iran, during March 2015-2016, were considered as the study population. The study's protocol was approved by the Ethics Committee of Guilan University of Medical Sciences, Rasht, Iran (cod: IR.GUMS.REC.1394.217). The sample size of the study was calculated at 60, based on the study by Lima and colleagues[15], considering the confidence interval of 95% and study power of 90%. The participants were selected based on the following inclusion criteria: patients who were candidate of strabismus surgery, who had no palpebral or orbital disorder, no history of surgery on orbital extraocular muscles, eye trauma, or ocular nerve palsy. Before recruitment of patients into the study, the researcher explained the design and objectives of the study to eligible patients and asked them to read and sign the written informed consent form. The eligible patients who gave consent for participation were enrolled into the study by convenient sampling method.

One day before surgery, all the participants underwent physical examination by an expert ophthalmologist (AR.M). During this visit, the physician measured the vertical PFH by considering the widest point between the upper and lower eyelid along pupil's axis, while the patient was asked to look at a far object in primary position. The corneal light reflex of the eyelids was measured by margin to reflex distance (MRD) in upper (UMRD) and lower eyelid (LMRD). Also, the physician performed complete eye examination for all the patients, including the measurement of central vision by central steady maintenance (CSM) for the children <4 years old and by Snellen chart for the patients >4 years old, measurement of eye deviation by prism, and cycloplegic refraction by 0.5% atropine eye drop (one drop each 8 hours). The same examinations were performed 1 and 3 month(s) after surgery. A single ophthalmic surgeon performed the surgical procedures.

Statistical analysis

The categorical variables were described by frequency (percentage) and the numeric variables by mean and 95% confidence interval (CI), according the results of Kolmogorov Smirnov test for evaluating the normal distribution of variables. To compare the changes in the numeric variables 1 and 3 month(s) after the surgery with the preoperative values, paired t test or Wilcoxon test were performed, based on the results of normal distribution of the variables. To determine the value of change according to variables such as type of surgery, eye side, patients' sex, and age, independent samples *t* test or ANOVA was used, while for variables without normal distribution, non-parametric tests, Mann Whitney U test, or Kruskal Wallis test were used. Association of variables

was tested by Pearson's or Spearman's correlation coefficient, according to the normal distribution of data. For the statistical analysis, the statistical software IBM SPSS Statistics for Windows version 21.0 (IBM Corp. 2012. Armonk, NY: IBM Corp.) was used. Significance level was considered as two-sided test results and P values <0.05.

Results

Of 58 patients who completed the study, 37 (63.8%) were female patients and 21 (36.2%) were male patients. Of 97 eyes, 47 were left eyes and 50 were right eyes. Mean±SD of the participants' age was 19.7±13.8 years (minimum of 1 year and maximum of 50 years). The most common type of surgery was medical rectus recession (38.1%), lateral rectus recession (20.6%), and lateral rectus recession+medial rectus resection (15.5%). The mean±SD of eye's deviation before and after the surgery in each type of surgery are shown in **table I**. As shown in this table, comparison of the postsurgical values with the pre-surgical values showed significant changes in all types of surgery (P<0.05; **table I**).

Mean changes in UMRD, LMRD, and PFH 1 and 3 month(s) after the surgery were compared with their baseline values and categorized based on the surgical type, and the results are shown in **table II**. As shown, significant differences were observed among different surgical types in LMRD 1 and 3 month(s) after the surgery compared with the baseline (P=0.003 and 0.002, respectively), as well as PFH 1 and 3 month(s) after the surgery compared with the baseline, and 3 months after the surgery compared with 1 month after the surgery (P<0.05; **table II**).

Studying the effect of time showed significant change in LMRD 1 and 3 month(s) after the surgery compared with the baseline in medial and lateral rectus recession, indicating an increasing trend (95% CI), but not in other types of surgery. Considering the effect of time, significant change in UMRD, 1 and 3 month(s) after the surgery compared with the baseline in vertical and lateral rectus recession, indicating an increasing trend (95% CI), but not in other types of surgery. Considering PFH, there were significant changes 1 and 3 month(s) after the surgery compared with the baseline in lateral and lateral rectus recession, indicating an increasing trend (95% CI), and 3 months after the surgery compared with the baseline in medial rectus recession+inferior oblique myomectomy (95% CI), indicating an increasing trend; however, the changes were not significant in other types of surgery. The trend of changes in UMRD, LMRD, and PFH are illustrated in **figure 1**.

The results of regression analysis for the effect of eye deviation correction with changes in UMRD, LMRD, and PFH 3 months after the surgery compared with the baseline values are shown in **table III**, according to the surgical type. As indicated, significant effects were observed in LMRD in medial and lateral rectus recession surgery (r=0.61 and 0.68, respectively; P<0.001) and PFH (r=0.60 and 0.75, respectively; P<0.001).

Discussion

The present study investigated the effect of each type of strabismus surgery on the change of PFH, UMRD, and LMRD, which showed that medial and lateral rectus recession surgery had significant effects on LMRD, and PFH, 3 months after the surgery compared with the baseline values. The mean age of our study population was about 20 years and the patients' age ranged from 1 to 50 years. Strabismus is mainly considered as a pediatric disease, as it is commonly observed because of the developmental disorder in childhood, for which most studies have focused on pediatric population[21,22]. However, adults may also have strabismus, uncorrected from childhood or because of the other reasons, such as trauma[23]. Considering no age range for patients' enrollment into our study confirmed the presence of strabismus in adults, as well as children and adolescents. As suggested by the related guidelines, strabismus surgery can be performed by different techniques, based on the type and severity of patients' strabismus[10]. In the present study, nine different surgical techniques were

Table I: The mean prism diopter of eye deviation before and after surgery in each surgical type.

	Total count	Before surgery	3 months after surgery	P value*
Esotropia – medial rectus recession	19	33.68±14.80	2.89±3.63	<0.001
Exotropia – lateral rectus recession	11	34.55±15.24	3.45±3.45	<0.001
Vertical tropia – superior – inferior rectus recession	5	33.00±17.18	6.60±8.23	0.003
Exotropia – lateral rectus recession + medial rectus resection	13	49.23±14.84	7.31±6.56	<0.001
Esotropia – lateral rectus recession+medial rectus resection	6	30.83±9.70	0	0.001
Hypertropia – inferior oblique myomectomy	3	5.77±13.33	3.33±5.77	0.003
Esotropia+superior – inferior rectus recession, lateral rectus recession+medial rectus resection and hypertropia – medial rectus recession+inferior oblique myomectomy	3	45.00±8.66	4.33±4.04	0.005
Exotropia+hypertropia – lateral rectus recession+inferior oblique myomectomy	1	45.00±00	4.00±00	0.005
Hypertropia – recession+anterior transposition inferior oblique muscle	1	15.00±0	0	<0.001

*The results of ANOVA, considered as significant at P<0.05. All values are reported as mean±standard deviation

Table II: Comparison of mean changes in UMRD, LMRD, and PFH 1 and 3 month(s) after surgery based on the surgical type.

	A	B	C	D	E	F	G	H	I	P value*
UMRD change 1 month after surgery vs. baseline	0.19±0.84	0.35±0.75	0.71±0.49	-0.07 ±0.70	0±0.63	0.33±0.58	0.17±0.58	0	0	0.577
UMRD change 3 months vs. 1 month	-0.03 ±0.60	0±0.65	-0.29 ±0.76	0±0.65	-0.33 ±0.52	0.33±0.58	0.17±0.75	-1.00 ±0	0	0.374
UMRD change 3 months vs. baseline	0.16±0.65	0.35±0.53	0.43±0.53	-0.07 ±0.88	-0.33 ±0.52	0.67±0.58	0.33±0.82	1.00±0	0	0.058
LMRD change 1 month vs. baseline	0.54±0.87	0.60±0.60	0.57±0.79	-0.20 ±1.01	-0.17 ±0.41	-1.00 ±0	0±0.63	1.00±0	0	0.003
LMRD change 3 months vs. 1 month	0.08±0.49	0.05±0.69	-0.14 ±0.38	0.13±0.74	0±0.63	0	0.17±0.75	0	-1.0±0	0.800
LMRD change 3 months vs. baseline value	0.62±0.92	0.65±0.67	0.43±0.79	-0.07 ±0.88	-0.17 ±0.41	-1.00 ±0	0.17±0.41	1.00±0	-1.00 ±0	0.002
PFH change 1 month vs. baseline	0.73±1.17	1.00±0.97	-1.71 ±4.42	-0.13 ±0.99	-0.17 ±0.75	–0.33 ±0.58	0.50±0.55	1.00±0	0	0.009
PFH change 3 months vs. 1 month	0.05±0.52	0±0.65	2.43±4.54	0.07±0.46	-0.33 ±0.82	0	0.17±0.41	-1.00 ±0	-1.00 ±0	0.003
PFH change 3 months vs. baseline value	0.78±1.11	1.00±0.92	0.71±0.95	-0.07 ±0.96	-0.50 ±0.55	-0.33 ±0.58	0.67±0.52	0	-1.00 ±0	0.003

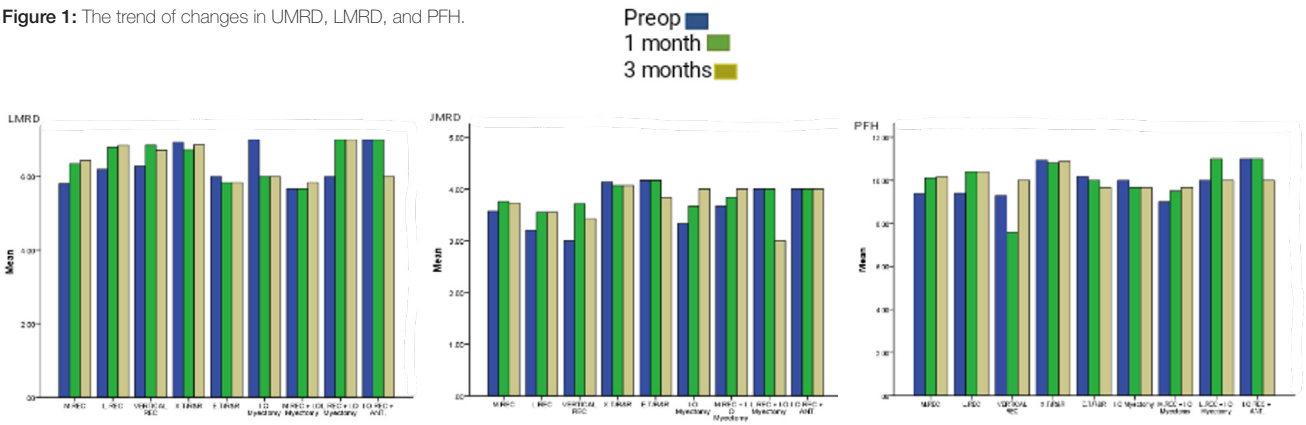
*The results of ANOVA, considered as significant at P<0.05. All values are reported as mean±standard deviation, A: Esotropia – medial rectus recession, B: Exotropia – lateral rectus recession, C: Vertical tropia – superior–inferior rectus recession, D: Exotropia – lateral rectus recession+medial rectus resection, E: Esotropia – lateral rectus recession+medial rectus resection, F: Hypertropia – inferior oblique myomectomy, G: Esotropia+superior – inferior rectus recession, lateral rectus recession+medial rectus resection and hypertropia – medial rectus recession+inferior oblique myomectomy, H: Exotropia+hypertropia – lateral rectus recession+inferior oblique myomectomy, I: Hypertropia – recession+anterior transposition inferior oblique muscle, MRD; margin to reflex distance, PFH; palpebral fissure height

Table III: Regression analysis for the effect of eye deviation correction with changes in UMRD, LMRD, and PFH 3 months after surgery compared with baseline values, based on the surgical type.

		A	B	C	D	E	F	G	H
LMRD	β–coefficient	0.611	0.698	0.031	0.092	0.343	1.00	0.345	1.00
	R square	0.373	0.488	0.001	0.009	0.118	1.00	0.119	1.00
	P value	<0.001	<0.001	0.941	0.734	0.451	0	0.448	0.014
	Lower bound 95% CI	0.065	0.038	-0.162	-0.169	-0.126	-0.167	-0.039	0.64
	Upper bound 95% CI	0.166	0.112	0.152	0.122	0.244	-0.167	0.076	0.114
UMRD	β–coefficient	0.204	0.550	0.650	0.150	0.485	0.816	0.398	1.00
	R square	0.042	0.302	0.422	0.023	0.235	0.667	0.159	1.00
	P value	0.219	0.010	0.081	0.579	0.270	0.184	0.376	0.014
	Lower bound 95% CI	-0.014	0.012	-0.013	-0.182	-0.126	-0.128	-0.070	-0.114
	Upper bound 95% CI	0.060	0.075	0.172	0.106	0.361	0.350	0.154	-0.064
PFH	β–coefficient	0.600	0.755	0.211	0.096	0.594	0.577	0.797	
	R square	0.361	0.570	0.045	0.009	0.353	0.333	0.635	
	P value	<0.001	<0.001	0.616	0.725	0.160	0.423	0.032	
	Lower bound 95% CI	0.076	0.069	-0.162	-0.184	-0.098	-0.295	0.011	
	Upper bound 95% CI	0.201	0.168	0.251	0.131	0.451	0.183	0.158	

Abbreviations: A; Esotropia – medial rectus recession, B; Exotropia – lateral rectus recession, C: Vertical tropia – superior–inferior rectus recession, D; Exotropia – lateral rectus recession+medial rectus resection, E; Esotropia – lateral rectus recession+medial rectus resection, F; Hypertropia – inferior oblique myomectomy, G; Esotropia+superior – inferior rectus recession, lateral rectus recession+medial rectus resection and hypertropia – medial rectus recession+inferior oblique myomectomy, H; Exotropia+hypertropia – lateral rectus recession+inferior oblique myomectomy.

Figure 1: The trend of changes in UMRD, LMRD, and PFH.



used for correction of the patients' strabismus. The most common types included medical rectus recession (38.1%), lateral rectus recession (20.6%), and lateral rectus recession+medial rectus resection (15.5%). The results of postsurgical assessment of eye deviation showed that all of these techniques resulted in significant decrease in eye deviation and the surgical results were thus considered as successful in all patients, undergoing different surgical types. These results are in line with the results of previous studies, indicating medial and lateral rectus recession as effective procedures[24]. However, several errors and complications have been reported for strabismus surgery, and it is suggested to be performed with great precision[25].

Complications related to eyelid position is one of the rarely reported complications of strabismus surgery, reported recently (since 2005)[17], which can be observed after strabismus by releasing and changing the position of extraocular muscles[13,14]. Nevertheless, it is of great importance, as it may not only affect the patients' appearance and interfere with the cosmetic correction purpose of strabismus surgery, but may also cause ocular problems for the patient. The results of our study showed significant increase in UMRD, 1 and 3 month(s) after the surgery in vertical and lateral rectus recession methods and in LMRD and PFH in medial and lateral rectus recession methods, which indicated that not all of the surgical types had significant effects on PFH, UMRD, and LMRD, although these results may also be resulted from the small number of sample size in the groups (≤6 patients). Lee and colleagues investigated palpebral fissure widening in 20 patients with intermittent exotropia who underwent unilateral rectus muscle recession and compared the baseline values with postsurgical measurements 1 week, 1 month, and 6 months after surgery[16]. They defined >6mm change in PFW as significant change and reported significant increase in PFW in 50% of patients after 1 week, in 35% after 1 month, and in 35% after 6 months[16]. These findings are in line with the results of the present study, indicating increased PFH in medial and lateral rectus recession surgical techniques. In another study, performed in Iran, Zandi and colleagues investigated PFH changes in 26 eyes of 19 patients with strabismus after lateral rectus recession and reported a mean PFH of 11.4 mm, 3 months after surgery, significantly higher than the pre-surgical values, and reported that the group undergoing intermuscular septum dissection had a lower mean PFH, 3 months after surgery[20]. The findings of the study by Zandi and colleagues, indicating an increase in PFH after 3 months in patients undergoing lateral rectus recession confirm the results of the present study, although we had no intervention to compare the results with, and the changes in the measurements of patients undergoing different surgical techniques were compared. In another study by de Sauza Lima and colleagues, 42 patients with esotropia and 17 with exotropia underwent extraocular muscle recession. The results of their study showed about 12% increase in vertical palpebral fissure 3 months after surgery[15], which is consistent with the results of the present study. Similar reports have been released by other studies, which measured PFH changes after muscle recession in patients with thyroid disorders[26,27] and some others have suggested combination of eyelid surgery with strabismus surgery[28].

As indicated above, the few studies on the measurement of the change in PFH after strabismus surgery have reported different outcomes, some have considered a cut-off point and reported the prevalence of patients with increased PFH[16] and some others have reported mean values[20]. In the present study, we considered the change in mean values and the effect of each type of surgery on this change. Based on the results of regression analysis, each unit change in medial and lateral rectus recession surgery resulted in about 0.6-0.7 mm increase in LMRD and PFH. These results are close to that reported by de Sauza Lima and colleagues, which showed a mean increase of about 1mm, 3 months after surgery; 0.9 mm in patients with esotropia and 1 mm in patients with exotropia[15]. Lagrèze and co-workers have also reported 1 mm increase in PFH by 7.7 mm change in muscle's position[17]. The researchers of the above mentioned studies[15,17] have also measured the variables manually, like us, while some others have suggested that digital measurement of PFH can result in more accurate values[29,30].

The present study had some limitations. The first limitation was related to the small sample size in some surgical groups, which could have affected the results. The second limitation of this study could be the short follow-up, as we only measured 1 and 3 months' results, while longer follow-ups may indicate other results. Furthermore, the measurements were manual, while digital measurements can provide more accurate results. Considering the fact that the patients were selected from one center, it is suggested not to generalize the results to all study groups.

Conclusion

The results of the present study showed that PFH, UMRD, and LMRD significantly increased after strabismus surgery. Therefore, it is important to inform patients about the possibility of these complications and increase surgeons' awareness about the adverse effects of these complications. Comparison of the results among different types of surgery showed significant effect of medial and lateral rectus recession surgery on PFH and LMRD. Considering the limitations of the present study, this issue has to be evaluated in future studies to indicate the eyelid changes after each type of surgery and suggest strategies to reduce this undesirable complication.

Conflict of interest

Authors do not have any conflict of interest to declare.

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ORIGINAL

The prevalence of single pulmonary nodules as the first sign of COVID-19 pneumonia in CT scans of patients suspected to COVID-19

La prevalencia de nódulos pulmonares únicos como el primer signo de neumonía por COVID-19 en tomografías computarizadas de pacientes sospechosos de COVID-19

Atefeh Shadkam[1], Ali Akbar Mahdavi[2], Masoomeh Raoufi[2], Hossein Mardanparvar[3], Zahra Fatehi[4]

*1. Residency of Radiology, Department of Radiology**
*2. Assistant Professor of Radiology, Department of Radiology**
3. Department of Nursing, Faculty of nursing & midwifery, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
*4. Residency of Radiology Department of Radiology**

**Imam Hossein Hospital, School of Medicine, Shahid Beheshti University of Medical Sciences. Tehran, Iran*

Corresponding author
Zahra Fatehi
E-mail: Mastanefatehi70@gmail.com

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Abstract

Background: The role of diffuse nodular lesions has been cited as a specific indication for COVID-19 progresiion and severity; however the place of single nodules in this role is quite ambiguous. The present study aimed to determine the prevalence of single pulmonary nodules as the first sign of COVID-19 pneumonia in CT scans of patients suspected to disease.
Methods: In this cross-sectional study, all consecutive patients suspected to COVID-19 referred and admitted to Imam Hussein Hospital in Tehran, Iran between February 20, 2020 and April 19, 2020 that assessed by CT scanning were prospectively assessed. All CT scans were interpreted by two independent high-experienced radiologists with high diagnostic agreement.
Results: In total, 5211 individuals suspected to COVID-19 were assessed by CT scanning in our center. Of those, the diagnosis of the disease was definitively confirmed in 1357 cases with the prevalence rate of 26.0%. Among the confirmed cases of the disease with CT positivity, 32 had single pulmonary nodules and therefore, the prevalence rate of single nodules to all initial suspected cases was revealed to be 0.6% and to all subjects with definitive diagnosis of disease with positive CTs to be 2.4%. The characteristics of nodules (size, type, or location) were independent to patients' age and gender.
Conclusion: The appearance of pulmonary single nodules may be predictive for early diagnosis and confirming COVID-19 disease in suspected cases.

Key words: COVID-19, single pulmonary nodules, COVID-19 pneumonia.

Resumen

Antecedentes: El papel de las lesiones nodulares difusas se ha citado como una indicación específica para la progresión y la gravedad de la COVID-19; Sin embargo, el lugar de los nódulos únicos en este papel es bastante ambiguo. El presente estudio tiene por objeto determinar la prevalencia de los nódulos pulmonares nódulos pulmonares únicos como primer signo de neumonía por COVID-19 en las TC de pacientes con sospecha de enfermedad.
Métodos: En este estudio transversal, todos los pacientes consecutivos con sospecha de COVID-19 remitidos e ingresados en el Hospital Imam Hussein Hospital de Teherán, Irán, entre el 20 de febrero de 2020 y el 19 de abril de 2020 fueron evaluados por TC prospectivamente. Todas las tomografías computarizadas fueron interpretadas por dos radiólogos independientes de gran experiencia con alta concordancia diagnóstica.
Resultados: En total, 5211 individuos con sospecha de COVID-19 fueron evaluados mediante TC en nuestro centro. De ellos, el diagnóstico de la enfermedad se confirmó definitivamente en 1357 casos, con una tasa de prevalencia del 26,0%. Entre los casos confirmados de la enfermedad con positividad en la TC, 32 tenían nódulos pulmonares únicos y, por tanto, la tasa de prevalencia de nódulos únicos en todos los casos iniciales sospechosos fue del 0,6% y en todos los sujetos con diagnóstico definitivo de la enfermedad con TAC positivo fue del 2,4%. Las características de los nódulos (tamaño, tipo o localización) fueron independientes de la edad y el sexo de los pacientes.
Conclusiones: La aparición de nódulos únicos pulmonares puede ser predictiva para el diagnóstico precoz y la confirmación de la enfermedad COVID-19 en los casos sospechosos.

Palabras clave: COVID-19, nódulos pulmonares únicos, neumonía por COVID-19.

Introduction

Pneumonia with an unknown cause was initially diagnosed in December 2019 in Wuhan, China and subsequent studies identified the new coronavirus as its related etiology[1-3]. This new virus called the coronavirus type 2 which causes severe acute respiratory syndrome or SARS-CoV-2 and thus, the resulting disease was named COVID-19 by the World Health Organization[4]. The virus is the seventh member of the Corona family of RNA viruses with envelope, along with other family viruses such as SARS and MERS. The first cluster of patients affected by the virus was identified among aquatic sellers in the city of Wuhan, and eventually the transfer from person to person was confirmed at the same time[5-7]. With the global spread of the virus, its count was reported as a pandemic in China and then in all countries[8]. Therefore, a large number of articles on clinical and epidemiological evidence were immediately published[9-11].

The diagnosis of COVID-19 disease was first determined by confirmation of coronavirus nucleic acid in the swap sample, sputum or respiratory secretions, or PCR on the patient's blood sample. However, the use of diagnostic kits was mostly time consuming. In addition, false negatives were gradually reported. Based on this, imaging tools, especially CT scans, were used to diagnose the severity and stages of the disease and were used with great precision, especially in assessing the severity of pneumonia caused by the virus[12,13]. In recent reports, between 70 and 80 percent of CT findings have been matched with clinical manifestations, and CT has been cited as an important and practical tool in the diagnosis and progression of the disease[14]. Accordingly, various manifestations of CT have been considered with the severity of the progression of the resulting pneumonia disease, and accordingly, five stages of the disease have been defined based on CT findings. In the ultra-early stage, single or multiple ground-glass opacities (GGO) can be seen along with GGO-coated nodules, patchy consolidations, and air-bronchogram signs; in the early stage, multiple GGO, patchy consolidation and increased thickness of the interlobular septum with interstitial edema, alveolar capillary congestion, and exudate fluid are seen; in rapid progression stage, the exacerbation of inflammatory lesions is seen in the form of consolidative opacities with air-bronchogram, which gradually change in size and density; in consolidation stage, their size and density decrease; and finally in the dissipation stage, the lesions may be more limited in number and extent, and only a limited number of consolidative opacities, reticular epithelium, and thickness of the introllobular septum may be observed[15].

However, it is important to note that due to the similar pathogenesis of COVID-19 with other pneumonias from other members of the coronavirus family, it is not possible to diagnose COVID-19 pneumonia solely on the basis of these findings[16,17]. In some recent studies, the role of single nodules, especially in cases with halo sign, has been cited as more specific indications for COVID-19[18,19]. Therefore, what assessed in the present was to determine the prevalence of single pulmonary nodules as the first sign of COVID-19 pneumonia in CT scans of patients with suspected disease.

Materials and methods

In this cross-sectional study, all consecutive patients suspected to COVID-19 referred and admitted to Imam Hussein Hospital in Tehran, Iran between February 20, 2020 and April 19, 2020 that assessed by CT scanning were prospectively assessed. On admission, baseline characteristics including demographic parameters and medical history were collected by interview and clinical manifestations were evaluated on admission by an emergency medicine physician. The results of a series of laboratory tests including the white blood cell count (WBC) (normal range 3.5-9.5×109/L), and lymphocytes (normal range 1.1-3.2×109/L)were recorded. All CT scans were performed by a single spiral CT (Siemens, Germany) and the radiographic images were interpreted by two independent high-experienced radiologists who were completely unaware of the diagnosis and therefore the agreement of the two radiologists was also assessed to obtain valid final diagnoses. The machine and the room were thoroughly disinfected after the examination of each patient. The images were analyzed for the following aspects: **1.** presence of single or multiple of pulmonary nodules; **2.** the type and size of nodules; **3.** how to spread nodules in the lungs; and **4.** the time of onset of pulmonary evidences on scans. The study endpoint was to determine the overall prevalence of single pulmonary nodules in patients with definitive diagnosis of the COVID-19 to all patients' population and also to suspected individuals. We also assessed the characteristics of single pulmonary nodules based on baseline parameters.

For statistical analysis, results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by frequency (percentage) for categorical variables. Continuous variables were compared using t test or Mann-Whitney test whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the study groups. Categorical variables were, on the other hand, compared using chi-square test. P values of ≤ 0.05 were considered statistically significant. For the statistical analysis, the statistical software SPSS version 23.0 for windows (IBM, Armonk, New York) was used.

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Results

In the study period (from February 20, 2020 and April 19, 2020), in total, 5211 individuals suspected to COVID-19 were assessed by CT scanning in our center. Of those, the diagnosis of the disease was definitively confirmed in 1357 cases with the prevalence rate of 26.0%. Among the confirmed cases of the disease with CT positivity, 32 had single pulmonary nodules and therefore, the prevalence rate of single nodules to all initial suspected cases was revealed to be 0.6% and to all subjects with definitive diagnosis of disease with positive CTs to be 2.4%.

The characteristics of COVID-19 patients with single nodules in CTs are summarized in **table I**. The average age of patients was 38.09±12.93 years ranged 22 to 72 years and 22 cases (68.8%) were male. Regarding lobes involved, the most common lobes included right lower lobe in 43.8% followed by left lower lobe in 34.4%. The mean size of single nodules was 11.97±7.76mm widely ranged 2.0 to 30.0mm. Most of the nodules were ground-glass type (90.6%) and others were solid. The mean time between the onset of suspicious clinical symptoms and the onset of imaging evidences in CT was 2.28±1.14 days ranged 1.0 to 5.0 days. With respect to laboratory findings, the mean WBC count was 7.83±3.84/mm^3 that higher than 10.000/mm^3 in 4 cases (12.5%). Also, the mean lymphocyte count was 21.95±14.14%, higher than 60% only in one patient (3.1%). Within the follow-up time, the CT images turned to clear in 26 cases (81.2%), while the lesions progressed in residual subjects. Requiring hospitalization due to the worsening of symptoms was reported in 4 patients (12.5%) and ICU admission in one patient (3.1%). Only one case died within the following-up that resulted in overall death rate of 3.1%.

Table I: The patients' characteristics and CT findings in patients with lung single nodules.

Mean age, year	38.09 ± 12.93
Male gender	22 (68.8%)
Involved lung lobes	
RLL	14 (43.8)
LLL	11 (34.4)
RUL	3 (9.4)
LUL	3 (9.4)
RML	1 (3.1)
Mean size of single nodule, mm	11.97 ± 7.76
Type of single nodule	
Ground-glass	29 (90.6)
Solid	3 (9.4)
Mean time between clinical and CT signs, day	2.28 ±1.14
Laboratory parameters	
Mean WBC count, /mm^3	7.83 ± 3.84
Mean lymphocyte count, %	21.95 ± 14.14
Mean HS-CRP	94.66 ± 87.08
Follow-up events	
CT changes	
Cleared	26 (81.2%)
Lesion progressed	6 (18.8%)
Hospitalization	4 (12.5%)
ICU admission	1 (3.1%)
Disease-related death	1 (3.1%)

The characteristics of the single nodules as well as disease outcome in men and women are presented in **table II** indicating no difference across the two genders. We did not reveal any significant association between patients' age and the study parameters of involved lung lobes (p=0.636), size of the nodule (p=0.463), type of nodule (p=0.223), the time between clinical and CT signs (p=0.885), WBC count (p=0.316), lymphocyte count (p=0.399), and HS-CRP level (p=0.814). the mean age in the subgroups with progressed and unchanged CT feature was 44.83±19.82 years and 36.54 ± 10.74 years respectively indicating no difference (p=0.160). Also, the mean age for the hospitalized and outpatient groups was 42.75±20.32 years and 37.43±11.94 years respectively with no statistical difference (p=0.450).

Table II: The CT findings in men and women.

Item	Men	Women	P value
Involved lung lobes			0.958
RLL	10 (45.5)	4 (40.0)	
LLL	7 (31.8)	4 (40.0)	
RUL	2 (9.1)	1 (10.0)	
LUL	2 (9.1)	1 (10.0)	
RML	1 (4.5)	0 90.0)	
Type of nodules			0.164
Ground-glass	21 (95.5)	8 (80.0)	
Solid	1 (4.5)	2 (20.0)	
Size of nodules	12.86 ± 8.66	10.00 ± 5.12	0.342
Time between clinical	2.27 ± 1.24	2.30 ± 0.94	0.951
and CT signs, day			
Mean WBC count, /mm³	8.24 ± 4.36	7.18 ± 3.17	0.650
Mean lymphocyte count, %	24.66 ± 16.70	17.60 ± 8.56	0.404
Mean HS-CRP	106.80 ± 98.28	74.43 ± 78.98	0.648
Lesion progressed	3 (13.6)	3 (30.0)	0.346
Hospitalization	2 (9.1)	2 (20.0)	0.572
ICU admission	1 (4.5)	0 (0.0)	0.999
	0 (0.0)	1 (10.0)	0.313

Discussion

Along with the appearance of ground-glass opacities, patchy consolidations, and air-bronchogram, the presence of multiple nodules with halo signs is a main evidence of definitive diagnosis of COVID-19, however based on our clinical experiences, some patients who were suspected to this infection have been found with the appearance of single pulmonary nodules as the initial manifestation. In other words, early appearing single nodules in lung CT scanning may be diagnostic in pulmonary involvements and thus the predictive for disease progression. In our survey, 2.4% of all positive CT images were appeared as single nodules. It was also found that the pointed nodules were observed in lower lung lobes, the size of nodules widely varied, and most were ground-glass types. Interestingly, some authors obtained similar results to our survey. As shown by Lomoro et al[20], the most common findings in patients' CT were bilateral ground-glass and multi-lobar opacities in 59.5% and patchy consolidations in 35.7%, diffuse fibrosis at 50%, subpleural lines at 35.7%, air-bronchogram sign at 26.2%, and single pulmonary nodules in 2.4%[20]. However most studies suggested diffuse and multiple pulmonary nodules as the prominent imaging sign of COVID-19. As indicated by Meng et al[21], 58 asymptomatic patients with COVID-19 pneumonia were evaluated by CT. At the time of admission, they had no clinical or laboratory symptoms. ground-glass opacities were confirmed in 94.8% of cases, and within the first few days, 27.6% of patients were marked. Other pathological changes in CT were also observed in 17% of patients during hospitalization, including bilateral diffuse nodules. In some other researches, single nodule was not found in CT scan. In a 2020 study by Zhou et al[22], 62 patients with COVID-19 pneumonia were evaluated with CT. Diffuse multiple pulmonary lesions were observed in 83.9% of patients without any evidence of single nodules. In another study by Li et al in 2020[23] on 131 COVID-19 cases, in only one patient, evidence of a single pulmonary nodule was seen as a sign of pneumonia[23]. In a study by Guan et al[24], 53 patients with COVID-19 underwent thin-section CT. Overall, CT in 88.7% of patients showed abnormal lesions. Meanwhile, the involvement of both lungs in 78.7% was reported, however single or multiple nodules were not observed in any of the patients. Based on the literatures, between 3 and 13 percent of patients with COVID-19 can be detected by multifocal solid nodules or halo-marked nodules, but appearance of single nodules is rare[25]. We believe that in most cases, the first nodular manifestations in CT scanning of such patients are as single pulmonary nodules that may gradually progress to diffuse multi-nodular lesions. Therefore, by discovering such singles nodules in suspected patients, the predicting positive cases for coronavirus type-2 infection can be possible, however confirming the predicting role of single pulmonary nodule for early predicting the disease should be reassessed in large patients'population.

Conflict of interest

Authors do not have any conflict of interest to declare.

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ORIGINAL

Medication adherence and quality of life associated with antihypertensive drugs in geriatrics in government hospital, Rajahmundry, Andhra Pradesh, India

Adherencia a la medicación y calidad de vida asociada a los fármacos antihipertensivos en geriatría en el hospital gubernamental, Rajahmundry, Andhra Pradesh, India

Mahsa Rabet Eshaghi, T.V. Narayana

Doctors of Pharmacy, Department of pharmacy practice, Vikas Institute of Pharmaceutical Sciences, Andhra Pradesh, India

Corresponding author
Mahsa Rabet Eshaghi
E-mail: mahsarabet64@gmail.com

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Abstract

Objective: The goal of the research is to to evaluate prescribing pattern, Medication Adherence and Quality of life of Geriatric patients.
Methods: A prospective and observational study was carried out for 6 months in In Government Hospital, Rajahmundry, Andhra Pradesh. A total of 120 patients were involved in the study. Prescribing pattern was evaluated by referring to patient case files comparing with JNC 7 guidelines. Patients medication adherence level was assessed by using Morisky medication adherence scale and quality of life by using MINICHAL questionnaire. After collection of complete data, appropriate descriptive and inferential statistical analysis was performed.
Result: A Total of 120 patients were enrolled in the study both from in-patient and outpatient department. The commonly prescribed drug in both the department is Calcium Channel Blockers (CCB's) as single dug therapy, CCB's account for 43.90 in In-Patient department, 66.66% in Out-patient department. Under combination therapy Angiotensin Receptors blockers (ARB) + Diuretics was commonly prescribed 69.23% in In-patient & 70.74% in Out-patient department. Majority of the study population were having good quality of life and having high level of medication adherence towards the therapy.
Conclusion: The most preferred prescribing therapy in both in-patient and out-patient was single drug therapy. Calcium Channel Blockers were the most frequently prescribed class of drugs in single drug therapy, Angiotensin Receptors blockers with Diuretics were the most commonly prescribed class of drugs in in-patient department and in out-patient department also Angiotensin Receptors blockers with Diuretics are the frequently prescribed combination of drugs. Majority of the study population were having the high level of adherence towards the anti-hypertensive therapy, which means they are in good compliance with the treatment and showed that many of the patients are having the good quality of life, we used MINIHCAL questionnaire to assess the quality of life of patients. Pharmacists positioned as the most accessible health care providers in the community, could improve patient's knowledge and adherence to the management of blood pressure. The hospital is in large compliance with JNC guidelines, in prescribing pattern of anti-hypertensive medications to the Geriatric patients.

Key words: Prescribing Pattern, Geriatrics, Quality of Life, Medication Adherence.

Resumen

Objetivo: El objetivo de la investigación es evaluar el patrón de prescripción, la adherencia a la medicación y la calidad de vida de los pacientes geriátricos.
Método: Se llevó a cabo un estudio prospectivo y observacional durante 6 meses en el Hospital Gubernamental de Rajahmundry, Andhra Pradesh. Un total de 120 pacientes participaron en el estudio. El patrón de prescripción se evaluó mediante la comparación de los expedientes de los pacientes con las directrices del JNC 7. El nivel de cumplimiento de la medicación de los pacientes se evaluó mediante la escala de cumplimiento de la medicación de Morisky y la calidad de vida mediante el cuestionario MINICHAL. Tras la recogida de todos los datos, se realizó un análisis estadístico descriptivo e inferencial.
Resultados: Un total de 120 pacientes se inscribieron en el estudio, tanto en el departamento de pacientes internos como en el de pacientes externos. El fármaco más prescrito en ambos departamentos son los bloqueadores de los canales del calcio (BCC) como terapia única, los BCC representan el 43,90 en el departamento de pacientes internos y el 66,66% en el departamento de pacientes externos. La terapia combinada de los bloqueadores de los receptores de angiotensina (ARA) y diuréticos se prescribió con frecuencia en el 69,23% de los pacientes internos y en el 70,74% de los pacientes externos. La mayoría de la población del estudio tenía una buena calidad de vida y un alto nivel de adherencia al tratamiento.
Conclusión: El tratamiento preferido, tanto en el ámbito hospitalario como en el ambulatorio, fue el tratamiento con un solo fármaco. Los bloqueadores de los canales de calcio fueron la clase de fármacos más frecuentemente prescritos en la terapia de un solo fármaco, los bloqueadores de los receptores de angiotensina con diuréticos fueron la clase de fármacos más comúnmente prescritos en el departamento de pacientes internos y en el departamento de pacientes externos también los bloqueadores de los receptores de angiotensina con diuréticos son la combinación de fármacos frecuentemente prescritos. La mayoría de la población del estudio tenía un alto nivel de adherencia a la terapia antihipertensiva, lo que significa que cumplían bien el tratamiento y mostraba que muchos de los pacientes tenían una buena calidad de vida; utilizamos el cuestionario MINIHCAL para evaluar la calidad de vida de los pacientes. Los farmacéuticos, al ser los proveedores de atención sanitaria más accesibles en la comunidad, podrían mejorar el conocimiento y la adherencia de los pacientes a la gestión de la presión arterial. El hospital cumple en gran medida con las directrices del JNC, en la pauta de prescripción de medicamentos antihipertensivos a los pacientes geriátricos.

Palabras clave: Patrón de prescripción, geriatría, calidad de vida, adherencia a la medicación.

Introduction

Hypertension is a significant public health challenge in the world because of its high prevalence and concomitant risks of cardiovascular and kidney diseases[1]. According to the World Health Organization (WHO), high blood pressure (BP) is a major public health problem that kills one in every eight people and is the world's third-leading silent killer [2]. Almost three-quarters of hypertensive people (639 million people) live in countries with limited health resources[1,2]. In Sub- Saharan Africa, it is a major independent risk factor for heart failure, stroke, and kidney failure. These complications arise as a result of a low rate of hypertension diagnosis, poor BP control, high morbidity and mortality, and low resources in health care settings[3]. A systematic review and meta-analysis study conducted in Ethiopia in 2015 estimated the prevalence of hypertension to be 19.6%[4]. Another systematic review and meta-analysis conducted in Ethiopia in 2015 found that the prevalence of hypertension ranged from 20% and 30%[5].

In the older adult population, increased levels of BP are associated with an increased risk of cardiovascular morbidity and mortality[6,7]. Thus, at the same level of BP, the risk of stroke, heart failure, coronary heart disease, peripheral artery disease, chronic kidney disease or dementia is several folds higher in elderly than in younger hypertensive patients[6]. Today, there is a strong evidence that hypertension in the elderly as well as in the very elderly must be treated and this is supported by international guidelines and a Cochrane meta-analysis[8-12]. A sub-analysis of the Systolic Blood Pressure Intervention Trial (SPRINT) in elderly has recently confirmed the benefits of lowering BP in hypertensive patients older than 75 years with some potential benefits on cognitive function and white matter lesions[13,14].

Not only compliance to therapy but also quality of life of elderly is another challenge for them. when the World Health Organization defined health as being not only the absence of disease and infirmity but also the presence of physical, mental, and social well-being, quality-of-life issues have become steadily more important in health care practice and research. The terms "quality of life" and, more specifically, "health-related quality of life" allude to the physical, psychological, and social spaces of health, seen as unmistakable territories that are affected by a person's experiences, beliefs, expectations, and perception[15]. We will briefly discuss in this article about evaluate the Prescribing trends, Medication Adherence and Quality of life (QoL) of Geriatric patients in Government Hospital, Rajahmundry, Andhra Pradesh.

Materials and methods

This study was a prospective observational study in Government Hospital, Rajahmundry, Andhra Pradesh, India. All the patients admitted to the wards and visiting outpatient department with inclusion criteria will be enrolled to the study. Sample size includes all hypertensive geriatric patients. The patient will be informed the details and their consent will be obtained. The data will be collected from the patient case sheet chart, by communicating with the physician and nurses and by interacting with patient data like demography, habits, past medical history, reason for admission, any co-morbidities, clinical data such as laboratory reports and therapeutic data including duration, frequency ,route, time of administration and concomitant medication.

This report will be collected and documented in suitably designed patient data collection form. Medication adherence will be evaluated by Moriskey Medication Adherence Scale. Quality of life will be evaluated by using quality of life questionnaire. Conclusion will be made from the available data concerning the project. This study data was entered and analyzed by using Microsoft Excel. Descriptive statistical methods like measures of central tendencies and variance was performed using Micros.

Result and discussion

In present study, out of 120 study population from In-patient and Out-patient department, majority of patients, 94 (78.33%) belonged to age group of 66-70 years. Similar study was conducted by Mohed A H et al[16] and the result was out of total of 100 prescriptions (72%) of patient were 65-67 years of age.3 Out of 120 patients enrolled 68 (48.57%) were from in-Patient and 72 (51.42%) were from out-Patient department. Out of 57 study population from in-patient department, majority 40 (70.17%) are from an age group of 60-77 years. Out of 63 study population from Out-patient department, majority 54 (85.71%) are from, an age group of 66-70 years. **Table I** In our study out of 120 patients enrolled in the study, majority of the study population were female, and out of 57 patients from in-patient department, female's patients were significantly high 40 (70.17%). Similar study was conducted by Rajasekhar G et al[17] conducted a similar study and the result was a total of 394 included 251 (63.70%) males and 143 (36.29%) females were present.

Table I: Age distribution of patients (n=120).

Age distribution (in years)	Number of patients	Percentage (%)
66-70	94	78.33
71-75	14	11.66
76-80	11	9.16
81-85	0	0
86-90	1	0.8
Total	120	100

In present study we have followed JNC 7 guidelines for analyzing the severity of hypertensive patients, and their condition classification and found out that, majority

35.08% of patients will fall under stage II hypertension in In-patient. In out-patient department, out of 63 patient's majority 42.85% of the patients are belongs to stage I hypertension, Similar study was conducted by *Mohed A H et all*[16] the result of study was a total of 100 prescriptions were analyzed in six month During the study (80%) of the patients were pre-hypertensive systolic (80-89mmHg) and diastolic (120-139 mmHg), followed by stage I and stage II hypertension. **Figure 1**

Figure 1: Classification of hypertensive patients with respect to severity of hypertension in In-patient and Out-patients

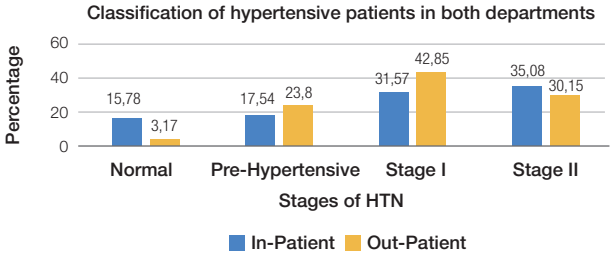

Table II: Single drug therapy among In-Patients and Out-Patients.

In-Patients (n_1) (41 Patients)					
Category	**Drug Name**	**Male (07)**	**Female (34)**	**Total**	**Percentage**
CCB's	Amlodipine	4	12	16	43.9
	Diltiazem	1	1	2	
	Nifedipine	0	1	0	
ACE inhibitors	Enalapril	1	1	2	12.19
	Ramipril	1	1	2	
	Pridironpril	0	1	1	
ARB'S	Telmisartan	1	9	10	31.07
	Valsartan	0	1	2	
	Losartan	0	1	1	
Beta-Blockers	Atenolol	0	3	3	17.07
	Metoprolol	1	3	4	
Out-Patients (n_2) (39 Patients)					
CCB's	Amlodipine	11	13	24	66.66
ACE inhibitors	Enalapril	0	1	1	5.12
	Pridironpril	0	1	1	
ARB'S	Telmisartan	3	6	9	25.64
	Losartan	0	1	1	
Beta-Blockers	Atenolol	0	2	2	7.69
	Metoprolol	1	0	1	

Prescription pattern of anti-hypertensive:

The prescription pattern of anti-hypertensive drugs was categorized into two types, Single drug therapy and Combinations therapy. Single drug therapy was most preferred therapy by physicians in both the departments. Under single dug therapy, CCB's account for 43.90%, Angiotensin-converting enzyme (ACE) Inhibitors for 12.19%, ARB's for 31.70% and Beta-Blockers for 17.07% in In-Patient department, whereas in Out-patient department 66.66% of study population were under CCB's, 5.12 were under ACEI, 25.64% were under ARB's and 7.69% were under Beta- Blockers (BB). Under combination drug therapy, CCB+BB account for 23.01%, CCB + ARB for 7.69%, ARB+D for 69.23%, in In-patient department, whereas in out-patient department ARB + BB account for 7.40%, CCB+BB and CCB+ARB and BB+D for 14.81% each, ARB+ (Diuretics) D for 70.74%, CCB+D for 7.40%. similar study was conducted by Gupta SK et al[18] and in that out of 106 patients, the most combinational therapy was calcium channel blockers + diuretics (19.8%), calcium channel blocker + beta blockers (7.5%), calcium channel blocker + ACE inhibitors (1.9%), ACE inhibitors and diuretics (2.8%), calcium channel blocker +angiotensin receptor blocker (1.9%), beta blocker + diuretics (1.9%), beta blocker + calcium channel blocker +angiotensin receptor blocker (0.9%), beta blocker + ACE inhibitors + diuretics (0.9%), beta blocker +angiotensin receptor blocker + diuretics (1.9%) and calcium channel blocker + beta blocker + ACE inhibitors + diuretics (0.9%). **Table II** & **III**.

Medication Adherence level in both the departments (MMAS 8)

Morisky Medication Adherence Scale (8-questionnaire) was used to find out-patients medication adherence, most of the people in both the departments are in high medication adherence level. Majority 44 (77.19%) of the people are in high adherence level in In-patients department, were as in Out-patient's department majority

Table III: Combination therapy among In-Patients and Out-Patients.

In-Patients (n_1) (13 patients)					
Category	**Drugs**	**Male (10)**	**Female (6)**	**Total**	**Percentage (%)**
CCB + BB	Amlodipine + Atenolol	1	1	3	23.01
CCB + ARB	Amlodipine + Telmisartan	0	1	1	7.69
ARB + DIURETCIS	Telmisartan + Chlorthalidone	3	2	5	69.23
	Telmisartan + Hydrochlorthi azide	3	1	4	
	Olmesartan + Hydrochlorthi azide	2	1	3	
Out-Patients (n_2) (27 Patients)					
ARB+BB	Telmisartan + Metoprolol	1	0	1	7.4
	Atenolol + Losartan	0	1	1	
CCB + BB	Amlodipine + Atenolol	1	1	2	14.81
CCB + ARB	Amlodipine + Telmisartan	1	3	4	14.81
BB+ DIURETCIS	Atenolol + Chlorthalidone	1	2	3	14.81
ARB + DIU-RETCIS	Losartan + Hydrochlorthi azide	4	2	6	70.74
	Telmisartan + Hydrochlorthi azide	2	3	5	
CCB+ DIU-RETCIS	Amlodipine + Hydrochlorothi-azide	1	1	2	7.4

52 (82.53%) of the people are in high adherence level. **Table IV**. Similar study was conducted by *Lee GKY et al.*, (2013)[19] using Morisky Medication Adherence. A good adherence is 6 point according to MMAS out of a total 8 point. The result was out of 1.114 patients 725 (65.1%) having a good adherence.

Table IV: Level of medication adherence in In-patient department (n1).

Level of Adherence	Number of patients	Percentage (%)
High	44	77.19
Medium	7	12.28
Low	6	10.52

Quality of life of patients involved in this study was analyzed by using MINICHAL questionnaire. The quality of life was better when the score was closer to zero. Most of the patients from in-patient department are having the good quality of life. Female patients are having good quality of life than males. Most of the patients from Out-patient department are having the good quality of life. Female patients are having good quality of life than males.

Mostly prescribed anti-hypertensive drugs in both in-patient and out-patient departments were calcium channel blockers (CCB). In in-patient department CCB were the most commonly 41.93% prescribed drugs in an age group of 66-70 years, where as in age group of 71-75 years both the CCB & ARBs equally prescribed, in out-patient department also CCB were the most commonly 67.74% prescribed drugs in an age group of 66-70 years, where as in age group of 71-75 years ARBs were the most 42.85% prescribed anti-hypertensive drugs. Mostly prescribed combination of anti-hypertensive drugs in both in-patient and out-patient departments were ARB's + Diuretics, 75% in age group of 66-70 years in In-patient, were as in out-patient it was 43.47% in an age group of 66-70 years. **Tables V** & **VI**.

Table V: Age related prescription pattern of anti-hypertensive drugs in In-patients and outpatient in single drug therapy.

In-patients (n1) (single drug therapy)								
Age group	ACEI	%	ARBS	%	BB	%	CCB	%
66-70	4	12.9	8	25.8	6	19.35	13	41.93
71-75	1	12.5	3	37.5	1	12.5	3	37.5
76-80	0	0	2	50	0	0	2	50
81-85	0	0	0	0	0	0	0	0
86-90	0	0	0	0	0	0	1	100
Out-patient (n1) (single drug therapy)								
66-70	1	3.22	7	22.58	2	6.45	21	67.74
71-75	1	14.28	3	42.85	1	14.28	2	28.57
76-80	0	0	0	0	0	0	1	100
81-85	0	0	0	0	0	0	0	0
86-90	0	0	0	0	0	0	0	0

Table VI: Age related prescription pattern of anti-hypertensive drugs in In-patients and outpatient in Combination therapy.

In-patients (n1) (Combination therapy)														
Age group	ARBs +CCB	%	ARBs +D	%	BB +ARBs	%	BB +CCB	%	BB +D	%	CCB +D	%	*a* +BB	%
66-70	1	12.5	4	50	0	0	2	25	0	0	0	0	1	12.5
71-75	0	0	0	0	0	0	0	0	0	0	0	0	0	0
76-80	0	0	3	75	0	0	1	25	0	0	0	0	0	0
81-85	0	0	0	0	0	0	0	0	0	0	0	0	0	0
86-90	0	0	1	100	0	0	0	0	0	0	0	0	0	0
Out-patients (n2) (Combination therapy)														
66-70	4	17.39	10	43.47	2	8.69	4	17.39	1	4.34	2	8.69	0	0
71-75	0	0	0	0	0	0	0	0	0	0	0	0	0	0
76-80	0	0	1	100	0	0	0	0	0	0	0	0	0	0
81-85	0	0	0	0	0	0	0	0	0	0	0	0	0	0
86-90	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Assessment of Health-Related Quality of Life of patients in both the departments

Quality of life of patients involved in this study was analyzed by using MINICHAL questionnaire. The quality of life was better when the score was closer to zero. Most of the patients from in-patient department are having the good quality of life. Female patients are having good quality of life than males. Most of the patients from Out-patient department are having the good quality of life. Female patients are having good quality of life than males. **Table VII**.

Conclusion

The present study was conducted in a Government Hospital, Rajahmundry, Andhra Pradesh., focusing mainly on Geriatrics. From the study we want to conclude that, females are the most group of population suffering with hypertension, compare to males. We used JNC 7 classification of hypertension to categorize the Stages of hypertension in present population, majority of the population were under stage I. The most preferred prescribing therapy

Table VII:
Health Related Quality of Life of patients in In-patient (n1) and Out-patients(n2) department.

In-patient				
Score	**Female**	**Male**	**Total**	**Percentage (%)**
0-5	14	4	18	31.27
6--10	16	6	22	38.59
11--15	7	4	11	19.29
16-20	2	1	3	5.26
21-25	1	1	2	3.5
26-30	0	0	0	0
31-33	1	0	1	1.75
Out-patient				
Score	**Female**	**Male**	**Total**	**Percentage (%)**
0-5	24	19	43	68.25
6--10	11	4	15	23.08
11--15	1	3	4	11.11
16-20	1	0	1	1.58
21-25	0	0	0	0
26-30	0	0	0	0
31-33	0	0	0	0

in both in-patient and out-patient was single drug therapy. Calcium Channel Blockers were the most frequently prescribed class of drugs in single drug therapy, Angiotensin Receptors blockers with Diuretics were the most commonly prescribed class of drugs in in-patient department and in out-patient department also Angiotensin Receptors blockers with Diuretics are the frequently prescribed combination of drugs. Majority of the study population were having the high level of adherence towards the anti-hypertensive therapy, which means they are in good compliance with the treatment and showed that many of the patients are having the good quality of life, we used MINIHCAL questionnaire to assess the quality of life of patients. Pharmacists positioned as the most accessible health care providers in the community, could improve patient's knowledge and adherence to the management of BP. The hospital is in large compliance with JNC guidelines, in prescribing pattern of anti-hypertensive medications to the Geriatric patients.

Conflict of interest

Authors do not have any conflict of interest to declare.

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ORIGINAL

La pandemia COVID-19 y los factores de riesgo psicosociales en personal de cuidados intensivos

The COVID-19 pandemic and psychosocial risk factors in intensive care personnel

Bolivar Alexander Caza Garzón[1], Darwin Raúl Noroña Salcedo[2], Vladimir Vega Falcón[2]

1. Universidad Regional Autónoma de Los Andes
2. Docente de la Universidad Regional Autónoma de los Andes (UNIANDES), Ecuador

Corresponding author
Vladimir Vega Falcón
E-mail: vega.vladimir@gmail.com

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Resumen

Objetivo: El objetivo fue determinar la influencia que la pandemia COVID-19 presentó en la exposición de los factores de riesgo psicosociales en la unidad de cuidados intensivos de una casa de salud, a través de la comparación de dos mediciones, antes y durante la pandemia.
Métodos: A una población constituida por 67 trabajadores, se les aplicó el cuestionario de factores de riesgo psicosocial del Ministerio de Trabajo de Ecuador (2018) en diciembre 2019 y enero 2021. Los datos fueron analizados con la prueba de Wilcoxon para comprobar diferencias estadísticamente significativas.
Resultados: En la segunda medición, el nivel promedio de exposición a los factores incrementó en un 43,6%, siendo *la falta de desarrollo de competencias* la dimensión con mayor aumento (55,3%), seguido de *otros puntos importantes* (que mide violencia y discriminación) con un 52,3%, y *la organización del trabajo* con 47,7%. En comparación con la primera medición, fueron veintinueve personas más que percibieron desfavorablemente las condiciones y organización de su trabajo en el contexto de la pandemia. Por otro lado, se registraron en todas las dimensiones diferencias significativas en relación a sus medias, con una significancia de 0,05 a través de la prueba no paramétrica de Wilcoxon.
Conclusiones: Como principales conclusiones, el estrés, la tensión y angustia suscitada a raíz de la emergencia sanitaria en el personal de cuidados intensivos, ha intensificado la probabilidad de enfermedades debido a la ausencia de procesos de capacitación, el incremento de la violencia/discriminación y la improvisación en la organización del trabajo.

Palabras clave: Factores de riesgo psicosocial, Emergencia sanitaria, Pandemia COVID-19.

Abstract

Objective: The objective was to determine the influence that the COVID-19 pandemic had on the exposure of psychosocial risk factors in the intensive care unit of a health center, through the comparison of two measurements, before and during the pandemic.
Methods: To a population constituted by 67 workers, the questionnaire of psychosocial risk factors of the Ministry of Labor of Ecuador (2018) was applied in December 2019 and January 2021. The data were analyzed with the Wilcoxon test to test statistically significant differences.
Results: In the second measurement, the average level of exposure to factors increased by 43.6%, with lack of skills development being the dimension with the highest increase (55.3%), followed by other important points (which measures violence and discrimination) with 52.3%, and work organization with 47.7%. Compared to the first measurement, there were twenty-nine more people who perceived unfavorably the conditions and organization of their work in the context of the pandemic. On the other hand, significant differences were recorded in all dimensions in relation to their means, with a significance of 0,05 through the nonparametric Wilcoxon test.
Conclusions: As main conclusions, the stress, tension and anguish aroused because of the health emergency in intensive care personnel, has intensified the probability of illness due to the absence of training processes, increased violence/discrimination and improvisation in the organization of work.

Key words: Psychosocial risk factors, Health emergency, COVID-19 pandemic.

Introducción

En la historia de la seguridad y salud ocupacional, se registran conquistas importantes en aras de asegurar un ambiente saludable y seguro para los trabajadores. Ejemplo de ello es la conformación (en la Edad Media) de los primeros gremios, asociaciones o agrupaciones de profesionales que, bajo la figura de la obligatoriedad de protección de sus patronos, demandan mejoras en las herramientas y condiciones laborales. Pero sería muchos años más tarde, en plena Revolución Industrial (siglo XVII), en donde se requiere mayor mano de obra en las textileras, talleres y áreas de producción para satisfacer, la generación de bienes y productos de consumo.

Es en este contexto de jornadas de más de doce horas diarias, sin las medidas mínimas de seguridad, en dónde se registran frecuentemente accidentes, mutilaciones y muertes en los operarios, muchos de los cuales se tratan de niños, aparecen legislaciones de amparo y protección que se basan en estudios de los contaminantes físicos, químicos y biológicos relacionados a disminuir las enfermedades, y, por otro lado, la evaluación de factores mecánicos para impedir la ocurrencia de los accidentes laborales.

La primera mitad del siglo XX da paso al desarrollo y perfeccionamiento de la metodología y las técnicas de evaluación y control de los contaminantes y los factores mecánicos, y por muchos años, estos cuatro factores de riesgo son los más representativos en la gestión técnica de prevención[1].

La globalización, la tecnificación del proceso de producción y la necesidad de contar con altos estándares de calidad y eficiencia, cambian las reglas en la elaboración de bienes y productos. Ya no es indispensable la mano de obra calificada debido al trabajo más rápido y efectivo de las máquinas. Como resultado se obtiene la precarización laboral y el desempleo y empieza una competencia académica y laboral para conservar los puestos de trabajo en una sociedad materialista de consumo.

Bajo el slogan de producir más con mayor ahorro de recursos, los trabajadores se adaptan a un contexto de trabajo a presión con altas demandas, y en donde el propio colaborador ubica muy alto sus límites mentales y físicos. Como es de esperarse, este frenesí de tensión, angustia y preocupación se traduce en enfermedades, accidentes y pérdidas económicas para las empresas[2].

Por ejemplo, con base a los resultados que proporciona la Comisión Europea (2010), las enfermedades que causan esta presión laboral corresponden al 18% de todos los problemas de salud en Europa, lo cual afecta hasta en dos veces más a los sectores de educación y salud. Por otro lado, el individuo, al experimentar esta tensión se incapacita y, tan solo en el Reino Unido, el costo por el absentismo derivado de estos problemas asciende a cinco mil millones de dólares al año. En países como Austria, el 16% de todas las indemnizaciones son por estrés laboral y en los Estados Unidos, para el año 2019, el 15% de todas las demandas laborales corresponden a compensaciones por incapacidades provenientes a la tensión y estrés[3].

Ante este escenario, una nueva ola de estudios aparece con el objetivo de describir, comprender y predecir estos fenómenos afines con la tensión emocional. Los factores ergonómicos y psicosociales son los nuevos riesgos que se ocupan del estudio de la adecuación del trabajo a las características antropométricas del hombre, y de las relaciones interpersonales y sentimientos del trabajador con su entorno laboral[4].

En términos más específicos, los factores psicosociales representan la percepción positiva o negativa y la posibilidad de daño que generan: el medio ambiente de trabajo; la organización de la empresa; la sobrecarga; la inequidad; la injusticia; la presencia de otros contaminantes; la alienación; la enajenación; la cultura organizacional; entre otros. Desde la consolidación del concepto, es difícil coincidir con una clasificación estable, en buena parte debido a que los factores conllevan el estudio de las características individuales del trabajador, así como las fuerzas de su entorno extralaboral, las características de su trabajo y el tipo de ambiente al que se enfrenta en su empresa.

No obstante, en los últimos 20 años del siglo XX, varios autores las definen en virtud de dos líneas conceptuales: como las interacciones entre el trabajador con el trabajo (administración, organización y contenido) y como agentes estresores. Con base al primer modelo, en 1984 la Organización Internacional del Trabajo (OIT) los define como todo elemento externo con el cual la persona se relaciona (las actividades que le corresponde, los compañeros, la burocracia, entre otros), y cuya presencia o carencia devenga en desequilibrios psicológicos. Esta noción abarca el relacionamiento del individuo con su entorno y la probabilidad de daño por su exposición[5].

Dos años más tarde, la misma OIT (1986), complementa la definición anterior refiriéndose, en primer lugar, como los daños que devienen de la experiencia y las percepciones del individuo, y en segundo lugar, señala que existen seis tipos de factores: contenido de la tarea; organización; gestión del trabajo; ambiente; funciones; y requerimientos de los colaboradores. Por primera vez, en esta conceptualización se señala la palabra riesgos, adoptando una postura más cercana a la enfermedad y al daño psicológico[6].

En referencia a las definiciones cercanas al modelo del estrés laboral, la OIT (1998), señala que los factores psicosociales

son estresores que representan retos y desafíos para el individuo generando tensión y el uso de sus competencias laborales para resolver estos problemas. Años más tarde, Moncada (2000) menciona que son el resultado de la acción de características del trabajo, las condiciones y la organización en la salud de los colaboradores[7].

Los factores psicosociales pueden fortalecer el trabajo, llevar a niveles más altos de desarrollo y de salud laboral[8]. Finalmente, la forma en cómo valora el individuo la experiencia laboral incluyendo los componentes externos de familia y amigos, le enfermará o le generará salud mental positiva[9].

Estas dos últimas definiciones denotan que los factores psicosociales pueden estar relacionados con aprendizaje y satisfacción laboral. Cuando en el ambiente de trabajo, se controlan los contaminantes, su personal cuenta con las competencias necesarias y se ha satisfecho con las necesidades de formación y capacitación; todos los elementos anteriormente descritos promoverán la creatividad, la innovación y el desarrollo de conocimientos y habilidades. Los trabajadores se encuentran felices, comprometidos y con una buena calidad de vida.

En este contexto, los factores psicosociales reciben el nombre de factores eugenésicos, puesto que incrementan la probabilidad de generar grupalidad, autoestima, competencias laborales y salud mental positiva. No obstante, si las percepciones son negativas frente a las malas condiciones, organización y gestión; los factores son de riesgo, y en este sentido aumentan la probabilidad para que el personal se enferme o se accidente[10].

Al considerar a los factores psicosociales en el modelo descriptivo del estés laboral, vale la pena detallar las teorías más relevantes que abordan al fenómeno con un alcance explicativo. El estrés laboral es una preocupación constante por parte de los organismos de salud y del trabajo, ya que existe suficiente evidencia científica que la vincula con enfermedades, accidentes laborales y pérdidas económicas en todo el mundo. Si bien la tensión emocional, que deviene de los problemas de la vida, está presente a lo largo de la historia humana, hay un punto de inflexión, nuevamente, en la mitad del siglo XX, cuando con el objetivo de privilegiar aún más la productividad, la eficiencia y la efectividad; se diseñan nuevas maneras de optimizar el trabajo.

Se empieza por tecnificar la industria a través de la producción en línea. Las personas se especializan en una sola tarea lo que hace precaria la mano de obra del trabajador. Se abre un nuevo abanico de campos de especialización, donde el ciudadano empieza a competir por puestos de trabajo que aseguran una vida digna para su familia. La persona comienza a auto exigirse más, a preocuparse por producir más, y en general a tensionarse por la incertidumbre del futuro[11].

Hans Selye acuña por primera vez la palabra estrés para describir un conjunto de sintomatología que padecen los enfermos de un hospital que, como factor común, trabajan más de ocho horas, los siete días de la semana, y bajo condiciones ambientales deplorables. Se da cuenta que experimentan un proceso de angustia compuesto por tres estados. Cuando sus pacientes conciencian la presencia de un problema, aumentan su frecuencia cardíaca y respiratoria, sienten miedo lo que provoca liberación de catecolaminas por parte de las glándulas suprarrenales que incrementan el gasto cardíaco en músculos (fase de alarma). Posterior, viene una fase de resistencia, en dónde el individuo trata de resolver el problema con las herramientas que cuenta[12].

No obstante, si estos recursos son insuficientes, la intranquilidad, ansiedad y preocupación continuarían aumentando escalarmente. Si el problema no es resuelto, la última etapa del proceso, la denomina como agotamiento emocional, en la cual la persona experimenta cansancio extremo, debilidad y fatiga. Esta etapa estaba muy próxima a la enfermedad[12].

Con los años aparecen más esquemas interpretativos del estrés, como, por ejemplo, el de Lazarus y Folkman (1989) que relatan que el fenómeno se produce cuando el trabajador consume sus recursos (habilidades, conocimientos, destrezas). A finales del siglo XX, con el advenimiento de las teorías de equidad, Siegrist (1993), indica que cuando se rompe el equilibrio entre el esfuerzo que brinda el colaborador y las recompensas a las que tiene derecho, es el momento exacto en el que aparece el estrés. Finalmente, Karasek (1995) interpreta el estrés como la presencia de alto control en la empresa. Cuando el ambiente laboral coarta la opción de innovación y creatividad de los trabajadores, y los expone a alta carga de trabajo sin apoyo social, el resultado no es otro que procesos desgastantes de tensión y decaimiento[13].

Pero no todo estrés es malo. El euestrés, al igual que la eugenesia en los factores psicosociales, se define como los desafíos que el colaborador necesita para desarrollar sus competencias, su innovación y creatividad. De acuerdo con este principio, el trabajador tiene necesidades de superación, que, si son satisfechas en los ambientes de trabajo, desarrollará sus conocimientos, su satisfacción y calidad de vida. Por el contrario, el diestrés, es el nombre correcto para describir los procesos mórbidos cuando existe una mala planificación laboral, ausencia o carencia de competencias y factores externos agobiantes. En este sentido la OIT, en la asamblea General de Julio de 1998, califica al estrés laboral como pandemia del siglo XX y vaticina que sería una de las cinco dolencias permanentes en la industria para el 2022[14].

De acuerdo con estos razonamientos, los factores psicosociales o estresores al que un trabajador se

enfrenta pueden devenir en salud o enfermedad en dependencia de la efectividad de la gestión de seguridad y salud ocupacional. Sin embargo, durante las catástrofes ambientales, accidentes mayores como terremotos o estados de emergencia que se decretan por la ocurrencia de la pandemia COVID-19, la tensión emocional, la angustia y preocupación de la población pueden incrementar la exposición y la probabilidad de daño a la salud.

El personal que brinda atención en las unidades de cuidados intensivos durante los meses de marzo a septiembre de 2020, en la pandemia origina cuadros clínicos de depresión y un contagio de la enfermedad en el 40% del personal a escala mundial. Además de esta situación, el desarraigo familiar que se sufre por los internistas que deben convivir separado de sus parientes en los meses más críticos de contagio, la incomodidad en el uso de los equipos de protección y ropa de trabajo, la falta de preparación del servicio hospitalario ante una contingencia de esta magnitud y al desabastecimiento de insumos médicos por parte del servicio hospitalario público.

No es de extrañarse entonces que, la intensidad con la que estos factores consumen los recursos y mecanismos de defensas del personal sanitario se dupliquen, especialmente en el período de mayor incertidumbre del virus conllevando a agotamiento emocional y en algunos casos la muerte[15].

Por otro lado, la recuperación del concepto de autoprotección del personal de cuidados intensivos, el mejoramiento de sus condiciones de trabajo, y el desarrollo de mejores formas de dirección y delegación del trabajo, comienzan con el análisis de una línea base, de interpretar cuáles son los factores que se incrementan como producto de la presencia de la pandemia, de conocer qué dimensiones de los factores están actualmente en indicadores altos. Esta información será la fuente para la elaboración de planes y programas de mitigación de los factores de riesgo que propendan al mejoramiento de las condiciones de trabajo y calidad de vida de los médicos y enfermeras de estas casas de salud y, por ende, el mejoramiento del servicio que se brinda a la comunidad.

Es por eso por lo que la presente investigación tiene el objetivo de analizar el impacto de la pandemia en la exposición de los factores de riesgo laborales en una unidad de cuidados intensivos de un hospital de la ciudad de Riobamba, a través de dos mediciones, una antes del estado de emergencia sanitario, y la segunda al cabo del año y un mes de decretarse el inicio de la pandemia COVID-19 en Ecuador. Para tal propósito se utiliza la encuesta que el propio Ministerio de Trabajo del Ecuador diseña para el análisis descriptivo de los factores de riesgo, y se construye un marco conceptual y metodológico sobre los cuales se interpretan los resultados finales del estudio.

Métodos

Se desarrolló un estudio de tipo observacional, transversal, prospectivo y descriptivo, en el que se utilizó la totalidad (67 personas) de la población del área de cuidados intensivos de un hospital nivel 1 de la ciudad de Riobamba, en Ecuador.

Se tomó en consideración criterios de selección para la confirmación de la población final. Se incluyeron a todos los trabajadores de la salud que laboraban en el área de cuidados intensivos por más de 6 meses de permanencia y que firmaron el consentimiento informado. Se excluyeron a quienes al momento del levantamiento de información se encontraban ausentes por baja médico o permiso de maternidad, o en proceso de desvinculación de la institución. Se eliminaron a aquellos informantes que remitieron el cuestionario incompleto.

El cuestionario utilizado fue elaborado por el Ministerio de Trabajo de Ecuador en 2018 y fue validado en una muestra conformada por 385 empresas en una población de 4.346 sujetos, obteniéndose un índice de fiabilidad de 0,96. Estuvo constituida por ocho dimensiones y obedeció a la teoría del estrés laboral de Siegrist (1989). Evaluó las demandas físicas y mentales carga y ritmo de trabajo; percepción de desarrollo de conocimientos/habilidades; desarrollo de competencias; capacidad de dirigir el trabajo liderazgo; capacidad de participar en decisiones margen de acción y control; distribución, comunicación y acceso de tecnología organización de trabajo, descanso y resarcimiento recuperación, redes sociales de apoyo soporte y apoyo, y violencia y discriminación otros puntos importantes.

La encuesta fue auto administrada y estuvo constituida por 58 afirmaciones con opción de respuesta de escala Likert: completamente de acuerdo (4); parcialmente de acuerdo (3); poco de acuerdo (2); en desacuerdo (1). Con base a las asignaciones numéricas, mientras mayor fue la sumatoria de los puntajes, menor fue la presencia de estrés laboral. Para el proceso de calificación, se sumaron las preguntas de cada dimensión y se compararon con la tabla de baremos.

La escala de valoración utilizada se presenta en la **tabla I**.

Tabla I: Calificación del instrumento.

RESULTADO POR DIMENSIONES	RIESGO BAJO	RIESGO MEDIO	RIESGO ALTO
Carga y ritmo de trabajo	13 a 16	8 a 12	4 a 7
Desarrollo de competencias	13 a 16	8 a 12	4 a 7
Liderazgo	18 a 24	12 a 17	6 a 11
Margen de acción y control	13 a 16	8 a 12	4 a 7
Organización del trabajo	18 a 24	12 a 17	6 a 11
Recuperación	16 a 20	10 a 15	5 a 9
Soporte y apoyo	16 a 20	10 a 15	5 a 9
Otros puntos importantes	73 a 96	49 a 72	24 a 48

Un riesgo alto significó que la probabilidad de presentar enfermedades e intervenir en accidentes fue elevada, para el riesgo medio dicha probabilidad fue moderada y en el riesgo bajo, la probabilidad y consecuencia fue mínima.

Además, se efectuaron dos tipos de análisis estadísticos. En primer término, se calcularon las frecuencias y porcentajes de las variables categóricas nominales (género; edad; puesto; estado civil; y escolaridad). También se calcularon los resultados de la encuesta de factores de riesgo con los porcentajes y frecuencias de las categorías alto, medio y bajo. Adicionalmente, se halló la sumatoria de las personas expuestas sumando los valores de alto y medio, y los registros de bajo representaron a los no expuestos.

Para la comprobación inferencial, se formuló una hipótesis de investigación que indicaba que habría diferencias estadísticamente significativas entre las mediciones del antes y durante la pandemia. Para tal propósito, se utilizaron las sumatorias numéricas globales de cada dimensión y el valor total de la encuesta de factores de riesgos.

Se calculó la normalidad de los datos a través de la prueba de Kolmogorov Smirnov, y una vez confirmada su no parametricidad, se efectuó el cálculo de análisis de varianzas a través de la prueba de Wilcoxon, con un nivel de significancia del 0,05 para muestras relacionadas. Las hipótesis de investigación fueron las siguientes:

Hi: La segunda medición, realizada durante la pandemia, es significativamente mayor con respecto a la primera medición en las ocho dimensiones del cuestionario de factores psicosociales de riesgo.

Ha: La segunda medición, realizada durante la pandemia, es significativamente menor con respecto a la primera medición en las ocho dimensiones del cuestionario de factores psicosociales de riesgo.

H0: Los valores de exposición registrados antes y durante la pandemia en las ocho dimensiones de la encuesta son iguales.

En referencia a las consideraciones éticas, el estudio fue aprobado por el comité de ética de la casa de salud estudiada, el cual recomendó sigilo en la divulgación del nombre del hospital. También, el personal firmó consentimiento informado en donde se dio a conocer los alcances y propósito de la investigación, así como el carácter de confidencial en el manejo de la información de los participantes. Además, se respetaron los principios éticos de la Declaración de Helsinki para los estudios con seres humanos, divulgados por la Asociación Médica Mundial, además de sus posteriores actualizaciones.

Finalmente, los resultados estuvieron a disposición del departamento de seguridad y salud de la institución estudiada, para la divulgación de resultados y el diseño e implementación de planes de mitigación de riesgos psicosociales.

Resultados

En la **tabla II** se exponen los resultados socio demográficos correspondientes a la población estudiada.

Tabla II: Datos sociodemográficos.

GÉNERO	FRECUENCIA	PORCENTAJE
Mujer	41	61,2
Hombre	26	38,8
Edad	**Frecuencia**	**Porcentaje**
21 - 27	14	20,9
27 - 35	29	43,3
35- 42	7	10,4
42- 50	10	14,9
más de 50	7	10,4
Puesto	**Frecuencia**	**Porcentaje**
Médico intensivista	2	3,0
Médico residente	27	40,3
Enfermeras	29	43,3
Auxiliar de enfermería	9	13,4
Estado civil	**Frecuencia**	**Porcentaje**
Solteros	16	23,9
Casados	30	44,8
Unión libre	15	22,4
Divorciados	6	9,0
Escolaridad	**Frecuencia**	**Porcentaje**
Tecnólogos/Bachiller	9	13,4
Tercer Nivel	56	83,6
Cuarto nivel	2	3,0

X=67

Resultados de la encuesta del MDT, antes y durante la pandemia COVID-19.

La **tabla III** muestra los resultados descriptivos correspondientes a la encuesta, con las valoraciones altas, medias y bajas, del antes y el durante la pandemia COVID-19.

Tabla III: Resultados descriptivos encuesta, valoraciones altas, medias y bajas del antes y el durante la pandemia COVID-19.

DIMENSIONES	ANTES			DURANTE		
	Alto	Medio	Bajo	Alto	Medio	Bajo
Carga y ritmo de trabajo	4 (6%)	22 (32,8%)	41 (61,2%)	10 (14,9%)	35 (52,2%)	22 (32,8%)
Desarrollo de competencias	0 (0%)	7 (10,4%)	60 (89,6%)	6 (9%)	38 (56,7%)	23 (34,3%)
Liderazgo	2 (3%)	10 (14,9%)	55 (82,1%)	7 (10,4%)	32 (47,8%)	23 (41,8%)
Margen de acción y control	1 (1,5%)	19 (28,4%)	47 (70,1%)	11 (16,4%)	37 (55,2%)	19 (28,4%)
Organización del trabajo	0 (0%)	4 (6%)	63 (94%)	6 (9%)	30 (44,8%)	31 (46,3%)
Recuperación	3 (4,5%)	20 (29,9%)	44 (65,7%)	7 (10,4%)	44 (65,7%)	16 (23,9%)
Soporte y apoyo	0 (0%)	10 (14,9%)	57 (85,1%)	12 (17,9%)	26 (38,8%)	29 (43,3%)
Otros puntos importantes	0 (0%)	7 (10,4%)	60 (89,6%)	0 (0%)	42 (62,7%)	25 (37,3%)

X=67

Para comprender de mejor manera el incremento de la exposición a los factores psicosociales de riesgo, se sumaron las valoraciones de los riesgos alto y medio, dado que ambas conllevaron un impacto moderado y considerable en la salud de los trabajadores. Esta sumatoria correspondió a las personas expuestas, mientras que el nivel bajo que presentó un potencial mínimo de daño, fueron considerados como los no expuestos.

En la **tabla IV** se evidencian los resultados correspondientes a la exposición del antes y durante la pandemia, detallándose el incremento de exposición.

Análisis inferencial, comprobación de hipótesis

Para la comprobación de las hipótesis, se utilizó la numeración de la escala de Likert (datos categóricos ordinales) y en específico las sumatorias de cada dimensión del instrumento para posteriormente, realizar la comprobación de medias de las evaluaciones de los factores psicosociales del antes y durante la pandemia COVID-19.

Los resultados correspondientes a la prueba de normalidad de la sumatoria de los factores de riesgo en la segunda medición, mediante la prueba de Kolmogorov-Smirnov, con la corrección de significación de Lilliefors, mostró un estadístico de ,143 con 67 gl y significación de ,002. Por ello, se pudo corroborar que los datos de la segunda medición no fueron paramétricos (segmentación asintótica menor a 0,05). Por la curva de distribución y el tipo de los datos, se seleccionó la prueba de Wilcoxon para dos muestras relacionadas.

En la **tabla V** se reflejan los resultados correspondientes a la comparación de las medidas de tendencia central y de dispersión entre el antes (1) y durante (2) la pandemia COVID-19.

La **tabla VI** expone los resultados de la comparación de medias no paramétricas, mediante la prueba de Wilcoxon.

Tabla IV: Resultados de exposición del antes y durante la pandemia e incremento de exposición.

Dimensiones	Antes		Durante		Incremento
	Expuestos	No expuestos	Expuestos	No expuestos	de exposición
Carga y ritmo de trabajo	26 (38,8%)	41 (61,2%)	45 (67,2%)	22 (32,8%)	19 (28,4%)
Desarrollo de competencias	7 (10,4%)	60 (89,6%)	44 (65,7%)	23 (34,3%)	37 (55,3%)
Liderazgo	12 (17,9%)	55 (82,1%)	39 (58,2%)	28 (41,8%)	27 (40,3%)
Margen de acción y control	20 (29,9%)	47 (70,1%)	48 (71,6%)	19 (28,4%)	28 (41,7%)
Organización del trabajo	4 (6,0%)	63 (94%)	36 (53,7%)	31 (46,3%)	32 (47,7%)
Recuperación	23 (34,3%)	44 (65,7%)	51 (76,1%)	16 (23,9%)	28 (41,8%)
Soporte y apoyo	10 (14,9%)	57 (85,1%)	38 (56,7%)	29 (43,3%)	28 (41,8%)
Otros puntos importantes	7 (10,4%)	60 (89,6%)	42 (62,7%)	25 (37,3%)	35 (52,3%)
					Promedio: 29 (43,66%)

X=67

Tabla V: Comparación de las medidas de tendencia central y de dispersión entre el antes y durante la pandemia COVID-19.

Estadísticos descriptivos	Media		Desviación estándar		Mínimo		Máximo	
	(1)	(2)	(1)	(2)	(1)	(2)	(1)	(2)
Carga y ritmo de trabajo	12,9	10,4	2,5	2,5	6	4	16	15
Desarrollo de competencias	14,5	11,4	1,7	2,3	8	6	16	16
Liderazgo	21,0	16,1	3,9	3,9	8	6	24	22
Margen de acción y control	13,5	10,7	2,5	2,5	5	5	16	15
Organización del trabajo	21,9	16,9	2,4	3,2	13	10	24	24
Recuperación	16,2	13,9	3,3	2,7	7	8	20	19
Soporte y apoyo	18,2	13,7	2,1	3,1	12	7	20	19
Otros puntos importantes	85,8	68,2	9,6	9,6	56	49	96	85
Total	203,9	160,1	24,7	23,6	127	113	232	204

Tabla VI: Comparación de medias no paramétricas. Prueba de Wilcoxon.

Estadísticos de prueba (comparación antes y durante)	Z	Sig. asintótica (bilateral)
Carga y ritmo de trabajo	-5,751[b]	0,000
Desarrollo de competencias	-6,998[b]	0,000
Liderazgo	-6,547[b]	0,000
Margen de acción y control	-6,360[b]	0,000
Organización del trabajo	-6,733[b]	0,000
Recuperación	-5,521[b]	0,000
Soporte y apoyo	-6,935[b]	0,000
Otros puntos importantes	-7,046[b]	0,000
Total	-7,088[b]	0,000

Discusión

De acuerdo con la **tabla II**, en el personal de la unidad de cuidados intensivos, se registra participación mayoritaria de las mujeres con el 61,2%, el promedio de la edad se ubica en los 35 años con una desviación estándar de 9,7. La mayoría de los sujetos encuestados laboran en calidad de médico residentes y enfermeros, con el 40,3% y el 43,3% respectivamente. Las personas casadas obtienen el 44,8% y en su mayoría la población

presenta una escolaridad universitaria completa (83,6%). Según los resultados de la **tabla III**, en las ocho dimensiones del instrumento de medición se constata incremento en el nivel de exposición, en el cual los participantes pasan de un riesgo bajo a uno moderado y alto. De acuerdo con la magnitud de dicho incremento, las dimensiones que registran mayor ampliación de sus indicadores son: la discriminación y violencia (otros puntos importantes), seguido del soporte y apoyo, recuperación, organización del trabajo, margen de acción –control, liderazgo, desarrollo de competencias y carga– ritmo de trabajo.

Según la **tabla IV**, en la primera medición de los factores psicosociales que se realiza en diciembre de 2019, la carga y ritmo de trabajo es la dimensión de mayor exposición. La sumatoria de los resultados altos y medios asciende al 38,8% con lo cual se evidencia una percepción negativa acerca de las demandas de los usuarios, de la imposibilidad de ser creativo e innovador, acerca del estrés y la ausencia del tiempo para el trabajo. Para la segunda medición, en esta misma dimensión, se registra un incremento del 28,4% (19 participantes que pasan de riesgo mínimo a moderado/alto). Es necesario indicar que, en la segunda medición, la carga y ritmo de trabajo, es la tercera dimensión con mayor exposición.

En segundo lugar, en la recuperación que hace referencia a la preocupación de la institución en que el trabajador pueda restaurar su energía psíquica, se evidencia incremento de 28 personas (41,8%) que pasan a un nivel de riesgo alto/medio. Es importante mencionar que esta dimensión es el factor menos favorable en la segunda medición.

En referencia al margen de acción y control que es la apreciación sobre la posibilidad de la participación en la toma de decisiones, el incremento es del 41,8% correspondiente a 28 individuos en riesgo alto/medio. Esta dimensión pasa de ser la tercera con mayor exposición a ubicarse en el segundo lugar en la medición que se realiza durante la pandemia.

El liderazgo, entendido en el cuestionario como la efectividad de los líderes en la gestión laboral, la percepción negativa sube en 40,3 puntos porcentuales lo que significa que 27 participantes se ubican en riesgo alto/medio. Esta variable de la prueba pasa del cuarto al segundo lugar de mayor exposición entre las dos mediciones.

Con base a los registros de soporte y apoyo que refiere a las redes sociales de ayuda, existen 28 personas que pasan de un riesgo mínimo a una valoración moderada/alta, lo que representa incremento del 41,8%. El soporte y apoyo pasa del quinto al séptimo lugar entre las dos mediciones realizadas.

Adicionalmente en el factor desarrollo de competencias, (que es el anhelo de los trabajadores por fortalecer sus habilidades), hay 37 (55,3%) personas que incrementan su riesgo psicosocial entre el antes y el durante la pandemia COVID-19. Del sexto puesto, esta dimensión pasa a colocarse en la cuarta posición entre los de mayor daño.

El factor de *otros puntos importantes*, que evalúa la discriminación y violencia, incrementa su nivel de riesgo en un 52,3%, lo que representa 35 personas que están afectadas. En la primera medición, esta dimensión está en séptima posición, y en la última evaluación se encuentra entre las cinco más expuestas.

La organización del trabajo es la única dimensión que tanto antes como durante la pandemia, se sitúa como la de menor riesgo entre las siete dimensiones restantes de la encuesta. La percepción negativa de los informantes referentes a la planificación y delegación de las tareas se incrementa del 52,3%, lo que significa que 35 personas estan afectadas con riesgo alto/medio.

Según la **tabla V**, los estadísticos descriptivos de las diferencias de las medias indican reducción en las sumatorias totales de todos los factores de la encuesta, en un promedio de -5,3 puntos entre ambas mediciones (antes y durante la pandemia COVID-19). La reducción no significa que la percepción a los factores haya mejorado, hay que recordar que las afirmaciones del cuestionario manejan una escala de Likert en el cual las respuestas altas indican ambiente saludable, y las valoraciones bajas probabilidad de daño.

Por lo tanto, en la resta final, se pierdenido 44 puntos (203,9-160,1) que reflejan mayor inconformidad con los factores evaluados. En este sentido, la dimensión que mayor reducción presenta fue otros puntos importantes (violencia y discriminación) con 18 puntos; organización del trabajo con 5 puntos menos, liderazgo (-4,9 puntos); soporte y apoyo (-4,5 puntos); desarrollo de las competencias (-3,1 puntos); margen de acción y control (-2,8 puntos); carga y ritmo de trabajo (-2,5 puntos); y recuperación (-2,3 puntos).

El análisis de la **tabla VI** permite confirmar que en todas las mediciones existen diferencias estadísticamente significativas (en todos los resultados se ubican valores por debajo del valor de 0,05), lo que a su vez rechaza la hipótesis nula de investigación, y como se analiza en dicha tabla, se comprueba la hipótesis de investigación: la pandemia COVID-19 incrementa la exposición de todos los factores psicosociales de riesgo evaluados.

Los resultados muestran que la dimensión que alcanza el riesgo más alto debido a la pandemia COVID-19 es el desarrollo de competencias.

Un estudio que se realiza en España por Alquézar (2020), acerca del impacto de la pandemia en los servicios hospitalarios, muestra que en los cambios estructurales y de rotación del personal de la Unidad de Cuidados Intensivos (UCI), los galenos no poseen la solvencia técnica para cubrir tales ciclos y no cuentan con las destrezas necesarias para la identificación y asistencia en los casos de mayor sospecha de infección. Esto a la postre, significa el aparecimiento de ideas obsesivas y depresión en el 25% de la población estudiada[16].

Por su parte, Monterrosa (2021), en una muestra de 294 médicos, determina que el 38,4% presenta trastorno de ansiedad generalizada derivada del temor al contagio. En este sentido, el personal admite que parte de ese miedo se genera por el desconocimiento en los procesos de intervención. El no contar con las competencias específicas de asistencia a pacientes con sospecha de COVID-19, ocasiona incertidumbre, vacilación e indecisión; situación que no recae tanto en la responsabilidad patronal, sino que, obedece más al contexto de una nueva enfermedad totalmente desconocida en los primeros meses del 2020[17].

En segundo lugar, la violencia y la discriminación (llamado como otros puntos importantes), es el siguiente incremento más significativo. Con base a las consideraciones hechas por Lorente (2020), en una investigación cuyo propósito es describir el aumento de la violencia suscitada por la emergencia sanitaria, explica que en los acontecimientos que ponen en riesgo la vida de las personas (como accidentes mayores y desastres naturales), aflora en la psique humana el instinto de conservación con el aparecimiento de instintos agresivos relacionados a la sobrevivencia[18].

No es de extrañarse entonces que, en situaciones de extrema conmoción se acreciente la violencia psicológica, la discriminación y el acoso laboral como respuesta irracional ante la emergencia. Lo anterior comprueba la teoría de la agresividad innata promulgada por Thomas Hobbes. No obstante, las víctimas más probables son las que presentan grados de vulnerabilidad representadas en género, discapacidad o interculturalidad[19].

La organización del trabajo también se considerada dañina para la salud por parte de los encuestados. En este sentido se analizan dos estudios que presentan similares resultados en población médica. Monterrosa (2020), en un estudio sobre el estrés laboral y con una población de 531 médicos concluye que el 72,9% lamentan la poca comunicación que reciben de su trabajo, la ausencia de metas claras y el no reconocimiento durante los meses con mayor pico de contagios[20].

Navinés (2021), en un estudio documental sobre estrés y burnout resalta la presencia de barreras que impiden la efectividad de la comunicación como una causal importante para el deterioro de la salud en casos de burnout de los últimos cinco años. Al respecto conviene señalar, que la percepción negativa de los informantes respecto al acceso de información obedece a la urgencia del estado de emergencia que modifica el desarrollo adecuado del trabajo. No obstante, esta misma dimensión se sitúa en el antes y durante, como la de menor exposición en comparación con el resto de los factores[21].

La dimensión de recuperación, que indica el interés de la organización de contar con trabajadores que puedan abstraerse en actividades familiares y de ocio para una buena salud; estudios similares que se realizan durante la pandemia, en personal médico, como el de Ayala (2020) y el de Cabay (2022), indican un registro porcentual de exposición de más del 45% de la población total investigada. Valor que es similar al que se obtiene en la segunda medición del estudio. No obstante, la gran diferencia que se presenta en el dato correspondiente al antes de la pandemia, es de apenas el 6%. Estos datos reflejan la situación que vive el personal de las UCI, que deben confinarse en cuartos cercanos a sus trabajos para impedir el contagio a sus seres queridos, en la primera mitad del año 2020[22,23].

Al igual que el anterior factor, el soporte y apoyo obtiene igual valor porcentual de incremento entre las mediciones. El soporte, amparo y auxilio de los miembros del equipo de trabajo también se ve con afectación durante la pandemia del COVID-19. Al respecto, antes de la pandemia los estudios que se realizan desde el 2015, evidencian que el personal de la salud se caracteriza por presentar indicadores positivos, como la consciencia social, pero también, registros bajos en grupalidad y creatividad.

La dificultad de desarrollar sentido de equipo y fraternidad obedece a la competitividad y rivalidad que esta profesión consigue a lo largo de los años. Con base a los estudios realizados por Pando (2006), y Migote (2013), es evidente que el prestigio, la reputación y la alta estima que la sociedad en general siente hacia la misión del galeno, interfiere con el desarrollo de las redes sociales de apoyo, que son factores eugenésicos que disminuyen la probabilidad de enfermedades y de accidentes laborales[24,25].

Sin embargo, en este estudio, esta disminución antes de la pandemia se ubica en el quinto orden de exposición, por lo que se podría intuir que el grupo de trabajo se muestra con un trabajo en equipo adecuado.

También cabe comparar el antes y durante de la dimensión margen de acción y control, en dónde se puede observar como la percepción negativa del ambiente que restringe la innovación y creatividad, se incrementa durante los meses de emergencia sanitaria; datos que son similares a los que obtienen Guanche (2020), Santos (2020) y Félez (2020), que estudian este

factor en personal de la salud coincidiendo en que esta coerción genera alto nivel de estrés y predisposición a las enfermedades mentales[26,27,28].

En las investigaciones referidas, los autores manifiestan que antes de la pandemia, la estructura laboral de la asistencia sanitaria pública enajena al trabajador de la salud, impidiéndole el uso de sus competencias en formas creativas de trabajo y restringiéndolos a maneras establecidas y rutinarias que resultan alienadas. Por tanto, la mayor exposición de factores psicosociales son la falta de pertenencia y la baja productividad.

Es importante analizar que esta dimensión antes de la pandemia es la tercera en el orden de riesgo y, en la medición siguiente, se ubica en la segunda posición. Pero también es conveniente examinar que la situación de emergencia sanitaria impide el desarrollo de la creatividad e innovación, puesto que los esfuerzos se concentran en salvar vidas y evitar los contagios.

La dimensión de liderazgo, en la primera medición se encuentra cuarta en el orden de exposición, y para la medición siguiente se consolida en el sexto lugar. Sin embargo, como en el resto de las variables, hay incremento considerable en su nivel de riesgo por acción de la pandemia. La inconformidad del personal sanitario frente a la gestión de los líderes se sustenta en la falta de dotación de insumos médicos y de entrega de equipos de protección personal.

Para Chomali (2021), las quejas en la gestión de la pandemia se deben a la ausencia de planes de contingencia de las unidades de salud y a la demora en la asignación presupuestaria de los gobiernos centrales para la contratación de más médicos y enfermeras[29].

La carga y ritmo de trabajo, es uno de los estresores de mayor presencia en el área de salud y de educación. Estudios que se realizan antes de la pandemia, como el de Carrión (2014), ubican a los médicos y enfermeras como las ocupaciones con el mayor nivel de solicitudes, requerimientos y responsabilidades[30]. Para Gómez (2004), la sobrecarga de trabajo resulta ser el factor de mayor estrés en la rama médica, por encima de la docencia y de los operadores de vuelo[31].

Las exigencias de las UCI durante la pandemia, según Delgado (2020), se duplican con turnos de más de dieciséis horas en los meses de mayor pico de contagio, el agotamiento emocional es muy extenuante registrándose renuncias, depresión e ideas auto líticas en el personal médico[32]. Con base a todos los estudios que se consultan, el hecho de que todas las dimensiones se incrementen del 28% al 44%, se explica por la conmoción social, la incertidumbre del futuro, el incremento de la carga de trabajo, la violencia laboral, la falta de horas de sueño, la ausencia de equipos de protección personal e insumos en los hospitales públicos de Ecuador.

El presente estudio evidencia que la COVID-19, reconocida como un "cisne negro" por ser un suceso raro, ocasionar alto impacto y tener predictibilidad retrospectiva (33), incrementa el riesgo de sufrir enfermedades y accidentes labores en todas las dimensiones de los factores psicosociales que se analizan, pues el personal se desempeña en condiciones atípicas que requieren ajustes de protocolos, modificaciones de turnos, y otras adaptaciones cotidianas[34].

Conclusiones

La emergencia sanitaria de la COVID-19 incrementó el riesgo de sufrir enfermedades y accidentes labores en todas las dimensiones de los factores psicosociales en el personal UCI de un hospital público de la ciudad de Riobamba. Veintinueve personas en promedio pasaron a estar consideradas dentro de la categoría de riesgo alto en comparación con la evaluación antes de la pandemia.

El aumento de la tensión, angustia y preocupación provocada por la crisis incrementó el daño psicosocial. En este sentido, la población investigada se encuentra afectada de especial forma, por el abandono de las autoridades del hospital en desarrollar sus conocimientos y habilidades a través de capacitación y perfeccionamiento, por el aumento de la violencia laboral, violencia psicológica y discriminación (especialmente a grupos vulnerables). Se muestran inconformes por la falta de organización y deficiencias en la delegación del trabajo y por la falta de equipos y tecnología. En menor medida muestran percepción negativa por el hecho de que no puedan mantener una armonía con su vida familiar, por la falta recuperación y por la supervisión alta de control. El liderazgo y la carga de trabajo son los factores de riesgo más bajo, pero que afectan a la tercera parte de los informantes.

Por las características del contenido de trabajo de los colaboradores de las UCI, este personal está permanentemente expuesto a sufrir daños derivados de la exposición de factores de riesgo psicosocial, por lo que la gestión de prevención debe ser continua y el abordaje debe contemplar medidas individuales (con base al análisis de fichas médicas y de morbilidad), colectivas (a nivel departamental) y organizacionales (inclusión de otras dependencias). La implementación de planes y programas de mitigación debe ir acompañado con mediciones anuales que indiquen el avance y mejoramiento de las condiciones y características de trabajo.

Conflicto de intereses

Los autores declaran no tener conflicto de intereses en relación a la presente investigación.

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ORIGINAL

Postural analysis in flat-footed subjects

Análisis postural en sujetos de pie plano

Joel Marouvo[1,2], Nelson Azevedo[3,4], Filipa Sousa[5,6], Orlando Fernandes[7,8], Maria António Castro[1,2,9]

1. RoboCorp Laboratory, i2a, Polytechnic Institute of Coimbra, Coimbra, Portugal 2. Centre for Mechanical Engineering, Materials and Processes (CEMMPRE), University of Coimbra, Coimbra, Portugal 3. Instituto Superior de Saúde, ISAVE, Amares, Portugal 4. Faculty of Sports, University of Porto, Porto, Portugal 5. Porto Biomechanics Laboratory (LABIOMEP-UP), University of Porto, Porto, Portugal 6. Faculty of Sport (FADEUP), CIFI2D, University of Porto, Porto, Portugal 7. Departamento de Desporto e Saúde, Escola de Saúde e Desenvolvimento Humano, Universidade de Évora, Évora, Portugal 8. Comprehensive Health Research Center (CHRC), Universidade de Évora, Évora Portugal. 9. School of Health Sciences, Polytechnic Institute of Leiria, Leiria, Portugal.

Corresponding author
Maria António Castro
E-mail: maria.castro@ipleiria.pt

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Abstract

Background: Processing somatosensory input requires cognitive resources, any additional processing can decrease stability. Postural alignment of the feet has been linked to altered lower-limb movements and postural stability. The study aimed to determine whether there were differences in kinematics and kinetics between subjects with and without flat foot conditions, about postural stability.

Material and methods: The sample consisted of 31 participants comprising 62 feet, 15 of whom were in the experimental group with the flat foot condition, while 16 were in the control group with the neutral foot condition. The Navicular Drop Test and Resting Calcaneal Stance Position test were used to categorize each group of participants before posture analysis. All participants were subjected to a bipedal weight-bearing stance posture stability analysis, using a 3D-Motion Capture system and a force platform, both in eyes-open and closed conditions.

Results: Considering kinematics differences between groups, the only statistically significant results found were for the ankle joint namely in the sagittal (*p=.047*), coronal (*p=.013*), and transverse (*p=.001*) planes. Regarding Center of Pressure outcomes, no statistically significant results were found (*p>.05*) regarding group differences. Statistically significant results were found regarding Total and Antero-Posterior excursion (*p=.027/.016*), Total and Antero-Posterior Total velocity (*p=.027/.016*), and Antero-Posterior and Medio-lateral Amplitude (*p=.011/.039*).

Conclusion: In both conditions, flat-footed subjects present few alterations compared to neutral foot participants, in bipedal weight-bearing stance. Due to the methodological deficiency regarding influencing factors, further research should also address methodological variables to focus only on the foot.

Key words: Foot Posture; linear analysis, flat feet, plantar pressure.

Resumen

Introducción: el procesamiento de información somatosensorial requiere recursos cognitivos, cualquier procesamiento adicional puede disminuir la estabilidad. La alineación postural de los pies se ha relacionado con movimientos alterados de las extremidades inferiores y estabilidad postural. El estudio tuvo como objetivo determinar si había diferencias en la cinemática y la cinética entre sujetos con y sin pie plano, sobre la estabilidad postural.

Métodos: La muestra estuvo compuesta por 31 participantes de 62 pies, de los cuales 15 estaban en el grupo experimental con condición de pie plano, mientras que 16 estaban en el grupo control con condición de pie neutro. La prueba de caída del navicular y la prueba de posición de la postura del calcáneo en reposo se utilizaron para categorizar a cada grupo de participantes antes del análisis de la postura. Todos los participantes fueron sometidos a un análisis de estabilidad de la postura de la postura con soporte de peso bípedo, utilizando un sistema de captura de movimiento 3D y una plataforma de fuerza, tanto en condiciones de ojos abiertos como cerrados.

Resultados: Considerando las diferencias cinemáticas entre los grupos, los únicos resultados estadísticamente significativos encontrados fueron para la articulación del tobillo en los planos sagitais (p=0,047), coronal (p=0,013) y transversal (p=0,001). En cuanto a los resultados del Centro de Presión, no se encontraron resultados estadísticamente significativos (p>.05) con respecto a las diferencias de grupo. Se encontraron resultados estadísticamente significativos en cuanto a Excursión Total y Antero-Posterior (p=.027/.016), Velocidad Total y Antero-Posterior Total (p=.027/.016), Amplitud Antero-Posterior y Medio-lateral (p =.011/.039).

Conclusión: En ambas condiciones, los sujetos con pie plano presentan pocas alteraciones en comparación con los participantes con pie neutro, en la postura de carga bípeda. Debido a la deficiencia metodológica con respecto a los factores que influyen, la investigación adicional también debe abordar las variables metodológicas para centrarse solo en el pie.

Palabras clave: Postura del Pie; análisis lineal, pies planos, presión plantar.

Introduction

Incorrect range of motion, ligament/joint laxity, neurological restrictions, and altered muscle activity can all contribute to flat feet (FF)[1]. Mechanical overloading injuries are more likely to occur in FF subjects than in subjects without this condition. Knee pain, cartilage damage, medial tibial stress syndrome, sacroiliac dysfunction, metatarsal stress fractures, plantar fasciitis, Achilles tendinitis, tibialis anterior inflammation, or patellofemoral pain can result from this alteration[1-4]. Patients with musculoskeletal pathologies exhibit different postural patterns regarding functional activity. In daily living activities, both static and dynamic postural controls are required to maintain the Center of Mass (CoM) above the Base of Support (BoS)[5]. Alterations in BoS, such as a larger area, will result in an increase in sensorimotor adaptation resulting in increased postural stability, thus preventing fall risks[6,7]. BoS changes induce body sway, thereby increasing intrinsic stiffness[6,7]. Additionally, to maintain postural stability, the body requires the lower limb's proprioceptive receptors to respond effectively to environmental changes[7-9]. Plantar pressure, proprioceptive feedback, visual and oculomotor information, and vestibular information contribute to posture stability[8,10-12]. Through its unique sensory capacity, the visual and oculomotor system contributes to balance, not only by estimating distance but also by providing information about body motion and sway[9,10,13]. Any additional cognitive processes can reduce stability sustaining because somatosensory input requires cognitive processing to sustain stability. This information is processed in the Central Nervous System (CNS) to create neuromotor necessary output commands to maintain stability[14,15].

Foot posture induces altered plantar pressure patterns and proximal joint motion. In response to altered sensory afferent signals, the CNS modulates joint stiffness and postural stability through muscle coactivation, thus affecting muscle function, foot biomechanics, and lower-limb biomechanics[16]. These occur globally and locally through postural and functional joint stabilization[4,14,15,17-20]. Thus, foot posture, through altered lower-limb motion pattern can induce injuries[21,22] and it has been associated with abnormal foot motion during gait[1,4,23-26]. In addition to being a sensitive map, the foot contains many cutaneous mechanoreceptors that provide important information about balance, posture, movement, and muscular sensitivity[27]. Moreover, afferent input from the foot sole can affect postural awareness, while FF increase can be triggered by neurological and muscular restrictions, ligament and joint laxity, excess motion, and muscle activity[1]. It is difficult to assess the postural stability of FF subjects without assessing plantar pressure patterns that can influence negatively the results[10]. On the other hand, in FF subjects, the plantar foot area increases compared to the neutral foot which can impair the plantar pressure feedback, resulting in the other receptors' compensation for maintaining postural stability[8,11]. Consequently, an imprecise assessment of plantar pressure results from reduced accuracy in sensory integration[8].

According to biomechanical principles, the body can be conceptualized as a network of segments connected worldwide by main forces interactions[28]. A combined effect of rotational alignment between segments and the cumulative effect of foot hyperpronation induced a postural re-alignment to conserve the Center of Pressure (CoP) in the subject BoS, with repercussions on both distal and proximal joints[29,30]. Any variation in lower-limbs joints can influence both positively or negatively the whole lower extremity kinematic and kinetic chain[31]. In previous research, authors stated that during excessive subtalar pronation, the calcaneus performs an eversion movement, producing medial and inferior talus slide motion along with internal rotation, provoking thereby an internal shank rotation[28-32]. Thus, this biomechanical modification results in an increase in medial rotation of the femur, which in turn increases the pressure between the femoral head and the posterior portion of the acetabulum[29,33]. Consequently, this will produce an anterior pelvis tilt[28-30]. Finally, due to the pelvis/lumbar spine relationship at the sacroiliac joint by widespread fibrous connection, the anterior pelvic tilt increases lumbar lordosis[28,29], spine instability, balance disorder, and structural abnormalities[29]. Exposing subjects to induced hyperpronation emphasizes an immediate effect on the intersegmental relationship and not necessarily a prolonged adaptive effect[28].

The purpose of this study was to see if there is a difference in kinematics and kinetics between subjects with and without FF conditions, regarding postural stability.

Methods

1. Participants

This observational descriptive study was carried out at *RoboCorp Laboratory*, at the *Polytechnic Institute of Coimbra* after approval of the *Ethics Committee of Polytechnic Institute of Coimbra* (13_CEPC2/2019) based on the revised version of the 2013 *Declaration of Helsinki*[34,35]. Additionally, the recommendations for the communication of observational studies recommendations were followed (Strengthening the Reporting of Observational Studies in Epidemiology-STROBE)[35]. The sample size was calculated with the aid of the *G*power 3.1.9* software (*G*power 3.1.9*, Kiel, Germany) based on the previously published paper of *Kim et al.* (2015). The sample size was determined as the number of participants necessary to reach a statistical power of 95%, an estimated alpha level of 0.05, considering a moderate effect size (d = 0.6) (ref *Kim et al.* (2015). Therefore, a required sample size of 18 was determined and, consequently, forty-three volunteers were recruited for this study. All subjects

were informed about the purpose of the study and the associated benefits, as well as any associated risks before any assessment was performed. Participants were guaranteed the right to withdraw at any time, and they were required to read and provide informed consent before participating. A total of thirty-one subjects aged between 18 and 35 years old met the eligibility criteria (13 women / 18 men – 23.26 yo ± 4.43 SD) (**Table I**). The inclusion criteria for the study were limited to subjects who presented bilateral FF or neutral foot (NF) who were aged between 18 to 40 years old.

Inclusion criteria in the FF group encompassed subjects that presented a >9mm Navicular Drop Test (NDT) and >4° Resting Calcaneal Stance Position (RCSP) scores. However, the inclusion criteria in the NF group involved participants with <9mm NDT and <4° RCSP scores. All participants were submitted to the NDT and RCSP to identify whether they had a FF or an NF as this test is clinically used by practitioners worldwide. The procedures were all performed by one practitioner who had more than six years of experience using these techniques. Following this, participants who presented the following criteria were not excluded from this study: (a) any disturbance that might affect posture analysis like orthopaedic, neurological, or visual impairment; (b) participation in a physiotherapy treatment program; (c) bone fracture or an ankle sprain in the last 6 months; (d) injury or surgery to the spine, hip, knee, or ankle; (e) aged less than 18 and more than 40 years old. Subsequently, 15 bilateral FF participants were assigned to the FF group, comprising a total of 30 feet, and 16 bilateral NF subjects were assigned to the NF group, comprising a total of 32 feet.

2. Procedures

2.1 Assessment

Foot posture was diagnosed based on clinical procedures including the Navicular Drop Test and the Resting Calcaneal Stance Position test, as those are clinically used by practitioners worldwide[29-31]. Both NF and FF conditions were evaluated bilaterally using the same assessment procedure in a weight-bearing barefoot stance position. They were performed by a single physiotherapist with more than 6 years of experience in the use of these techniques. The same procedure was used for both groups. In the first step, the navicular drop severity was evaluated using the NDT, where three measurements are summed up to determine its severity. The practitioner holds a plastic ruler perpendicularly to the ground and records the ground-navicular bone distance (millimeters). Then, the practitioner inverts the talus into a neutral position and repeats the procedure. The difference between both assessment positions quantifies the navicular drop severity[8]. Afterward, the angle between the rearfoot and the leg was assessed by the same practitioner using the Resting Calcaneal Stance Position test, where the mean of three measurement values defines the angle. This angle is formed by the longitudinal bisecting line of the calcaneus and the longitudinal bisecting line of the distal third of the leg, which was drawn by the investigator in a prone position, regarding the methodology previously used by *Tsai et al.* (2006). A rigid goniometer was used to measure this angle (Enraf-Nonius B.V, Rotterdam, The Netherlands).

Following the aforementioned tests, a three-dimensional computerized posture analysis was performed on both the FF and NF groups to assess movement characteristics such as joint angular kinematics and Center of Pressure parameters. A bilateral weight-bearing stance position was measured with a 10-camera Qualisys® 3D Motion Capture System (Qualisys AB, Götebor, Sweden) with a predictive error of 25 mm and a maximum residual set at 6 mm. This last one was coupled with a force platform *Bertec® FP4060* (Bertec Corporation, USA). A full-body marker setup based on the IOR model[36] comprising fifty-three reflective kinematic markers was used on specific anatomical positions of the participants, namely on the thorax, the head, and the lower limbs. Tracking markers, i.e., four marker clusters, were placed over the thighs and shanks to improve segment tracking accuracy. Therefore, kinematic data were collected in a previously calibrated volume, with a calibration error below 0.7 mm and recorded at a 200 Hz sampling frequency for the kinematics and a 1000 Hz sampling frequency for CoP characteristics.

Before posture acquisition, subjects were asked to perform a bilateral stance posture assessment regarding model creation processing. Therefore, subjects were instructed to stay upon a force platform for 60 sec with eyes open (EO) and repeated it with eyes closed (EC). There was a ten-second rest period between trials. The assessment was done with subjects in a quiet, comfortable barefoot posture upon the force platform while keeping their arms at the side and they were asked to look at a reference point for 5 seconds to stabilize the position before recording the data[37]. No other restrictions were placed on participants. Trials in which all of the markers were clear and possible to identify were defined as valid and if any participants failed to maintain their position, the trial was repeated.

2.2 Data processing and analysis

Initially, the recorded kinematic data were pre-processed using the Qualisys Track Manager v2.15 (Qualisys AB, Götebor, Sweden) software. The resulting data were then exported to Visual3D (C-Motion, Germantown, MD, USA) for further analysis. The marker's trajectories were then filtered with a *6-Hz Butterworth* low-pass filter and a 3-D model was created to analyse the relative angles of ankle, knee, and hip joints and, pelvis[38]. A 3D model was created to analyse the relative angles of the ankle, knee,

and hip joints. Finally, Visual 3D (C-Motion, Germantown, MD, USA) software commands were computed and identically replicated for each subject to identify outcomes measures, namely joint angular kinematics (ankle, knee, hip, and pelvis angle). Also, the CoP excursion, velocity, and area were evaluated. Alongside, the *Matlab-R2020b* (MathWorks Inc., USA) software was utilized for the CoP data processing. Initially, all CoP data were downsampled to a 200Hz frequency and, then filtered with a *7th-order Butterworth 50-Hz low-pass filter* to reduce some high-frequency parasitic signals. Finally, a routine was created to identify CoP outcomes.

3. Statistical analysis

The data were statistically processed with the *IBM SPSS Statistics 27.0* software (IBM Corporation, New York, USA). In this observational descriptive study, the appropriate summary statistics were applied to the descriptive analysis of the sample. Before any further statistical procedure, the normality of the distribution was explored. The samples presented a normal distribution based on the *Shapiro-Wilk* test regarding kinematic variables ($p>.05$, $t>0.074$) and several CoP variables ($p>.725$, $t>0.976$). For the remaining CoP variables, the sample presented a non-normal distribution using the *Shapiro-Wilk* test ($p<.001$, $t>0.617$). Continuous variables were described using the median/variance and mean/standard deviation based on the sample distribution. The differences between the groups were assessed according to the *T-test for independent samples* and *U-Mann Whitney* in the comparison between the experimental and control group. Then, the differences between both condition assessments, EC and EO were assessed according to the *T-test for paired samples* and the *Wilcoxon test*. The level of significance was set at 5% ($p<.05$) for all hypothesis tests.

Results

1. Sample and Groups characteristics

The sample characteristics are specified in **table I** alongside the mean values of the different tests for both groups. In the procedure, 30 FF and 32 NF were identified through inclusion criteria. Both subjects were identified and allocated to different groups using the NDT and RCSP score assessment.

2. Kinematics Analysis

Considering the result kinematics values regarding the differences between groups, the only statistically significant results found were all concerning the ankle joint namely in the sagittal ($diff=1.93°$, $p=.047$), coronal ($diff=2.62°$, $p=.013$), and transverse ($diff=5.02°$, $p=.001$) planes. The other joints did not show statistically significant differences between groups ($p>.05$). All the results those results are presented in **table II**.

3. CoP analysis

No statistically significant results were found ($p>.05$) regarding CoP between groups, both in the EO and EC conditions. Between conditions, statistically significant results were found regarding several outcomes, namely the Total CoP excursion ($p=.027$), Antero-Posterior Total excursion ($p=.016$), Total CoP velocity ($p=.027$), Antero-Posterior Total velocity ($p=.016$), Antero-Posterior and Medio-lateral Amplitude ($p=.011/.039$). **Table III** presents all of the results over the CoP characteristics along with **Figures 1** and **2**, which show examples of Statokinesigram and phase plane analysis.

Table I: Sample characteristics.

Group	n	NDT *(mm)*	RCSP *(°)*	Age *(years)*	Height *(m)*	Weight *(kg)*
NF	*16*	5.06 ± *2.42*	1.44 ± *1.19*	21.69 ± *2.98*	1.72 ± *0.09*	75.92 ± *17.03*
FF	*15*	11.35 ± *1.43*	5.52 ± *2.22*	24.93 ± *5.17*	1.68 ± *0.10*	74.32 ± *12.90*
Total	*31*	-		23.26 ± *4.43*	1.70 ± *0.98*	75.14 ± *14.94*

Mean ± Standard Deviation; NF = Neutral Foot; FF = Flatfoot.

Table II: Groups kinematics characteristics in Eyes Open assessment.

		NF	FF	*p-value*
Ankle *(°)*	*Dorsiflexion - Plantarflexion*	-3.77 ± *3.91*	-1.83 ± *3.54*	*0.047*
	Abduction - Adduction	-8.38 ± *3.63*	-5.75 ± *4.34*	*0.013*
	Internal – External rotation	-13.31 ± *6.15*	-8.29 ± *4.96*	*0.001*
Knee *(°)*	*Flexion - Extension*	-2.07 ± *5.88*	-3.88 ± *4.98*	*0.198*
	Abduction - Adduction	1.42 ± *4.26*	0.65 ± *5.44*	*0.536*
	Internal - External rotation	18.05 ± *10.57*	16.10 ± *6.62*	*0.393*
Hip *(°)*	*Flexion - Extension*	-1.48 ± *9.40*	-1.08 ± *7.67*	*0.856*
	Abduction - Adduction	-0.62 ± *3.68*	-1.93 ± *5.29*	*0.268*
	Internal - External rotation	3.24 ± *9.71*	-0.77 ± *7.21*	*0.071*
Pelvis *(°)*	*Anterior – posterior Tilt*	-9.13 ± *7.93*	-9.47 ± *5.97*	*0.894*
	Lateral Tilt	-0.66 ± *2.34*	-1.09 ± *2.64*	*0.635*
	Rotation	-0.28 ± *5.69*	-0.05 ± *2.64*	*0.889*

Mean ± Standard Deviation; NF = Neutral Foot; FF = Flatfoot; Negative value = extension / internal rotation / adduction / anterior tilt; Positive value = flexion / external rotation / abduction / posterior tilt.

Table III: Center of Pressure characteristics.

		EO			EC			EO vs EC
		NF	FF	*p-value*	NF	FF	*p-value*	*p-value*
Excursion *(mm)*	*Total*	2476.82 ± *468.21*	2492.82 ± *414.32*	*0.922*	2457.15 ± *451.55*	2570.49 ± *425.14*	*0.508*	*0.027*
	Antero-Posterior	1871.44 ± *352.55*	1908.29 ± *314.98*	*0.766*	1876.18 ± *334.31*	1975.31 ± *337.02*	*0.450*	*0.016*
	Medio-Lateral	1247.68 ± *239.55*	1229.89 ± *212.08*	*0.832*	1218.89 ± *243.16*	1256.04 ± *199.83*	*0.667*	*0.210*
Velocity *(mm/s)*	*Total*	495.41 ± *93.65*	498.61 ± *82.87*	*0.922*	491.47 ± *90.32*	514.14 ± *85.03*	*0.508*	*0.027*
	Antero-Posterior	374.32 ± *70.52*	381.69 ± *63.00*	*0.766*	375.27 ± *66.87*	395.09 ± *67.41*	*0.450*	*0.016*
	Medio-Lateral	249.56 ± *47.91*	245.99 ± *42.42*	*0.832*	243.80 ± *48.63*	251.23 ± *39.97*	*0.667*	*0.210*
Amplitude *(mm)*	*Antero-Posterior*	30.33 ± *12.80*	27.64 ± *11.03*	*0.637*	38.85 ± *20.58*	38.58 ± *26.01*	*0.793*	*0.011*
	Medio-Lateral	17.09 ± *7.91*	17.30 ± *12.27*	*0.759*	19.84 ± *12.48*	17.75 ± *11.48*	*0.867*	*0.039*
Area *(mm^2)*		284.47 ± *250.93*	221.37 ± *165.93*	*0.498*	379.09 ± *453.38*	376.25 ± *557.17*	*1.000*	*0.486*

Mean ± Standard Deviation; NF = Neutral Foot; FF = Flatfoot; EO = Eyes Open; EC = Eyes Closed

Figure 1: Statokinesigram.

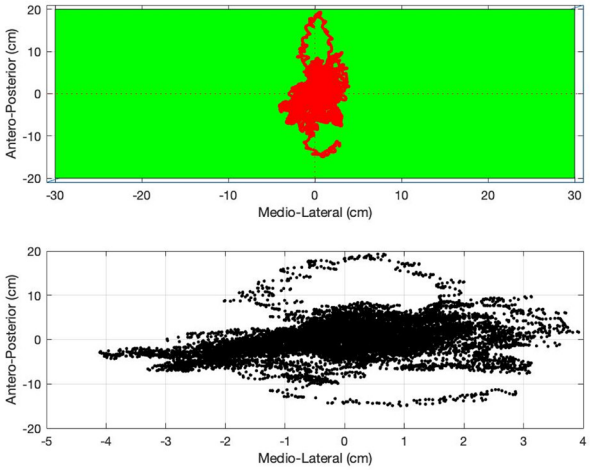
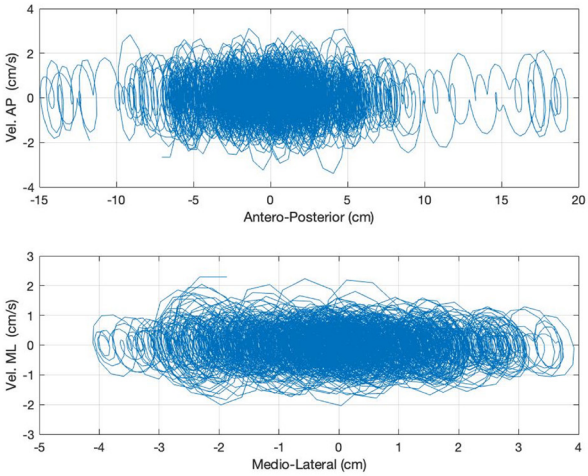


Figure 2: Phase Plane graphs.



Discussion

The current study is the first of its kind to investigate differences between FF and NF in terms of overall lower-limb kinematics, CoP characteristics, and eligibility criteria, such as NDT and RSCP testing. Studies have previously investigated kinematics and postural stability variations using different inclusion criteria and conditions, such as bilateral FF or induced bilateral excessive ankle eversion.

In our observational study not all results present statistically significant differences between the NF and FF group concerning kinematics outcomes. In our overall lower-limb analysis, only the ankle joint presents variation between groups in all planes. In the FF group, subjects presented higher dorsiflexion (*p=.047*), abduction (*p=.013*), and external rotation (*p=.001*) ROM compared to the control group. The results can be translated into a drop of the navicular bone and a collapse of the entire medial longitudinal arch, i.e., alterations that are present in FF subjects. These findings are also in agreement with the results of clinical tests used to evaluate FF conditions, namely the NDT and RCSP. Many authors analyzed the kinematic outcomes in FF subjects concerning several posture assessment conditions. However, those investigated mainly the correlations between joint motion and differences between groups. Others analysed the induced hyperpronation effect using a few wedges. *Duval et al.* (2010) found differences between subjects, yet not all those were statistically significant[39]. Subtalar pronation, relative to neutral position increases internal knee and hip rotation. Though, the authors found only a significant association between subtalar angle and knee and hip rotation (*p<.001*) which follows *Khamis et al.* (2007-2015) results. However, foot pronation and supination did not statistically significantly correlate with pelvic tilt and lumbar lordosis (*p=.074*). These results are in contradiction with those found by *Farokhmanesh et al.* (2014), Ghasemi et al. (2016), Khamis et al. (2007-2015) who established a statistically significant increase in lumbar lordosis (*p<.05*). These differences may arise from the fact that the authors examined functional changes created by the wedges rather than structural changes occurring continuously in bilateral flatfoot subjects. Despite this, more research is needed due to differences in samples, setups, and quality of the studies.

Also, *Duval et al.* (2010) found that thigh internal rotation produced an anterior pelvis tilt (*p<.001*)[39]. Although, in the same condition, *Farokhmanesh et al.* (2014) found alterations between subjects, with a statistically significant increase in thoracic kyphosis (*p<.008*) related to subtalar pronation that accords with *Ghasemi et al.* (2016) findings (*p<.001*). Finally, this last one analyzed sacral angle related to foot pronation and noticed a statistically significant increase in induced hyperpronation conditions (*p<.001*). No paper relating differences between groups using the combination of NDT and RCSP to assess FF condition was found. The difference between results can be explained by the selection of the inclusion and exclusion criteria, specifically the NDT-RCSP combination. Both tests are considered clinical tests, used to assess foot complex mobility[40,41]. They were considered user-friendly but presented few limitations. Instead, several authors used Footprint parameters, namely using a few indexes to quantify and characterize foot posture FF, NF, and cavus foot[42]. However, NDT and Footprint parameters present good association and reliability based on the few published papers[40-42]. Nevertheless, those contradictions made unclear the emergence of a posture pattern often described in FF subjects. Nonetheless, more studies need to incorporate methodological variables to only focus on foot alteration based on methodological variations.

In our study, CoP characteristics were also investigated and analyzed. We did not find any statistically significant results between groups, in both assessment conditions, regarding CoP total, anteroposterior or mediolateral excursion, amplitude, and area (*p>.05*). Those are contradictory to the found results by *Tahmasebi et al.* (2014), who stated a statistically significant increase in anteroposterior CoP excursion (*p=.034*) in EO condition amongst FF subjects that can be due to group inclusion criteria where the authors utilized the FootPrint Arch Index and Arch Angle which is considered as a FootPrint parameter. Also, another published study by *Koshino et al.* (2020), find a statistically significant increase in Antero-Posterior and Medio-Lateral total excursion among FF subjects compared to NF subjects (*p<.023*). Likewise, we investigated the total, anteroposterior, and mediolateral CoP velocity where we did not find ether statistically significant differences (*p>.05*) between groups, which is contradictory to the result found by *Tahmasebi et al.* (2014). The authors related a statistically significant increase in total, anteroposterior and mediolateral CoP velocity in FF subjects compared to NF subjects (*p=.000*). However, along with the previous two mentioned articles, in our research, we did not find more published papers that related differences in CoP characteristics among FF subjects. In the literature research, none of the selected papers investigated the EC condition assessment nor the postural system modulation. Analysis of postural stability in FF subjects can be challenging without controlling or assessing the visual and oculomotor systems, which can adversely affect results[10]. In our study, contradictory to the postural stability system evaluation, we did not find any statistically significant differences between both conditions assessments, EO and EC. Additionally, the BoS area used to assess impairments in different foot posture conditions differs from previous searches, along with visual input assessment. Several studies used the unilateral stance position with Kinetic Stability Index, CoP excursion, and velocity outcomes analysis. They stated that a decreased kinetic sensitivity can increase postural sway and instability in that position[8,9,43] as long as Antero, Mediolateral CoP excursion, and speed increase in FF subjects with EC and EO[27]. BoS variations lead to stability adaptation. In a bipedal stance, the mediolateral Center of Mass (CoM) position is usually positioned above the BoS area while it is reduced in unilateral stance, and accompanied by postural corrections, using ankle, knee, or hip strategy, which increases postural instability and body sway[6,7]. When proprioception is limited, FF participants might be prone to kinetic instability since inaccurate body sway estimation can be caused by reduced accuracy in the sensory integration process[6,7]. In our study, we used a weight-bearing bipedal stance position. The subject needs information from all postural receptors to maintain stability in that condition. As the position provides a higher BoS area, there is little external stimulus influencing the position maintenance, i.e., the postural system is fully functional and without reporting CoP impairments, nor differences between various foot posture conditions. Finally, along with those conditions, in FF subjects, plantar foot area increases compared to NF subjects which impairs pressure feedback resulting in receptors' compensation for maintaining postural stability[8,11]. The method required to assess this parameter differs between authors according to the chosen test. In *Tahmasebi et al.* (2014) study, the authors used the combined method of Arch Index and the Footprint Angle, i.e., clinical methods. However, *Koshino et al.* (2020) used the Foot Posture Index (FPI-6), i.e., questionnaire evaluation, and finally the combined use of the NDT and RSCP was utilized in our study, i.e., mobility tests. Those represent three different methods to diagnose the FF condition, which can impair the results and comparation.

Considering the overall kinematic and CoP characteristics outcomes and assessed variables, we can state that FF subjects did present few alterations compared to NF participants, in bipedal weight-bearing stance, both in EC and EO conditions. However, considering the lack of consensus regarding utilized outcomes and assessment conditions, further studies need to be performed to create more robust evidence. Regarding methodological deficiency regarding influencing aspects, further studies need to encompass methodological variables handling to focus only on foot alteration.

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Interests conflict

The researchers declare that they have no conflict of interest.

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ORIGINAL

Exercise participation and associated factors in patients with stroke at the stage of sequelae period

Participación en el ejercicio y factores asociados en pacientes con ictus en el periodo de secuelas

Jiajia Sun[1*], Yuling Yang[2,3*], Li Wang[2]

1. School of Nursing, Suzhou Vocational Health College, Suzhou, 215009, China
2. School of Nursing, Medical College, Soochow University, Suzhou, 215006, China
3. Department of rehabilitation department, Affiliated Hospital of Jiangnan University, Wuxi, 214122, China

[*]*These authors contributed equally to this work.*

Corresponding author
Li Wang
E-mail: li-wang-1@suda.edu.cn

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Abstract

Objectives: Exercise is important for stroke rehabilitation. However, exercise participation in patients with stroke may not be ideal, and the factors affecting exercise participation may be complicated. This study was aimed to investigate exercise participation status and analyze its associated factors in patients with stroke at the stage of sequelae period (more than 6 months from the last onset).
Methods: A total of 193 patients with stroke at the stage of sequelae period recruited through a convenient sampling method participated in the present study and underwent investigation with questionnaires. Single-factor analysis and multiple linear regression analysis were used to analyze the factors influencing exercise participation in the subjects.
Results: The average exercise level of the patients was 8.1 Mets-h/week, which belonged to the low exercise level. Most patients (64.8%) participated in only one exercise mode, and easy exercise modes were dominant. Single-factor analysis showed that exercise volume differences were found with various factors, including educational degree, working status, marital status, primary caregiver, exercise habit, and the degree of self-care. Multiple linear regression analysis showed that the factors associated with patients' exercise volume included belief in exercise benefits, exercise risk concerns, and exercise support from family.
Conclusions: The exercise volume of patients with stroke at the stage of sequelae period is low, and their exercise modes are monotonous. Belief in exercise benefits, exercise risk concerns and family support are the main factors influencing the exercise level in these patients. Patients who believe that exercise after stroke can promote recovery, have a low exercise risk concerns and families' support have a higher exercise volume.

Key words: Stroke, exercise, rehabilitation, sequelae, physical function.

Resumen

Objetivos: El ejercicio es importante para la rehabilitación del ictus. Sin embargo, la participación en el ejercicio en pacientes con ictus puede no ser ideal, y los factores que afectan a la participación en el ejercicio pueden ser complicados.Investigar el estado de participación en el ejercicio y analizar sus factores asociados en pacientes con ictus en la etapa del período de secuelas (más de 6 meses desde el último inicio).
Métodos: Un total de 193 pacientes con ictus en la fase de secuelas, reclutados mediante un método de muestreo conveniente, participaron en el presente estudio y se sometieron a una investigación con cuestionarios. Se utilizó el análisis de factor único y el análisis de regresión lineal múltiple para analizar los factores que influyen en la participación en el ejercicio de los sujetos.
Resultados: El nivel medio de ejercicio de los pacientes fue de 8,1 Mets-h/semana, que pertenecía al nivel de ejercicio bajo. La mayoría de los pacientes (64,8%) participaron en una sola modalidad de ejercicio, y predominaron las modalidades de ejercicio fáciles. El análisis de un solo factor mostró que las diferencias en el volumen de ejercicio se encontraban con varios factores, como el grado de estudios, el estado laboral, el estado civil, el cuidador principal, el hábito de ejercicio y el grado de autocuidado. El análisis de regresión lineal múltiple mostró que los factores asociados con el volumen de ejercicio de los pacientes incluían la creencia en los beneficios del ejercicio, la preocupación por el riesgo del ejercicio y el apoyo de la familia al ejercicio.
Conclusiones: El volumen de ejercicio de los pacientes con ictus en la fase del periodo de secuelas es bajo, y sus modos de ejercicio son monótonos. La creencia en los beneficios del ejercicio, la preocupación por el riesgo del ejercicio y el apoyo de la familia son los principales factores que influyen en el nivel de ejercicio en estos pacientes. Los pacientes que creen que el ejercicio después del ictus puede promover la recuperación, tienen una baja preocupación por el riesgo del ejercicio y el apoyo de la familia tienen un mayor volumen de ejercicio.

Palabras clave: Ictus, ejercicio, rehabilitación, secuelas, función física.

Introduction

With the characteristics of high incidence, prevalence, mortality, morbidity and recurrence rate, stroke has become the second most common cause of death and stroke-caused disability is continuously increasing[1-3]. The latest study on the Global Burden of Disease Study shows that the overall lifetime risk of stroke in China is 39.9%[4], ranking first in the world, which means that approximately 2 out of every 5 people will suffer from stroke in their lifetime.

Regular exercise has been proven to be beneficial for the rehabilitation of patients with stroke by improving their cardiovascular function[5], pulmonary function[6], body flexibility[7], walking ability[8], muscle strength[9], bone mineral density[10] and quality of life[11] and reducing the stroke recurrence rate[3]. In the rehabilitation guidelines for patients with stroke at the stage of sequelae period, it is recommended that stroke patients regularly participate in exercise, including aerobic exercise, strength training and flexibility training[12]. However, there are studies showing that 70% of patients fail to do so[13], which escalates the negative effects of stroke. Due to the existence of stroke and a series of sequelae, the factors affecting the exercise participation of patients with stroke may be complicated.

The purpose of the present study was to investigate exercise participation in Chinese patients with stroke at the stage of sequelae period (more than 6 months from the last onset) and analyse its associated factors, thereby providing a reference for efforts to improve exercise participation levels.

Material and methods

Participants

With the convenience sampling method, patients with stroke at the stage of sequelae period were recruited from communities and hospitals in Suzhou, China. The recruitment criteria included ① patients who conformed to the stroke diagnosis standard of The Fourth National Conference of Cerebrovascular Diseases and were confirmed by CT or MRI and ② patients who had stroke 6 months prior. Patients with mental disorders, severe cardiovascular disease, or any exercise contraindication therefore not appropriate for exercise or incapable of understanding the investigated questions were excluded. The study purpose and participant's rights and responsibility related to this study were explained to the patients in detail. After full informed consent was obtained, subjects who gave their formed consent were involved in the study. This study was approved by the Ethics Committee of The First Affiliated Hospital of Soochow University (2017024) and conducted in compliance with the guidelines stated in the WMA Declaration of Helsinki and its later amendments or comparable ethical standards.

Questionnaires

Two questionnaires were applied in this study to collect the general information and exercise participation status of patients with stroke. Considering that most stroke patients were old and had difficulty reading and understanding, the survey was performed in a way that investigators dictated the questions to patients and filled in based on patients' answers. Once finished, the completed questionnaires were shown to participants for confirmation.

Questionnaire of general information

The questionnaire of general information included demographic data, disease-related data and the activity of daily living scale (ADL scale). The questions for demographic data (including sex, age, working status, educational status, etc.) and the disease-related data [included course of disease (since the first onset), types of stroke, number of sequelae, history of smoking, etc.] were self-designed. Self-care ability was measured using the ADL scale, which comprises 10 items, including eating, bathing, grooming, dressing, bowel control, toileting, bed and wheelchair transfer, walking on the ground, and stairs. Based on the patient's need for help (or lack) and its degree, the ADL scale is divided into 4 grades of 15, 10,5, and 0 points, with a full score of 100 points[14].

Questionnaires of exercise participation

Exercise participation was investigated by a self-designed questionnaire and a questionnaire modified from the Amateur Exercise Level Questionnaire (AELQ)[15]. The self-designed questionnaire included questions on regular exercise habits before and after stroke, beliefs about exercise benefits, exercise risk concerns, and social support for exercise from medical staff, hospitals, families, and communities. AELQ was revised from the "Variable Exercise Activity Questionnaire" by Professor Bagen Liao based on the characteristics of Chinese people, and it has proven to be suitable for various kinds of populations[16]. AELQ is subject to investigation, in the past year, subjects' exercise participation in 40 exercise modes, including walking, running, climbing, riding bike, etc. Patients were asked to select the exercise mode he/she performed in the past 12 months, fill in the average monthly exercise frequency in each month, and the average exercise time per session. The total exercise volume (Mets-h/week) was calculated based on the formula: months × average monthly exercise frequency × average exercise time each time × METs ÷ 60 min/h ÷ 52 wk/year. Subjects were divided into four groups according to their exercise volume: the nonexercise group (< 10.0 Mets-h/week), low-level exercise group (10~19.9 Mets-h/week), medium level exercise group (20 ~ 39.9 Mets-h/week), and high-level exercise group (more than or equal to 40 Mets-h/week)[16,17].

Statistical Analysis

Data were analysed using the SPSS 24.0 software package (IBM, Armonk, NY, USA). Descriptive statistics of frequency and percentage were used to summarize original data. The Kruskal-Wallis test was used to compare results between and among groups. Correlations between different parameters were analysed with bivariate correlation analysis. Multiple linear regression analysis was used to determine the factors associated with exercise volume. Alpha level was set at P less than 0.05.

Results

A total of 200 patients with stroke at the stage of sequelae period were recruited, and 193 (96.5%) completed and returned the questionnaires that were eligible for data analysis.

1. Sociodemographic characteristics of patients

The 193 subjects (72.4±12.4 years old) included 109 males and 84 females (56.5% vs. 43.5%). Their demographic data and disease-related information are shown in **table I**.

2. Clinical data of patients

In this survey, patients' disease course (starting from the onset of the first time of stroke) ranged from 6 months to 27 years, and 47.2% of patients were 1-5 years old. A total of 78.8% of patients had ischemic stroke, 30.1% of patients had stroke recurrence, 81.3% of patients had various degrees of dysfunction, and 63.2% of patients had reduced physical activity compared with before stroke. Detailed disease-related information is shown in **table II**.

3. Exercise-related information of patients

There were 35.8% of the patients who exercised regularly before stroke and 56.5% after stroke. Most (79.8%) patients believed that exercise could promote their recovery, and 62.2% of patients worried about exercise risk. Information on social support for exercise is presented in **table III**.

The mean exercise volume in all patients was 8.1 Mets-h/week (ranging from 0.1 to 83.4 Mets-h/week), which belonged to the nonexercise level. More than half of the subjects (56.5%) belonged to the nonexercise group (**Table IV**).

A total of 64.8% of the patients performed only one mode of exercise, 28.5% performed two, and only 6.7% performed three or more. The three most common exercise modes were walking (n=144, 84.7%), stair climbing (n=47, 27.6%) and indoor activities (n=36, 21.2%).

4. Single factor analysis of exercise volume

The Kruskal–Wallis test showed that exercise volumes were significantly different among different categories of variables, including educational level, working status, marital status, main caregiver, self-care ability, exercise regularly before stroke, and exercise-related parameters (belief of exercise benefits, exercise risk concerns, exercise support from family, exercise equipment in community) (**Table V**).

Specifically, there was a higher exercise volume among patients with a higher educational level than among those with a primary school education or below (Z=72.30, P=0.001). Patients under unemployed

Table I: Sociodemographic characteristics of patients.

Variables	Category	Number	Proportion (%)
Age (years old)	<50	11	5.7
	50~69	56	29.0
	≥70	126	65.3
Sex	Male	109	56.5
	Female	84	43.5
Education level	Primary school and below	54	28.0
	Junior high school	52	26.9
	High school and College	57	29.5
	Undergraduate and above	30	15.5
Working status	Employed	14	7.2
	Retired	163	84.5
	Unemployed	16	8.3
Average monthly income (Yuan)	<3000	85	44.0
	3000~4999	49	25.4
	≥5000	59	30.6
Marital status	Married	149	77.2
	Widowed and divorced	44	22.8
Religions belief	Yes	17	8.8
	No	176	91.2
Medical payment	Urban Medicare	170	88.1
	Rural Medicare	17	8.8
	Commercial insurance	2	1.0
	Self-paid	4	2.1

Table II: Clinical data of patients.

Variables	Category	Number	Proportion (%)
Course of disease (year)	<1 1~5 5~10 ≥10	8 91 55 39	4.1 47.2 28.5 20.2
Diagnosis of type	Hemorrhagic Ischemic Mixed	30 152 11	15.5 78.8 5.7
Number of strokes	1 2~3 >3	135 42 16	69.9 21.8 8.3
Number of legacy symptoms	0 1~2 ≥3	36 107 50	18.7 55.4 25.9
Self-care ability	Fully self-care Slightly dysfunction Moderately dysfunction Severely dysfunction	149 23 9 12	77.2 11.9 4.7 6.2
Number of complications	0 1~2 ≥3	34 152 7	17.6 78.8 3.6
Smoking	Yes No	18 175	9.3 90.7
Drinking	Yes No	16 177	8.3 91.7
Main care giver	Family member Nannies or nurses Oneself	90 17 86	46.6 8.8 44.6
Physical activity compared with before stroke	Significant increase Slightly increase Unchanged Slightly decrease Significant decrease	3 14 54 29 93	1.6 7.3 28.0 15.0 48.2

Table III: Exercise-related information of patients.

Variables	Category	Number	Proportion (%)
Exercise habit before stroke	Yes, ≥3times/week Yes, 1~2times/week No	65 4 124	33.7 2.1 64.2
Exercise habit after stroke	Yes,≥3times/week Yes, 1~2times/week No	104 5 84	53.9 2.6 43.5
Belief of exercise benefits	Yes No	154 39	79.8 20.2
Exercise risk concerns	Yes No	120 73	62.2 37.8
Medical staff stress the importance of exercise	Yes No	134 59	69.4 30.6
The hospital provides exercise demonstration facilities	Yes No	156 37	80.8 19.2
Exercise support from family	Yes No	96 97	49.7 50.3
Exercise equipment in community	Yes No	139 54	72.0 28.0

Table IV: Exercise volume of patients.

Variables	Number (%)	Mean (P_{25}, P_{75}) Mets-h/week
Total	193 (100)	8.1 (2.7, 19.1)
No exercise group	109 (56.5)	3.2 (1.1, 6.3)
Low level exercise group	43 (22.3)	14.4 (12.9, 17.8)
Medium level exercise group	31(16.1)	26.8 (23.1, 32.0)
High level exercise group	10 (5.1)	49.9 (44.5, 58.1)

statuses or at widowed/divorced statuses had lower exercise volumes than retired and employed or married patients (Z=117.79, *P*= 0.028, Z=102.29, *P*=0.015). The patients who could take care of themselves had higher exercise volumes than those were taken care by family members and nannies or nurses (Z=90.23, *P*=0.048). The patients with slight dysfunction had lower exercise volumes than those without dysfunction (Z=104.02, *P*=0.016). The patients who exercised two times/week before stroke had a lower exercise volume than those who exercised more than three times/week (Z=116.31, *P*=0.003). The patients who believed the exercise benefits had higher (H=108.92, *P*<0.01) and the ones worried about exercise risk had lower (H=82.01, *P*=0.004) exercise volume than those who did not. The patients with exercise support from family and exercise equipment in the community had higher exercise volumes than those without (H=118.15, *P*<0.01, H=104.54, *P*=0.003). Exercise volumes were not significantly different among patients at different ages (Z=129.95, *P*=0.057).

5. Multiple linear regression analysis of exercise volume

Multiple linear regression analysis showed that the factors significantly associated with exercise volume in these patients included three aspects: belief in exercise benefits, exercise risk concerns, and exercise support from family (**Table VI**). The patients who had beliefs about exercise benefits and exercise support from family had higher exercise volumes than the patients who had no. The patients who had exercise risk concerns showed lower exercise volumes than the patients who had no worry about exercise risk.

Table V: Single factor analysis of exercise volume.

Variables	Classification	M (P_{25}, P_{75}) Mets-h/week	H/ Z	*P*
Age (years old)	<50 50-69 >70	13.3 (8.3, 21.5) 7.7 (3.9, 24.0) 7.3 (1.7, 16.6)	129.95 103.05 91.43	0.057
Educational level	Primary school or below Junior high school High school and College Undergraduate and above	4.3 (1.6, 9.5) 8.1 (2.4, 19.2)[a] 11.6 (5.6, 24.1)[a] 10.9 (3.8, 23.4)a	72.30 97.12 115.18 106.73	0.001*
Working status	Employed Retired Unemployed	12.9 (5.2, 21.1) 8.1 (2.4, 19.6) 4.3 (1.2, 7.8)[ab]	117.79 98.31 65.50	0.028*
Marital status	Married Widowed or divorced	8.7 (3.2, 20.9) 4.5 (1.1, 13.8)[a]	102.29 79.09	0.015*
Main care giver	Family member Nannies or nurses Oneself	6.5 (1.6, 16.5) 4.3 (2.0, 12.6) 11.9 (4.0, 21.1)[ab]	90.23 79.44 107.56	0.048*
Self-care ability	Fully self-care Slightly dysfunction Moderately dysfunction Severely dysfunction	9.6 (3.2, 20.9) 4.3 (1.4, 8.7)[a] 4.7 (1.3, 11.7) 4.0 (0.8, 13.3)	104.02 72.85 71.67 75.13	0.016**
Exercise habit before stroke	Yes, >3 times/week Yes, 1-2 times/week No	14.4 (5.5, 23.2) 5.8 (2.7, 24.5) 6.2 (1.6, 14.0)	116.31 92.00 87.04	0.003*
Belief of exercise benefits	Yes No	11.1 (4.3, 21.1) 2.2 (0.7, 4.6)	108.92 49.95	<0.01**
Exercise risk concerns	Yes No	5.4 (1.1, 13.7) 9.6 (3.2, 21.1)	82.01 106.12	0.004*
Exercise support from family	Yes No	13.1 (5.5, 24.0) 4.3 (1.6, 12.9)	118.15 76.07	<0.01**
Exercise equipment in community	Yes No	3.2 (10.3, 21.1) 4.7 (1.7, 10.8)	104.54 77.59	0.003*

*: p <0.05, **: p <0.01; a: significantly different from the first category; b: significantly different from the second category.

Table VI: Multiple linear regression analysis of exercise volume.

Independent variables	ß	ß'	SE	T	*p*	Corrected R squared	F	*P*
Constant	32.74		7.37	4.44	< 0.001	0.25	6.07	<0.001
Belief of exercise benefits	-5.45	-0.16	2.48	-2.20	0.029			
Exercise risk concerns	4.86	0.17	1.89	2.52	0.011			
Exercise support from family	-7.27	-0.27	1.92	-3.79	< 0.001			

Reference variables were set as the ones with the answer of "yes".

Discussion

In the present study, exercise participation status and associated influencing factors were investigated in 193 patients with stroke at the stage of sequelae period through AELQ combined with self-designed questionnaires.

1. The general and disease related information

Among the 193 patients with stroke in this study, more patients were males and elderly and had ischemic stroke type, which is consistent with the epidemic facts of stroke[4]. The long course of disease (6 months to 27 years) and high percentage of dysfunction (81.3%) demonstrate that patients with stroke may be plagued by disease sequelae for a long time and that rehabilitation, including exercise, is necessary and important.

2. Exercise status of stroke patients in sequelae

In this study, the overall exercise volume of the patients with stroke was low (~8.1 Mets-h/week), which belonged to the nonexercise level. According to the American Heart Association/American Stroke Association stroke rehabilitation guideline recommendation, the patients with stroke at the stage of sequelae period should participate in moderate intensity exercise no less than three times a week for 20 to 60 minutes per session[13], which equals ~24.70 Mets-h/week. However, 84.7% of the patients in the present study were far below this level. The harm of a sedentary lifestyle or shortage of exercise has been discovered in many studies, including leading to reduced cardiopulmonary adaptability, causing cardiovascular diseases, and further reducing the patient's physical fitness. Based on our findings, primary health care workers should pay more attention to stroke prevention and rehabilitation knowledge education, especially emphasizing the importance of poststroke exercises, raising patients' awareness of post stroke exercises, and thereby promoting exercise participation[18].

Apart from the low exercise volume, the exercise modes adopted by the patients with stroke were generally monotonous (93.3% engaged in one or two kinds of exercise, and only 6.7% participated in more than three), and easy and convenient exercise modes with little demand on skill, furniture, and effort (such as walking and climbing stairs) dominated. This is consistent with previous findings that most elderly individuals in the community participate in simple exercises[19]. The preferable easy exercise mode may be accounted for by the fact that most patients lack exercise skills for other exercises, especially those need special learning and practice, such as swimming, Ta Chi, ball games, etc.

This study and previous studies have shown that the most common exercise method used by patients with sequelae of stroke is walking[20]. Walking is an effective exercise method with many advantages, such as convenience, little demand for space and skills, and easy adjustment of walking speed (exercise intensity)[13]. With the improvement of the social economy and health consciousness, products such as pedometers and sports bracelets have been created to encourage people to participate in walking[21].

The guidelines for exercise rehabilitation in patients with stroke note that exercises requiring the coordination of different parts of the body are better than those requiring only a single part of the muscle[13]. Some exercises, such as yoga, are mild (not intensive) and need all parts of the body to participate, which is suitable for stroke patients[22]. Therefore, it is necessary to create conditions helping and encouraging patients with stroke to learn and develop more exercise skills and participate in diverse modes of exercise.

3. Factors associated with exercise participation

3.1 Belief of exercise benefits

In our study, we found that the belief of exercise benefits was one of the factors associated with the exercise level in these patients with stroke at the stage of sequelae period. Among the patients investigated, 79.8% believed that exercise would benefit health recovery. A positive attitude towards exercise for stroke and belief in the benefits of exercise promote more participation in sports, thereby improving physical activity and exercise levels[23].

3.2 Exercise risk concerns

This study found that worrying about the risk of exercise is associated with lower exercise levels in these patients. Among the patients investigated, 62.2% had exercise risk concerns, and this percentage was quite high. Stroke happens more commonly in older populations, who have a high incidence of chronic diseases, which will reduce their physical ability and control, thereby increasing worries about the risks of exercise. The high incidence of sequelae after stroke must also contribute to increased worries. In fact, many studies have pointed out that poststroke exercises generally do not cause secondary injuries[11,24], and exercises should not be given up because of excessive fear of exercise risks. The American Heart Association/American Stroke Association pointed out that patients should take a pre-physical fitness test under the guidance of a physician before exercise[13] to clarify exercise tolerance. In this survey, no patients mentioned that they had received pre-exercise physical function assessment and guidance. To improve exercise participation in these patients, it is necessary to take measures to increase their exercise-related knowledge and decrease their concerns about exercise risks.

3.3 Exercise support from family and marital status

This study found that the patients who had support from family members for exercise had a higher level of

exercise, which was consistent with previous findings[25]. Camak et al found that family supervision is one of the factors to improve the exercise level of stroke patients in the sequelae stage[25]. The result of this factor is consistent with the result of marital status from single factor analysis, which showed that patients of married status had higher exercise volume than widowed or divorced patients. In China, partners are the most common caregivers for older people[26]. Some patients may not be able to exercise independently, and in this case, the assistance of family members is important and necessary to help them overcome the difficulties in exercises. Additionally, family members can modify living furnishings, prepare exercise equipment, and reduce the burden of housework, thereby promoting the exercise participation of patients.

3.4 Other factors

Apart from the above mentioned contributors to exercise volume, univariate analyses indicated that exercise volume in patients with stroke demonstrated differences across a large number of variables, including educational level, working status, marital status, main caregiver, self-care ability, exercise habit before stroke, and exercise equipment in the community.

The lower exercise volume in unemployed patients than in working and retired patients may be related to the greater stress for survival and less contact with society. With higher educational level, the patients usually have stronger ability to learn and understand knowledge, which may help increase the patients' understanding importance and knowledge of post stroke exercise, thereby helping improve their exercise volume. In addition, a study found that patients with higher education levels often have better personal financial conditions, pay more attention to their own health and are more equipped to carry out high-quality exercises, which may also improve their exercise levels. The patients who could take care of themselves had a higher exercise volume, which may also be related to their higher self-care ability. It is generally believed that people with exercise habits have better health awareness and adherence to long-term exercise, which explains the higher levels of exercise in patients with exercise habits before stroke. Patients with exercise facilities in the community have relatively higher levels of exercise, suggesting the benefits of material support. This is consistent with previous findings that patients' rehabilitation needs the support of relevant infrastructure and that perfect exercise facilities in the community will facilitate patients to develop good exercise habits and awareness[27]. Our investigation also showed that most patients (72%) lived in communities with exercise equipment, which may be related to the study location, Suzhou, a city with relatively good living conditions.

Additionally, this study showed that the exercise volumes of patients at different ages were close to significant (P=0.057). Such results may be related to the small sample size in this study. Liu Yafang pointed out that younger stroke patients need to shoulder the responsibility of the family and society and have a higher degree of urgency and demand for rehabilitation. This is a strong motivation for young patients to participate in sports exercise[28]. Aging itself will bring about a series of deteriorations in physical functions, resulting in reduced energy and limited limb function. Most elderly people have problems such as being too weak and having concurrent diseases[29], which may hinder their participation in exercise.

Conclusions

In summary, the exercise participation in the patients with stroke at the stage of sequelae period is not ideal, illustrated mainly by the extremely low exercise volume and the monotonous exercise modes involved. Having the belief of exercise benefits, exercise risk concerns and families' support are the main factors influencing the exercise level in these patients. Amount of exercise are different in patients of different educational level, working status, marital status, exercise habit before stroke, and self-care ability. It is lower if the patients are less educated, unemployed, having no accompany, with less self-care ability or living in the communities without exercise furniture. Our study provides data on patients with a high risk of insufficient exercise participation who may benefit from interventions that focus on multiple associated factors related to health education and promotion.

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Interests conflict

The authors declare that they have no conflict of interest.

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ORIGINAL

Acoustic characteristics of speech in adolescents with suicidal attempt. Voice, speech and suicidal behaviour

Características acústicas del habla en adolescentes con intento de suicidio. Voz, habla y comportamiento suicida

Carla Figueroa Saavedra[1,2], Virginia Guillén Cañas[3], Gerson Jara Cabrera[4], Claudia Guajardo Sáez[5]

1. Académica de Fonoaudiología Facultad de Ciencias de la Salud. Universidad Autónoma de Chile.
2. Doctoranda en Dpto. de Neurociencias. Facultad de Medicina y Enfermería. Universidad del País Vasco (UPV/EHU).
3. Académica en Dpto. de Neurociencias. Facultad de Medicina y Enfermería. Universidad del País Vasco (UPV/EHU).
4. Académico de Fonoaudiología. Facultad de Medicina. Universidad de La Frontera.
5. Académica de Fonoaudiología Facultad de Ciencias de la Salud. Universidad Autónoma de Chile.

Corresponding author
Carla Figueroa Saavedra
E-mail: carla.figueroa@uautonoma.cl

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Abstract

Introduction: Suicide represents the second leading cause of death among adolescents. There are studies that link voice to suicidal risk.
Methods: The research was conducted through a cross-sectional study, and the sample was selected through non-probability sampling, which included 40 adolescents between 16 and 19 years old from the city of Temuco. After the identification of suicidal attempts, the participants underwent voice and speech acoustic evaluation.
Results: A parameter that showed differences was Jitter (p<0,05). As to the spontaneous speech tasks assessment, it was possible to observe differences in the formants concerning the vast majority of the vowels measured (p<0,05).Some voice and speech indicators differ depending on the group and the task requested.
Conclusion: Therefore, these indicators might provide useful information for assessing suicidal behavior.

Key words: Voice, suicidal attempt, suicide.

Resumen

Introducción: El suicidio representa la segunda causa de muerte entre los adolescentes. Hay estudios que relacionan la voz con el riesgo de suicidio.
Material y métodos: La investigación se realizó a través de un estudio transversal, y la muestra fue seleccionada a través de un muestreo no probabilístico, que incluyó a 40 adolescentes entre 16 y 19 años de la ciudad de Temuco. Tras la identificación de los intentos de suicidio, los participantes fueron sometidos a una evaluación acústica de la voz y del habla.
Resultados: Un parámetro que mostró diferencias fue el Jitter (p<0,05). En cuanto a la evaluación de las tareas de habla espontánea, fue posible observar diferencias en los formantes relativos a la gran mayoría de las vocales medidas (p<0,05).Algunos indicadores de voz y habla difieren según el grupo y la tarea solicitada.
Conclusión: Por lo tanto, estos indicadores podrían proporcionar información útil para evaluar la conducta suicida.

Palabras clave: Voz, intento de suicidio, suicidio.

Introduction

In 2012, 804.000 deaths caused by suicide were registered worldwide, which represents a global annual suicide rate, age-adjusted, of 11,4 per 100.000 inhabitants - 15,0 regarding men and 8,0 regarding women[1]. All over the world, facing the effect that the COVID-19 pandemic will generate, an increase in suicides in the short or long term is expected[2].

Generally, suicide rates differ between genders and throughout life, while methods differ among different countries. Suicides are the second leading cause of premature death among fifteen to twenty-nine-year-old individuals, while traffic accidents are the main cause[3].

As it happens in many countries, the increase in mortality among adolescents caused by external causes is especially worrying in Chile as well. Within the 15 to 29-year-old group, suicide rates increased from 10.9 per 100.000 in the year 2013 to 11 per 100.000 in the year 2017. Moreover, the national suicide rate increased from 9.9 to 10.2 per 100.000 during the same period[4]. This doesn't include suicidal attempts, which are up to 20 times more frequent than consummated suicide cases[5].

Non-fatal suicidal thoughts and behavior (named "suicidal behavior" from this point on) are more specifically classified into three categories: suicidal ideation, which refers to thoughts about ending one's life; suicide plan, which refers to planning a specific method through which it is intended to die; and suicidal attempt, which refers to the participation in potentially self-injurious behavior in which there is at least some intention to die and ends in consummated suicide[6,7]

Suicidal behavior represents a unique study opportunity within the framework of suicide prevention, given that there is a relation between non-mortal suicidal behavior and consummated suicide[8].

The effective evaluation of suicidal risk depends on the availability of sensitive and specific measures of long-term risk factors, short-term warning signs, and recognition of the complexity and variability of suicidal risk over time. Unlike many procedures that evaluate relatively stable phenomena, yet there is no proof or test panel that precisely identifies the emergence of a suicidal crisis[9]. For that reason, many health and education professionals don't have the skills required to effectively interact with suicidal teens[10]. Furthermore, most parents don't even have knowledge concerning suicidal thoughts, which causes that many adolescents go unnoticed, with the consequent risk that this implies[11]. Currently, the emergence of new technologies allows generating new ways of intervening online. However, these must have systems in place to ensure that online providers can assess the suicidal risk. Therefore, developing new assessment and knowledge systems for the infant-juvenile population might contribute to decreasing suicidal behavior[12]. In this respect, voice and speech-based technology has been described as a useful tool for recognizing suicidal risk[13].

Phonatory system

The voice is defined as the principal form of communication of the human being. Its characteristics are: pitch, quality and intensity, which provide an acoustic declaration of personal, physical and psychological identity, and even people's emotional state[14-16].

Scherer, (2003) states that voice is part of the motor component of the expression of emotions and, therefore, the determinants of some types of voice modifications are the physiological changes that accompany emotions. Emotions must be considered as a complex functional system, being so complex that emotional responses have physiological components of the voice in order to correctly manifest the emotional behavior[18].

The voice is produced through the combined action of the phonatory system, respiratory system, resonance system, postural system and regulatory systems such as the endocrine, gastrointestinal and auditory system, whose combination allows oral production. Lastly, the role of both central and peripheral nervous system cannot be forgotten since they control, coordinate and regulate the functions of these systems in our organism, and allow the execution of voluntary and involuntary actions[19].

From a physiological point of view, regarding voice production, the myoelastic-aerodynamic theory considers that the aerodynamic properties of exhaled air are the most important motor elements for chordal oscillation, in interplay with the elasticity of the laryngeal muscles tissues[20].

The sound produced by the larynx is a complex wave, the same for all vowels, but when crossing the oropharyngeal pavilion from the glottis to the lips, the initial sound modifies its timbre acquiring the vowel color that it has when it comes out of the mouth. This is caused by the shape and dimension of the vocal tract[20]. The resonators modify the fundamental tone; in the human body, these are found above the vocal cords (epilaryngeal tube, pharynx, mouth and nasal cavity), acting as a filter, enriching some harmonics that are multiples of the fundamental frequency, and damping others, thus producing the acoustic phenomena that we know as human voice[21].

At the same time, this process is regulated through somatosensory zones of the thalamus that are transmitted to several parts of the cortex and basal ganglia[22]. Thereby, the phonation process is related to the central and peripheral nervous system, which controls and verifies

that the functions of the effector muscular system are completely fulfilled, referring to the structural and functional components of the larynx and the phonatory system.

Speech

Following the dual flow model, the act of speech is a complex conduct, integrated by linguistic and high-level motor control cognitive mechanisms. The genesis of speech starts with the communicative intention, which leads to the transformation of lexical units that need the production of vowels in a specific temporary organization. At the same time, these units must be adjusted to the context in terms of rhythm, intensity and prosody[23].

The final stages require the coordination of several sensorimotor systems, including phonation. Thereby, the complexity of speech production is subject to the interaction of sensorimotor systems with linguistic processes, which include grammatical, syntactic, semantic and cognitive processes; within the latter, we can find executive function processes such as verbal memory and audiovisual attention[23].

Voice and speech in suicidal behavior

Complementing the last idea, the behavior of some voice and speech traits have been described as indicators that provide information for the detection of suicidal crisis and depressive states, constituting background to be considered by health personnel[24-26]

In this sense, the changes in acoustic parameters can be explained in view of the fact that objectively measuring the acoustic signal caused by speech and voice production, the observable and measurable output of the behavior of neurological and physiological subsystems that coordinate to create oral emission and its respective articulation is being quantified[27,28].

Therefore, the consideration of voice and speech as an indicator of emotional state can contribute to the knowledge of the great public health problem that suicide represents[1]. Although there have been up to now extensive attempts to determine the factors that lead a person to kill themselves, the study of these elements alone have not resulted in an integral model of suicidal behavior, neither has this knowledge contributed to a greater capability of health professionals to predict suicide[9].

For all of these reasons the research of new ways to evaluate suicidal behavior will allow developing vocal biomarkers that account for physiological processes, representing a fast, non-invasive and objective evaluation alternative. Thereby, delving into the study of voice and speech opens new possibilities for the prevention and treatment of the suicidal risk population. It is important to highlight that this evaluation method does not pretend to replace other professionals and mechanisms that already exist, but providing a tool that complements assessment, offering an interdisciplinary outlook for approaching these types of disorders.

Due to the above, the objective of this research was to determine the relationship between acoustic parameters of voice and speech and the presence/absence of suicidal attempt (SA) in adolescents from Temuco, Chile.

Materials and Methods

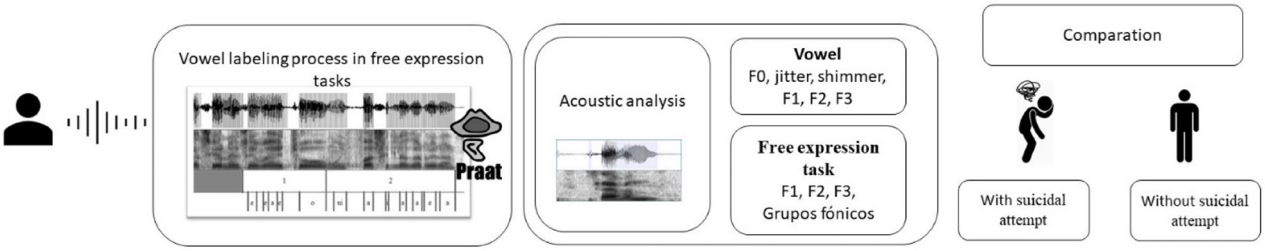
The study was based on a cross-sectional design. The sample was selected through non-probability sampling which was composed of 40 adolescents whose ages ranged from 18 to 19 years old, all of them regularly attended secondary schools in the city of Temuco, Chile. The adolescents were divided into two groups: 1) Group 1 composed of adolescents who reported at least one suicide attempt (N=20), 2) Group 2 composed of adolescents who did not report any suicidal attempts within the last 12 months (N=20). As to inclusion criteria, the following were considered: 1) Being sixteen years old or younger, 2) Being a regular student in an educational establishment, and 3) Self-reporting good health conditions. The exclusion criteria were: 1) Having been medically diagnosed with a speech and/or voice neurological disorder, 2) Background of cardiac pathology, 3) Having been diagnosed with a voice disorder, 4) Consumption of medication that affects voice and speech production, 5) Daily tobacco consumption, 6) Having an influenza virus infection at the time of the evaluation.

Regarding instruments, anamnesis and the Okasha Suicidality Scale was applied to every participant[29]. It is an instrument that has validity criteria for the Chilean population[30], also a self-administered scale, and identifies individuals with suicide risk[30]. On the other hand, the voice and speech of the participants were assessed through: 1) Production and sustaining of the vowel /a/; 2) The answer to two open questions, specifically “What is the best that has happened to you recently?” and “What is the worst that has happened to you recently?”.

Acoustic analysis

In order to measure the voice acoustic parameters, a sustained vocalization —checking maximum phonation time at comfortable pitch and intensity— was recorded. Regarding the connected speech samples, the participants were asked two questions: “What is the best that has happened to you recently?” and “What is the worst that has happened to you recently?”. Concerning the quantitative processing of voice data, audio signals manipulation, and observation of voice emission parameters characteristics, the PRAAT® free software was used (Boersma & Weenink, 2018), installed in an HP notebook (Pavilion model, and connected to a SCARLETT 212 GD MK2 Focusrite interface. (shown in **figure 1**).

Figure 1: Process of analysis of the voice and speech.



An ECM8000 ultra-linear condenser microphone installed on a pedestal placed 15 centimeters away from the participants' mouths was used. The recordings were performed in a previously calibrated Eckel Noise Control Technologies ® CL-13 model sound-cushioned camera.

The study variables linked to the voice's acoustic characteristics were:

- Presence of suicide attempts, sorting the subjects between two groups: the first one includes the students with at least one suicide attempt and the second one includes the students without suicide attempts.

As to phonatory tasks, the variables were the following (See **table I**):

1. Emission and sustaining of the vowel /a/, checking maximum phonation time at comfortable pitch and intensity

- Average value of fundamental frequency (F0)
- Minimum and maximum values of fundamental frequency
- Frequency perturbation (Jitter ppq5)
- Duration of the emission
- Formants values (F1, F2, F3)
- Connected speech through free expression
- Fundamental frequency
- Formants
- Intonation phrase
- Numbers of vowels

Table I: Summary of speech and voice phonatory tasks and their methods of measurement.

Phonatory tasks		
Variable	**Concept definition**	**Method of measurement**
Fundamental frequency	Voice fundamental frequency (f0) is defined as the first harmonic. It is physiologically determined by the number of glottal cycles performed by the vocal folds in 1 second and it is the natural result of these structures' duration. (Oliveira, Gama, & Magalhães, 2019)	This variable was assessed through the sustained emission of the vowel /a/, using the PRAAT software which was installed in an HP notebook connected to an interface (SCARLETT 212 GD MK2 Focusrite).
Formants	Resonance of the vocal tract. When the sound of the voice goes through the vocal tract it undergoes some changes, that is to say, the attenuation or amplification of determined harmonic groups in order to define some relative amplitude maxima within the spectrum, which are called formants[52].	This variable was assessed through a phonatory task that requested the sustained and comfortable production of the vowel /a/. The formant values were collected by the broadband spectrogram obtained through the Praat software.
Jitter (ppq5)	Unit of measurement of frequency perturbation obtained through the average of 5 consecutive periods.	This variable was assessed through the sustained emission of the vowel /a/ at comfortable pitch and intensity, using the PRAAT software which was installed in an HP notebook connected to a SCARLETT 212 GD MK2 Focusrite interface.
Duration of the emission	Amount of time a person can sustain the sound of the vowel /a/ when produced after one deep breath at comfortable pitch and intensity.	This variable was assessed through the sustained emission of the vowel /a/ at comfortable pitch and intensity, using the PRAAT software which was installed in an HP notebook connected to a SCARLETT 212 GD MK2 Focusrite interface.
Connected speech tasks through free expression		
Variable	**Concept definition**	**Method of measurement**
Intonation phrase	The portion of speech between two successive pauses of articulation, which involves several intensity groups but can also be reduced to only one word[53].	This variable was assessed through the identification of intonation phrase and their vowels, using the PRAAT software through a script.

It is relevant to clarify that some studies, such as the one conducted by Baken y Orlikoff[31], point out that preliminary evidence suggests the possibility that adult women might have more vocal jitter than men, at least concerning some vowels. The vowel /a/ is used in order to circumvent this drawback as it avoids the effects that the vocal tract could cause on the vibratory pattern of the vocal folds. The beginning and end of the emission are deleted, only considering the most stable region for analysis. Lastly, jitter (ppq 5) was calculated, which is recommended for research due to its softening effect as, with it, the frequency variability does not reach significance between genders[32].

Results

The pilot study group was composed of 20 adolescents with suicidal attempt (SA) and 20 adolescents without suicidal attempt (SA). The group with SA was composed of 18 women and the group without SA was composed of 13 women. The age median was 18 years old (16-19) for the group that reported SA and 19 years old (17-19) for the group that did not report SA.

As to the results of the voice and speech assessments, it was observed that the parameters that showed significant differences were: Jitter (p<0,05) and maximum phonation time (p<0,05). Concerning Jitter, it was observed that the group of adolescents that did not report previous SA showed a lower Jitter. With respect to maximum phonation time, it was observed that the maximum phonation time was greater within the group with SA (see **table II**).

Regarding the report of formants, it was possible to observe that facing the question "What is the best that has happened to you recently?", the group that reported committing SA presented significantly greater formant values when compared to the group that did not report SA within the last 12 months. (**Table III**)

As to the comparison of intonation phrase within the female group, it was possible to observe that the emitted intonation phrase were significantly lower within the group with SA (p<0,05). Concerning the assessments associated with the group of vowels per phonic group, it was possible to observe that the fundamental frequency

Table II: Comparison of voice and speech acoustic parameters in accordance with the presence or absence of suicidal attempt (SA) in the vocalization task.

		Without SA		With SA		T test	*p*
N		20		20			
Variables	[a]V. task	$\bar{x}$	σ	$\bar{x}$	σ		
F1 normalized	/a/	696.23	89.23	763.61	98,10	-67,38	.027*
		Without SA		**With SA**		**Man Whitney U test**	*p*
N		20		20			
		Me	**Range**	**Me**	**Range**		
F2 Normalized	/a/	1393.79	790.25	1431.10	454.22	182	.465
F3 Normalized	/a/	2542	1166.35	2574.22	3058.04	200	.794
Maximum phonation time	/a/	6.093	20.10	3.20	8.2	82.00	.001**
Jitter (local)	/a/	0.17	1.63	0.28	.54	85	.001**
Shimmer (local)	/a/	2.74	0.176	.030	.1455	163.00	.327

[a] Vocalization task

Table III: Description and comparison of Formants in accordance with the presence of suicidal attempt (SA) in the free expression task.

What is the best that has happened to you recently?							
		Without SA		**With SA**		**T test**	*p*
N		20		20			
Variables	Vowel	x	σ	Me	σ		
F1 normalized	/a/	563	139	643	168	-4,47	0,000**
F2 normalized	/a/	1538	243	1659	282	-3,83	0,000**
F3 normalized	/a/	2507	272	2616	282	-3,345	0,001**
F1 normalized	/e/	466	135	521	136	-3,645	0,000**
F2 normalized	/e/	1729	324	1917	331	-5,13	0,000**
F3 normalized	/e/	2597	287	2753	297	-4,78	0,000**
F2 normalized	/i/	1943	396	2119	326	-2,77	0,006**
F2 normalized	/u/	1379	292	1438	400	-0,624	0,535
F3 normalized	/u/	2538	259	2755	287	-2,834	0,006**
		Me	**IQ**	***Me***	**IQ**	**Man Whitney U test**	
F1 normalized	/i/	380	115	421	133	1623	0,009**
F3 normalized	/i/	2602	425	2843	433	1409	0,006**
F1 normalized	/o/	467	123	499	163	7111	0,006**
F2 normalized	/o/	1320	343	1450	402	6810	0,001**
F3 normalized	/o/	2511	386	2645	346	6462	0,000**
F1 normalized	/u/	382	107	451	82	215	0,025*

of the vowel, vowel minimum, and vowel maximum were greater within the group with SA. However, these differences were not significant. (**Table IV**)

Regarding the report of formants, it was possible to observe that facing the question "What is the worst that has happened to you recently?", the group that reported committing SA showed greater formant values when compared to the group that did not report SA within the last 12 months; these differences were observed for every vowel but not for every formant (**Table V**).

As to the results of intonation phrase within the female group, facing the question "What is the worst that has happened to you recently?", it was observed that the number of Intonation phrase was significantly lower

Table IV: Comparison of speech parameters in accordance with the presence of suicidal attempt (SA). Women.

Open question: What is the best that has happened to you recently?						
	Without SA		With SA		Man Whitney U test	*p*
N[a]	659		436			
Variables	Me	Range	Me	Range		
N° of IF[1]	4	16	3	13	113230,50	,00**
$\bar{x}$ F0 IF[2]	180,25	235,50	210,24	277,24	86716,00	,00**
$\bar{x}$ F0 Vowel[3] Vowel a	207,92	37	210,17	46	5507,000	0,930
F0 Min. Vowel Vowel a	200,62	38	204,75	47	5266,000	0,528
F0 Max. Vowel Vowel a	215,83	47	222,22	53	5407,000	0,754
$\bar{x}$ Vowel[3] Vowel e	210,83	45	215,87	40	6700,000	0,910
F0 Min. Vowel Vowel e	201,65	47	208,70	39	6465,000	0,568
F0 Max. Vowel Vowel e	227,08	43	222,69	43	6358,000	0,436
$\bar{x}$ F0 Vowel[3] Vowel i	206,23	34	212,31	31	928,000	0,987
F0 Min. Vowel Vowel i	200,81	36	205,94	28	928,000	0,987
F0 Max. Vowel Vowel i	211,00	36	221,67	35	892,000	0,750
$\bar{x}$ F0 Vowel[3] Vowel o	210,37	43	222,30	45	3945,000	0,584
F0 Min. Vowel Vowel o	203,65	40	215,00	44	3965,000	0,6221
F0 Max. Vowel Vowel o	210,63	46	228,38	55	4137,000	0,991
$\bar{x}$ F0 Vowel[3] Vowel u	210,34	44	204,87	38	106,000	0,851
F0 Min. Vowel Vowel u	205,03	43	203,24	35	109,000	0,950
F0 Max. Vowel Vowel u	215,43	45	214,13	37	103,000	0,754

N[a]: Number of vowels per record; [1]Number of Intonation phrase, [2]Mean of the Intonation phrase Fundamental Frequency, [3]Mean of the Vowel Frequency.

Table V: Description and comparison of Formants in accordance with the presence of suicidal attempt (SA) in the free expression task.

What is the best that has happened to you recently?							
		Without SA		With SA		Man Whitney U test	*p*
N		20		20			
Variables	Vowel	*Me*	IQ	*Me*	IQ		
F1 normalized	/a/	592	187	677	267	23002	0,000**
F2 normalized	/a/	1515	286	1612	385	27064	0,001**
F3 normalized	/a/	2512	365	2738	516	23325	0,000**
F1 normalized	/e/	468	116	488	153	46516	0,013*
F2 normalized	/e/	1819	440	1961	540	40795	0,000**
F3 normalized	/e/	2610	439	2846	427	35534	0,000**
F1 normalized	/i/	410	103	401	87	8814	0,386
F2 normalized	/i/	2153	534	2261	840	8261	0,087
F3 normalized	/i/	2887	462	2964	504	7615	0,007**
F1 normalized	/o/	495	123	517	172	18718	0,211
F2 normalized	/o/	1298	449	1333	468	18199	0,090
F3 normalized	/o/	2600	413	2655	535	17356	0,016**
F1 normalized	/u/	449	105	438	97	1714	0,276
F2 normalized	/u/	1281	474	1192	342	1807	0,529
F3 normalized	/u/	2574	498	2763	430	1353	0,004**

within the group with SA (p<0,05). Concerning the assessments associated with the group of vowels, the fundamental frequency of the vowel, vowel minimum, and vowel maximum were significantly greater within the group with SA (p<0,05), for the vowel /o/ and the vowel /i/ (**Table VI**).

Discussion/Conclusion

Suicidal behavior is composed of different stages that can go from the wish to die to consummated suicide[33-35]. This behavior is steadily increasing, especially among adolescents and children[36]. Suicidal behavior -alongside other mental states such as depression- are complex phenomena to study since they are influenced by several factors, among which social, familial, personal, and biological factors can be found. Therefore, the knowledge and exploration of new tools that account for this phenomenon is fundamental[9].

In this sense, voice production is a complex system that is sensitive to mild physiological and cognitive changes which, at the same time, causes noticeable acoustic changes[37]. Consequently, the present research assessed the association between voice and speech characteristics regarding a group of patients with suicidal attempts. Among the results, it was found that the voice and speech of patients with suicidal attempts differ concerning some variables when compared to patients without suicidal attempts.

As to assessments associated with the Fundamental frequency of vowels, it was observed that this was greater within the group that presented suicidal attempts. Regarding this matter, it becomes of great importance to point out that impulsive suicidal behavior has been linked to dopamine signaling mechanisms[38], which influences the information processing in the prefrontal cortex and, at the same time, regulates the functional balance between direct and indirect basal ganglia circuits; therefore, the dopaminergic function might be associated with voice modifications presented in psychiatric problems[39].

The findings of this research complement other studies that have found lower fundamental frequencies concerning depressive and suicidal speech[25,40]. On the other hand, it is relevant to mention that there are studies where no significant correlation between F0 variables, depression, and other mental alterations is reported[27,41,42]

Table VI: Comparison of speech parameters in accordance with the presence of suicidal attempt (SA). Women.

Open question: What is the worst that has happened to you recently?						
	Without SA		With SA		Man Whitney	*p*
Nª	659		436		U test	
Variables	Me	Range	Me	Range		
N° of PG[1]	6	7	5	5	101933	,000**
x̄ F0 PG[2]	210,20	43	214,96	41	109327	,000**
x̄ F0 Vowel[3] Vowel a	207,92	37	210,17	46	8370,000	0,201
F0 Min. Vowel Vowel a	200,62	38	204,75	47	8627,000	0,377
F0 Max. Vowel Vowel a	215,63	47	222,22	53	8062,000	0,79
x̄ F0 Vowel[3] Vowel e	210,83	45	215,87	40	10468,000	0,195
F0 Min. Vowel Vowel e	201,65	47	208,70	39	10195,000	0,098
F0 Max. Vowel Vowel e	227,08	43	222,69	43	11373,000	0,914
x̄ F0 Vowel[3] Vowel i	206,23	34	212,31	31	1606,000	0,049**
F0 Min. Vowel Vowel i	200,81	36	205,94	28	1738,000	0,182
F0 Max. Vowel Vowel i	211,00	36	221,67	35	1420,000	0,004**
x̄ F0 Vowel[3] Vowel o	210,37	43	222,30	45	3390,000	0.000**
F0 Min. Vowel Vowel o	203,65	40	215,00	44	3502,000	0,000**
F0 Max. Vowel Vowel o	219,63	46	228,38	55	4510,000	0,198
x̄ F0 Vowel[3] Vowel u	210,34	44	204,87	38	717,000	0,796
F0 Min. Vowel Vowel u	205,03	43	203,24	35	733,000	0,923
F0 Max. Vowel Vowel u	215,43	45	214,13	37	742,000	0,996

Nª: Number of vowels per record; [1]Number of Intonation phrase , [2]Mean of the Phonic Group's Fundamental Frequency, [3]Mean of the Vowel Frequency.

When trying to answer why this happens, literature leads us to the heterogeneous nature of the symptoms associated with suicidal behavior, being necessary to understand that F0 is a marker of the physical state of the vocal folds and a marker of the emotional state of the speaker but that, alongside many other factors, it does not only depend on the gender or the lack of standardization of F0 extraction techniques but also on other biological and physical factors[43].

For that reason, the differences obtained between different studies may occur because individuals with depression, suicidal ideation and suicidal attempts can differ with respect to their personality traits in many ways[44] Therefore, F0 can be influenced by mood changes, agitation, anxiety and the speakers' personality[43].

Concerning the results obtained on the short-term frequency perturbation measurements, the Jitter values were significantly lower within the groups with suicidal attempts. These results differ from other studies that present slightly greater values for patients with suicide risk, which can be attributed to anxiety[25]. Physiologically, there are factors that influence the short-term variability of the fundamental frequency. One of the factors described is the cardiovascular mechanism, which causes the systematic variation of the fundamental frequency during the cardiac cycle, i.e., heart rate variations alter the systole period, thus altering the vibratory cycles of the speaker; this is one of the reasons for greater short-term vocal fluctuation in patients with suicide attempts. The second factor is the neuromuscular mechanism, which causes the inherent muscle noise generated by the imperfect integration of individual motor units due to the sustained contraction of the laryngeal musculature. These mechanisms, when under emotional stress due to the influence of the sympathetic and parasympathetic activation of the autonomic nervous system, cause changes in the muscular tone which, at the same time, alters the vibration of the vocal folds[25]. However, although one of the most used measures regarding speech in people with depression and suicide attempt includes the Jitter, the lack of standardization of extraction techniques influences the values and makes comparing results between studies very difficult[45,46]. Another factor of confusion when using the Jitter is the type of voice signal from which the measure is extracted, being possible to observe two types of tasks: 1) sustained vocalization and 2) connected speech (Laver et al., 1992); this can be explained since, due to its periodicity, the use of sustained vowels allows a simpler extraction of these characteristics but leaves them exposed to errors because of the different sound pressure levels between and within individuals, which potentially turns it unreliable for clinical analysis[45]. Accordingly, the connected speech analysis is harder than the sustained vowel analysis due to the problems associated with the search for suitable sound sections in a given emission[47].

Another variable that showed significant differences was formants, as the group with suicide attempts obtained greater values than the control group. Physiologically, this can be explained by muscle tension alterations caused by the autonomic and somatic nervous system (Scherer, 1986), as well as the neurotransmitter function, as it has been observed that the GABA neurotransmitter has been linked to changes in muscle tension[48]. These changes modify the configuration and dynamics of the vocal tract, which, at the same time, are susceptible to being captured by formant characteristics that are related to the acoustic characteristics of the vocal tract[43].

It is important to state that the limitations of this study are related to sample size since there is no formal record of the adolescents with suicidal attempts in the establishments, thus, the way of researching is through assessments for every subject, and, thereby, the selection of individuals with suicidal attempts is reduced to a figure close to 15% 49. On the other hand, researching adolescents with suicidal risk requires a multidisciplinary work team that can take on the attention of these teens. It is well known that our country invests very little of its GDP in mental health, so mental health programs have been poorly implemented, being unable to address this problem in the affected population[50].

Among the possible explanations for the conflicting results obtained with respect to other studies, it is possible to observe: 1) lack of heterogeneity of the parameters studied, 2) their evaluation methods, 3) instruments used, 4) possible non-declared comorbidities, 5) non-declared use of medication that affect voice and speech production. All of these circumstances represent potential confounding factors for the results.

Lastly, the findings of this research suggest that voice and speech are signs that must be assessed in the population with suicidal risk. However, it is necessary to continue assessing the acoustic characteristics based on the profiles of suicidal behavior, as it seems that ideation and attempt —with or without depression— are manifested with different characteristics in the voice and speech of adolescents.

It is considered that voice and speech as indicators of emotional state can contribute to suicidal behavior knowledge. This research concludes that the acoustic parameters of voice and speech represent an assessment measure for the adolescent population with suicidal behavior. Despite this conclusion, it is still necessary to continue developing studies in the same line in order to correct the effect of the profiles and sample sizes.

Statements

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Statement of Ethics
The research presented in the manuscript was conducted ethically in accordance with the World Medical Association Declaration of Helsinki and the appropriate guidelines for human studies and was approved by Scientific Ethical Committee of The University of La Frontera with number (109-9).

Parents and adolescents have given their written informed consent. Besides, the schools have given their consent to recruit the adolescents at their facility.

Conflicts of Interest Statement
The authors have no conflicts of interest to disclose.

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ORIGINAL

The knowledge of clinical dental students on the oral effects and consequences of cannabis use: implications for curricular modification

El conocimiento de los estudiantes de odontología clínica sobre los efectos orales y las consecuencias del consumo de cannabis: implicaciones para la modificación del plan de estudios

Shivaughn M. Marchan[1], Meagan Thorpe[1], Ramaa Balkaran[2]

1. Unit of Restorative Dentistry, School of Dentistry
2. Unit of Oral Diseases, School of Dentistry
Faculty of Medical Sciences The University of the West Indies, Mount Hope Medical Complex, Champs Fleurs, Trinidad and Tobago

Corresponding author
Dr. Shivaughn Marchan
E-mail: Shivaughn.marchan@sta.uwi.edu

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Abstract

Background: This preliminary study aimed to assess the knowledge of clinical dental students and interns on the pathological and management consequences of cannabis use. Additionally, the study aimed to understand perceptions and current practices of clinical dental students with respect to offering cessation advice to patients using cannabis.
Methods: Data were collected from clinical dental students, with the use of a 17-item questionnaire developed de novo for use in this study at a dental school in the English-Speaking Caribbean. A target population, of 122 clinical students, was identified, and paper-based surveys were sent to all students.
Results: There was an overall response rate of 98% (n=120). Most students (70%) enquired about patients' cannabis use as part of medical history while only 84% of this percentage documented this information in the patients' notes. Reported knowledge on oral health consequences of cannabis was significantly lower in student year groups 3 and 4 (23%) compared to Year 5 students and interns (35%). Almost all students (97%) believed that dental practitioners should play a role in educating patients about the general health consequences of cannabis use. Most respondents (93%) believed that they did not have sufficient knowledge to give cannabis cessation advice. Most (88%) reported a lack of training with cannabis cessation advice.
Conclusion: The results of this study have implications for both pre-clinical and clinical curricular change related to the multi-disciplinary health care management of patients who use or abuse cannabis.

Key words: Cannabis, dental students, cessation advice, curricular change.

Resumen

Antecedentes: Este estudio preliminar tenía como objetivo evaluar los conocimientos de los estudiantes de odontología clínica y los internos sobre las consecuencias patológicas y de gestión del consumo de cannabis. Además, el estudio pretendía comprender las percepciones y las prácticas actuales de los estudiantes de odontología clínica con respecto a la oferta de consejos para dejar de consumir cannabis a los pacientes.
Métodos: Se recogieron datos de estudiantes de odontología clínica, con el uso de un cuestionario de 17 ítems desarrollado de novo para su uso en este estudio en una escuela de odontología en el Caribe de habla inglesa. Se identificó una población objetivo, de 122 estudiantes clínicos, y se enviaron encuestas en papel a todos los estudiantes.
Resultados: La tasa de respuesta global fue del 98% (n=120). La mayoría de los estudiantes (70%) preguntó sobre el consumo de cannabis de los pacientes como parte de la historia clínica, mientras que sólo el 84% de este porcentaje documentó esta información en las notas de los pacientes. Los conocimientos declarados sobre las consecuencias del cannabis para la salud bucodental fueron significativamente menores en los grupos de estudiantes de los años 3 y 4 (23%) en comparación con los estudiantes del año 5 y los internos (35%). Casi todos los estudiantes (97%) creían que los odontólogos deberían desempeñar un papel en la educación de los pacientes sobre las consecuencias del consumo de cannabis para la salud en general. La mayoría de los encuestados (93%) creía que no tenía conocimientos suficientes para aconsejar sobre el abandono del cannabis. La mayoría (88%) informó de la falta de formación para dar consejos sobre el abandono del cannabis.
Conclusión: Los resultados de este estudio tienen implicaciones para el cambio curricular tanto preclínico como clínico relacionado con el manejo sanitario multidisciplinar de los pacientes que usan o abusan del cannabis.

Palabras clave: Cannabis, estudiantes de odontología, consejo de cesación, cambio curricular.

Introduction

The Government of the Republic of Trinidad and Tobago, in 2019, decriminalized the use of cannabis[1]. Specifically, individuals could possess up to 30 grams of cannabis for personal use. Furthermore, households could cultivate a limited number of cannabis plants for personal use. In the Trinidadian context, cannabis could be used both medicinally or recreationally, however, the act provides no distinction between these. While there is no current knowledge on the use of cannabis for medical purposes in Trinidad and Tobago, there is evidence of the prevalence of recreational cannabis use. A six-month prevalence rate of 13% for cannabis use was found in a cohort of undergraduate students of the Trinidadian campus of the University of the West Indies[2]. A study on the attitudes of persons within a Port-of -Spain suburb on persons who abused drugs, found that 36.1% of respondents of the study had themselves used cannabis at least once[3]. Despite the recent legislative change, attitudes of persons in Trinidadian society remain one of negativity for those persons who use cannabis[3]. Change in the legislative framework regarding the use of cannabis could potentially increase the prevalence of recreational drug use in this jurisdiction that is not openly discussed with health care professionals.

In the dental setting, patients who use or abuse substances such as cannabis can complicate history taking, modify the presentation of disease, reduce the effectiveness of local anaesthesia, and interfere with compliance to treatment recommendations and instructions for oral care[4]. Just as dental professionals take an active role in providing tobacco cessation advice to patients, dentists as health care providers should be equipped with the knowledge to facilitate conversations with patients about cannabis use and its associated risks on both oral and general health[5]. Furthermore, patients at risk for addictive behaviours should be recognized and appropriate referrals made to medical personnel. In the United States, the Commission on Dental Accreditation includes as an educational standard (Standard 2-24e) for the training of dentists, management as it relates to the patients that use or abuse substances such as cannabis. No such standards are mentioned in the documentation of the Caribbean Accreditation Authority as it relates to educational standards for dental schools. A review of the curriculum of the sole dental school in the country, The University of the West Indies, School of Dentistry (SoD) does not explicitly cover the management of patients who may use cannabis in any form.

Current literature examines the knowledge, attitudes, and behaviours of health care workers in general as it relates to the use of medical cannabis use[6]. Very little is known about the perceptions of dental professionals towards patients who engage in recreational cannabis use. Furthermore, research is lacking on the professional interactions between dental clinicians and patients as it relates to documentation of cannabis use and conversations on cessation. This study aims to primarily determine if dental students, at the UWI-SoD, have any knowledge on the oral and general health effects of cannabis usage. Secondarily, the study aims to ascertain what, if any cessation advice is given to patients by dental students at any time during dental management or if modifications are made to treatment based on the knowledge of cannabis use by patients and what are the limitations perceived by students as barriers to giving cessation advice to patients who are users of cannabis.

Methods

Before the start of the study, ethical approval was granted by the St. Augustine Campus of The University of The West Indies, Research Ethics Committee. (Reference No. CREC-SA.0085/11/2019) and permission granted by the Registrar of the campus. A survey instrument was developed prior to the start of the study and subjected to face validity by graduate dentists and educational specialists. The questions on this de novo instrument were reviewed several times to ensure clarity in terms of language and content relevant to dental students. The 17-item, paper-based, survey instrument was administered to clinical students (Years 3 through 5 and dental interns) over a 2-month period in February and March 2020. At this research site internship is considered postgraduate training in general dentistry and interns have been classified as students for the purpose of this study.

The instrument contained 10 dichotomous closed-ended questions (yes/no), 3 open-ended questions, 1 multiple response question, with the remainder of the items eliciting demographic information, namely, age, gender, and year of study. The dichotomous closed-ended questions were intended to determine the students' knowledge of common oral problems associated with cannabis use and the perceptions and attitudes of the students on the role they could play in providing cessation and health advice related to cannabis use. All clinical students and interns of the school were approached directly by one author (**MT**).

Before deployment of the survey, an explanation of the aims of the research and the responsibility of research subjects was discussed with all potential respondents, and written informed consent was gained from those interested in taking part in the survey. Data was entered and analysed using Statistical Package for Social Sciences (SPSS) Version 28 (IBM, Chicago). Frequency distributions were used to analyse data. Cross tabulations and independent chi-squared tests were used to examine limitations to giving cannabis cessation advice to patients by students.

Results

There were 120 respondents (98% response rate) out of the target population of 122. The majority respondents (81%) were female, while the remaining (19%) were male. Most respondents (30.8%) came from the final year group (Year 5), while interns and Year 3 students each accounted for 25.8% of respondents. Students in the fourth year of training accounted for only 17.5% of total respondents.

Most (70%) of the respondents reported that they specifically enquire about a patient's cannabis history while 84% reported this information is then reported in the patient's clinical notes, either in the area dedicated to history taking or within a clinical note. A small percentage (7.5%) of students agreed they possessed sufficient knowledge and training to offer advice to patients on cessation of cannabis use or arrange for appropriate follow-up.

Only 24% of respondents in the lower clinical year groups (Year 3 and 4) were able to list at least one or more oral pathologies associated with cannabis use, versus 35% in the higher clinical years (Years 5 and interns). Most students (> 50%), across all clinical years, were unaware of any oral pathologies associated with cannabis use. Of those students that were aware of the use of cannabis causing oral pathologies, most of the pathologies described were: xerostomia, periodontal disease, oral cancer, pigmentation of the oral mucosa, and smoker's palate. Across all year groups, 40% of students did not attribute cannabis use to a reduction in the effectiveness of local anaesthesia, with Year 3 students (19.2%) contributing to most of this overall percentage.

In the context of patient education, dental students were more likely to communicate the oral consequences of cannabis use (60%) versus the general health consequences (12.5%). This aligns with the beliefs of clinical students that dental professionals should play a role in educating patients about the oral consequences of cannabis use (96.6%). Most students (88.3%) did offer cessation advice to users of cannabis despite 93% of all students stating that they had insufficient knowledge to give meaningful cannabis cessation advice. Of those that did offer advice, 11.7% of these students used strategies that are often used for tobacco cessation. When students were asked to identify limitations, other than knowledge or training, in providing cessation advice to patients the major limitations were offered: lack of time during the clinical session (65.8%), patients being only interested in dental treatment (59.2%), perceptions that patients will be not compliant (45.8%), lack of appropriate referral services (47.5%), lack of awareness that dental professionals should be giving such advice (38.3%).

When limitations to giving cessation advice were examined significant differences were found between the limitations of lack of training*lack of awareness that dentists could give this type of advice (p=0.01) and between the limitations in the lack of training*appropriate referral services(p=0.08). When cross-tabulations and independent chi-squared tests were performed to determine differences between year group and stated limitations, there were insignificant differences between year group*patients not being receptive to such advice (p=0.21).

Discussion

Much of the research concerning the attitudes, knowledge, and belief of health care professionals regarding cannabis use amongst patients have examined cohorts of medical students, general medical practitioners, medical specialists, pharmacists, and nursing practitioners[6-8]. Research has also focused on the views of these professionals as it relates to the use of medical cannabis use[9]. This study is particularly timely since recent legislative change has the potential for an increase in the recreational use of cannabis in the general population with an associated increase in users of cannabis seeking dental care[10].

As health care practitioners, dentists must be able to not only identify risk factors contributory to pathology within their specific specialty area but must be cognizant of general health effects of cannabis use, be confident to have conversations with patients about cannabis use and be able to make referrals to medical practitioners if they perceive that patients may benefit from such. Just as tobacco cessation counselling in dental settings is consistent with the shift from management of dental disease alone to holistic management of health with a focus on prevention, there is a role for dentists as part of interprofessional teams that assess substance abuse risk[11,12]. The perceptions of dental students of such expanded role as health care professionals in this present study are ambiguous since 96.6% of students believed that they had a role to play in educating patients on the oral consequences of cannabis use but only 12.5% were likely to communicate the general health consequences of cannabis use.

Dentists must be able to offer specific and targeted patient counselling as it relates to diagnosed oral pathology associated with cannabis use. There is concern however that this studied group could adequately communicate risk associated with cannabis use to various oral pathologies since more than 50% of students were not aware of any pathologies associated with cannabis use. Dental professionals must also be aware of any modifications required during dental management of patients who use or abuse cannabis-related products[13-15]. While most surveyed students correctly attributed cannabis use with

potentially affecting the quality of local anaesthesia, 40% of students did not possess this knowledge. Specifically, improvements in curricula delivery are required for entry-level clinical students (Year 3) to ensure that modifications are made to dental management plans for patients who are cannabis users.

Central to the prevention of oral cancer, is tobacco cessation advice. Training in tobacco cessation forms part of the curricula of many dental schools[16,17]. At the UWI-SoD tobacco cessation is covered in both the disciplines of preventive dentistry and oral medicine. Furthermore, topics on cannabis use in the form of marijuana are covered together with smoking and smokeless tobacco in discussing the etiology of oral cancer. Patients who smoke tobacco are more likely to use cannabis[18]. Such patients with concomitant tobacco and cannabis use are less compliant with tobacco cessation advice, possibly due to the addictive properties of cannabis[18]. Clinicians, such as dental professionals, who are trying to aid tobacco cessation should routinely and continuously assess cannabis use as part of tobacco cessation strategies[18]. While 70% of students enquired if patients used cannabis, what is unclear is if this was an isolated event associated with the medical history at an intake appointment, or if this question was asked at various times throughout patient management. This would have to be assessed with future research.

Time during clinical sessions as a limitation to discussing cannabis use aligns with the research of Clareboets et al who examined the barriers of clinical dental students in giving tobacco cessation advice[19]. In this current study, the limitation of time was indicated as a reason for not engaging in cessation conversations in 65.8% of students compared to 51% of students in the work of Clareboets et al who described time as a strong barrier in giving cessation advice[19]. Given the nature of clinical dental training and emphasis on the acquisition of psychomotor skills, students may prioritize wet-handed dentistry over the acquisition of what they perceive to be as less important non-clinical soft skills.

The literature also discusses patient disinterest as a barrier to tobacco smoking cessation[11,19]. While tobacco cessation advice cannot be equated with cannabis cessation advice, the barriers that have been established in studies of dental students giving tobacco cessation seem to parallel limitations to giving cannabis cessation advice. Globally, general dentists are not normally integrated into medical decision-making teams within hospitals or primary care settings and identification of medical personnel and resources can be challenging for appropriate referral of patients at risk for substance abuse such as cannabis[12]. This is clearly demonstrated in the stated barrier of the lack of appropriate referral services, which 47.5% of students listed as a limitation to providing cessation advice. This barrier as well as unawareness that dental professionals should be involved in giving cessation advice to cannabis users underscores the need for robust curricula that includes inter-professional clinical education amongst various cadres of medical and health professionals[20]. In the context of the decriminalized cannabis legislation, health care workers should understand and be prepared to discuss the implications of recreational cannabis use.

Most students (93%) believed that they had insufficient knowledge to give meaningful cannabis cessation advice, however, most respondents claimed to give some sort of cessation advice. This may suggest that respondents are not comfortable discussing oral and general health implications of cannabis use with patients, possibly due to the sensitivity of the topic. Clareboets et al., in discussing barriers to students giving tobacco cessation advice, reported that broaching such sensitive topics could lead to a reduction in rapport with patients[19]. The same could be true of dental students trying to give cannabis cessation advice. Future research would have to ascertain exactly what advice is given to patients that students believe have problematic cannabis use, in the absence of established guidelines to manage such patients.

The strategy for tobacco cessation used by dental professionals of "Ask, Advise, Assess, Assist, Arrange" can be modified and used together with motivational interviewing as a starting point in the cannabis cessation conversation[21]. Such strategies can work in tandem since the motivation of persons with addictive behaviours has been identified as a factor for reducing cannabis use[22]. Dental professionals can play a pivotal role in providing cessation advice focussed on the known oral effects of cannabis use. While it is important for dental students to have a working knowledge of the oral effects, dental challenges, and general health consequences of cannabis use; it is also important that identification of such patients occur with screening, followed by appropriate documentation of a patient's cannabis history, cessation advice and arranging counselling for all patients with an identified problematic use. These described strategies once correctly implemented can ensure that graduate dentists can engage with patients in discussing such a sensitive topic as routine and improve patients' acceptance of such services[23].

What is apparent from the significance found between lack of training and appropriate referral services and the lack of training and lack of awareness that dentists can give such advice, is the fact that dental students lack confidence as health care professionals that could coordinate follow-up patient management related to cannabis use. Such issues can be addressed with robust cross-discipline interprofessional education including students of medicine, psychology, and specialists such as psychiatrists. Insignificant differences found between the year group and the perceptions that patients will

not be responsive to advice may be explained by a continued lack of confidence to have conversations related to cannabis even as students' progress through clinical training.

Conclusion

Knowledge on the oral health effects of cannabis and the implications of cannabis use on dental management of patients was poor amongst the surveyed clinical students at this teaching hospital. This is despite most students stating that dental professionals had a role to play in offering cessation advice to patients who used cannabis. Dental professionals in this locale need to be aware of the consequences of cannabis use given that its use can become more pervasive with the recent decriminalization of cannabis for personal use and in the context that cannabis could become more readily available to the general population. Curricular change would need to occur in both pre-clinical and clinical training where content on the effects of cannabis use in various forms is delivered in courses of oral pathology, oral medicine and public health. The effects of cannabis use on dental management should be discussed in courses related to local anaesthesia training and pharmacology and cessation and motivational interviewing technique included in courses of preventive dentistry. Students should be audited in the clinical setting to ensure that patients are identified through history taking and screening and arrangements made for either follow-up cessation activities or referral to medical personnel. Such curricular change can incorporate principles of interprofessional learning with other students of health care sciences to ensure a holistic approach in dealing with patients prone to addictive behaviours. Educational activities must stress the importance of making clinical decisions for patients based on scientific evidence regarding the pathologic and pharmacologic effects of cannabis, and not on the societal stigma associated with drug use.

Statement of ethics

The study protocol was reviewed by the Ethics Committee of The University of the West Indies, St. Augustine and granted an exemption from requiring full ethical approval (CREC-SA.0085/11/2019). Written consent was gained from all respondents prior to participation in the study.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Author contributions

This research was conceptualized by Author 1 and Author 3. Data collection was completed by Author 2, Data entry was completed by Author 2 and Author 3, and data analysis completed by Author 1 and Author 3. Author 1 was the primary author of the present manuscript. All authors reviewed, edited and approved the final draft of the manuscript.

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None

Data availability statement

The data that supports this work can be made available upon request.

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ORIGINAL

Relationship of pregnant women's knowledge about sexuality during pregnancy with sexuality quality

Relación de los conocimientos de las mujeres embarazadas sobre la sexualidad durante el embarazo con la calidad de la sexualidadv

Debi Novita Siregar, Eva Latifah Nurhayati, Sunarti, Elis Anggeria, Karmila Br Kaban, Ade Lestari

Faculty of Nursing and Midwifery, Universitas Prima Indonesia

Corresponding author
Eva Latifah Nurhayati
E-mail: evalatifahnurhayati@unprimdn.ac.id

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Abstract

Introduction and aim: There are no restrictions and restrictions on sex during pregnancy as long as it is done safely and correctly. A safe and healthy relationship will improve the quality of life for married couples. Sexual intercourse has no risk to the unborn baby. The baby in the womb remains safe because it is protected by an amniotic sac which has the function to protect the baby from problems. The purpose of this study was to analyze the relationship between the knowledge of pregnant women about sexuality during pregnancy and the quality of sexuality during pregnancy.
Methods: This research method is a cross-sectional design with a quantitative approach. The population in this study amounted to 150 people, the sample in this study amounted to 50 people with a sampling technique using non-probability sampling with a consecutive sampling method.
Results: The result of this study is that there is a relationship between the knowledge of pregnant women about sexuality during pregnancy and the quality of sexuality during pregnancy with a p-value of 0.000.
Conclusion: There are a relationship between knowledge about sexuality and the quality of sexuality during pregnancy.

Key words: Knowledge, Sexuality, quality of sexuality, pregnancy.

Resumen

Introducción y objetivos: No hay restricciones ni limitaciones en las relaciones sexuales durante el embarazo, siempre que se hagan de forma segura y correcta. Una relación segura y saludable mejorará la calidad de vida de las parejas casadas. Las relaciones sexuales no suponen ningún riesgo para el feto. El bebé en el vientre materno permanece seguro porque está protegido por una bolsa amniótica que tiene la función de proteger al bebé de los problemas. El objetivo de este estudio era analizar la relación entre los conocimientos de las mujeres embarazadas sobre la sexualidad durante el embarazo y la calidad de la sexualidad durante el mismo.
Metodología: Este método de investigación es un diseño transversal con un enfoque cuantitativo. La población en este estudio ascendió a 150 personas, la muestra en este estudio ascendió a 50 personas con una técnica de muestreo utilizando un muestreo no probabilístico con un método de muestreo consecutivo.
Resultados: El resultado de este estudio es que existe una relación entre el conocimiento de las mujeres embarazadas sobre la sexualidad durante el embarazo y la calidad de la sexualidad durante el embarazo con un valor p de 0,000.
Conclusión: Existe una relación entre los conocimientos sobre la sexualidad y la calidad de la sexualidad durante el embarazo.

Palabras clave: Conocimiento, sexualidad, calidad de la sexualidad, embarazo.

Introduction

Pregnancy is a symbol of a woman's femininity because pregnancy is part of a woman's life cycle. All women can experience something self-understanding if they have not succeeded in getting pregnant, but on the other hand, pregnancy can cause a woman to experience pain and death. During pregnancy, women experience physical, psychological, social, and sexual changes[1]. Pregnant women can still have sexual intercourse as long as the sexual relationship does not endanger pregnancy[2].

Sexual intercourse is a necessity for survival for husband and wife, not to mention during pregnancy, and husband and wife need each other, love, and give satisfaction and intimacy. Sexual intercourse activities provide harmony in the household of husband and wife, not including during pregnancy and after giving birth1. Doing and not having sex during pregnancy is due to the low knowledge of pregnant women about safe sex during pregnancy[3].

There are no restrictions and restrictions on sex during pregnancy as long as it is done safely and correctly, the safe position is the supine position with the husband's stomach without putting pressure on the mother's stomach[3]. There are three main categories of beliefs about sexuality during pregnancy: erroneous beliefs, a holistic approach to sexuality, and limited sexual counselling[4]. Sexuality and sexual well-being during pregnancy are associated with fear of harming the fetus, satisfaction with intimate partner relationships, attitudes toward sexuality, physical self-image, and overall well-being[5].

The most important factor in determining sexual satisfaction is the aspect of the relationship with a partner, and closeness with a partner is very important[6]. The husband will be very concerned about the condition of his wife who is starting to get pregnant and stay away from sex for fear of hurting the baby. There are husbands whose sexual desire for pregnant women is higher[7].

Pregnancy raises a range of concerns about the course and its consequences, leaving women very vulnerable and requiring appropriate care based on adaptability[8]. During pregnancy under normal circumstances, intercourse can be carried out until the end of pregnancy, although there are some experts who think that no longer have sex for 14 days until delivery. Intercourse is not allowed if bleeding occurs, has a history of repeated miscarriages, abortion, premature imminent, premature rupture of membranes[9].

Health care professionals should be trained to assess sexual difficulties in pregnant women and recommend possible solutions[10]. Health workers must be active in providing information on sexual relations during pregnancy so that people's opinions that do not understand such as having sex will make the fetus sick, will cause miscarriage/fetal death, bleeding, or defects in the fetus become a correct opinion or a positive opinion so that it will not events occur from one's thoughts.

This research has novelty from other research. This study assesses the knowledge of pregnant women about sexuality during pregnancy with the quality of sexuality during pregnancy. This study wants to see that pregnant women can still carry out sexual activities with a sense of security so that during pregnancy the husband and wife need each other, love, and give satisfaction and intimacy so as to provide harmony in the married couple's household.

Methods

This type of research uses a cross-sectional design with a quantitative approach. This research was conducted to determine the relationship or influence between one variable and another variable[11]. This study aims to analyze the relationship between the knowledge of pregnant women about sexuality during pregnancy and the quality of sexuality during pregnancy at Ely Clinic Medan.

The population in this study was all pregnant women who had prenatal care as many as 150 people. The sampling technique in this study is non-probability sampling with a consecutive sampling method. The number of samples in this study was 50 people. The data collection technique used a questionnaire prepared by the researcher by pregnant women who were given an explanation about the research conducted and were given Consent After Explanation (PSP) after being willing to become respondents. The statement consists of a positive statement (favourable) with a yes or no answer choice. A score of 1 if yes and a score of 0 if no. Fill out the questionnaire by putting a tick (√) on the answer that is considered Yes.

The data analysis technique is used in univariate and bivariate analysis. Univariate analysis using the frequency distribution of knowledge of pregnant women about sexuality and the quality of sexuality during pregnancy. bivariate analysis to find out if there is a relationship between the knowledge of pregnant women about sexuality during pregnancy with the quality of sexuality during pregnancy. The statistical test used was non-parametric with the Chi Square method because the data were not normally distributed based on the results of the normality test with Kolmogorov Smirnov[12]. This research was carried out after obtaining an ethical feasibility letter from the Ethics Commission of the University of Prima Indonesia with the Number: 008/KEPK/UNPRI/V/2019.

Result

Univariate Analysis

Table I: Knowledge of pregnant women about sexuality during pregnancy.

No	Knowledge	ƒ	%
1	Well	7	14
2	Enough	22	44
3	Not enough	21	42
	Total	**50**	**100**

Table I can be concluded that from the 50 samples, the majority were moderately knowledgeable, 22 people (44%) and the minority had good knowledge, 7 (14%).

Table II: Quality of sexuality during pregnancy.

No	Knowledge	ƒ	%
1	Well	7	14
2	Enough	22	44
3	Not enough	21	42
	Total	**50**	**100**

Table II can be concluded that the majority of pregnant women have sufficient sexuality quality as many as 22 people (44%) and the minority has good quality as many as 7 people (14%).

Bivariate Analysis

Bivariate analysis is to determine the relationship between the knowledge of pregnant women about sexuality during pregnancy and the quality of sexuality during pregnancy

Table III: Relationship between knowledge of pregnant women about sexuality during pregnancy and quality of sexuality during pregnancy.

No	Knowledge	Quality						Total	*P-value*
		Good		Enough		Not enough			
		ƒ	%	ƒ	%	ƒ	%		
1	Well	7	14	0	0	0	0	7	0.000
2	Enough	0	0	22	44	0	0	22	
3	Not enough	0	0	0	0	21	42	21	
	Total	**7**	**14**	**22**	**44**	**21**	**42**	**50**	

Table III can be concluded that the majority of pregnant women have sufficient knowledge of the quality of sexuality during pregnancy as well, namely a number of 22 people (44%0 and a minority of pregnant women with good knowledge of good sexuality quality during pregnancy as many as 7 people (14%). Based on the data, it can be concluded that It is known that the test results Chi-Square Tests when the p-value is 0.000 < 0.05 so that the conclusion is Ho is rejected, it is concluded that there is a relationship between the knowledge of pregnant women about sexuality during pregnancy and the quality of sexuality during pregnancy at Elly Clinic Medan.

Discussion

Based on the data obtained, the results showed that the majority of pregnant women had sufficient knowledge about sexuality during pregnancy, and the minority had good knowledge of sexuality during pregnancy. This is because respondents are worried about having sex during pregnancy, especially in the 1st trimester of pregnancy, because husband and wife are worried that it will cause bleeding if they have sex in the first weeks of pregnancy. In the first trimester of pregnancy, women are most likely to choose sexual intercourse in the missionary position. The position that is often done when having sexual relations by the respondents is the missionary position, where the husband can be more careful when having sexual relations by being able to see his partner's stomach so that he can be more careful or careful[13].

Changes in sexuality during pregnancy are observed with less sexual contact, less desire, and less excitement[14]. Changes in sexual behavior and sexual problems often occur during a person's first pregnancy, often having negative consequences on the person and the future of the relationship[15].

Respondents feel safe having sexuality in the second trimester when mothers feel safe and are not too worried when having sexual relations. Women are most sexually active during the second trimester[13]. Pregnant women associate changes in sexual behavior with physical and psychological discomfort during pregnancy in recognizing changes in sexual behavior caused by pregnancy[16]. There are significant changes in the biological aspects of the mother's sexual activity before and during pregnancy, especially in the second and third trimesters of pregnancy which results in a decrease in blood volume[17].

Respondents stated that in the third-trimester sexual relations were less frequent because the husband was worried that he was afraid that having sex would endanger the baby in his wife's womb. Sexual satisfaction does not change in pregnancy compared to pre-pregnancy patterns despite a decrease in sexual activity during the third trimester[18]. A safe and healthy relationship will improve the quality of life for married couples[1]. Couples should be informed about the decreased libido, desire, and orgasm that usually occurs during pregnancy, especially in the last trimester[19]. The sexual function of pregnant women in late pregnancy is affected[10]. In the third trimester of pregnancy, women put their sexual appetites aside and concentrate on the well-being of their newborn baby[20].

Female sexual dysfunction was found in pregnant women, and depression remained constant compared to non-pregnant women, with no effect on sexual function[21]. There is no relationship between pregnancy and postpartum sexuality. All participants who experienced pre-pregnancy sexual dysfunction continued to experience it throughout pregnancy, and most of them had a significant degree of sexual dysfunction after delivery[22].

Sexual intercourse has no risk to the unborn baby. The

baby in the womb is still safe because it is protected by an amniotic sac which has a function to protect the baby from problems such as infection so that it is possible for the baby to experience an infection or the impact of having sex. If fertilization occupies a good place in the uterus, then the chances of miscarriage or childbirth are very small. If there is a miscarriage or premature delivery (delivery before 37 weeks of gestation), then there are other causes due to sexual intercourse that led to labor[23]. Incorrect knowledge will affect sexual relations during pregnancy, where partners think that sexual intercourse will be harmful to the fetus in the womb.

According to the researcher's assumption that sexual intercourse during pregnancy may be carried out where the husband and wife must know the position of sexuality during pregnancy which is adjusted for gestational age. Sexual intercourse should not be carried out if there are other problems in pregnancy such as intercourse is not allowed if there is bleeding, a history of miscarriage, abortion/Partum, and premature rupture of membranes.

Conclusions and recommendations

The conclusion in this study is that the majority of knowledge about sexuality during pregnancy with the quality of sexuality is sufficient with a value of p-value 0.000 < 0.05 so that the conclusion is Ho is rejected, it is concluded that there is a relationship between knowledge of pregnant women about sexuality during pregnancy and quality of sexuality during pregnancy at Elly Clinic Medan.

Research Conflict

In this study, the researcher stated that during the study there was no conflict of interest.

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ORIGINAL

A perspective influence of the Epsilon variant of COVID-19 on Catechol-O-Methyltransferase Val158Met leads to the emergence of human papilloma virus-Gueye, which is wrongly described as monkey pox

La influencia de la variante Epsilon de COVID-19 en la catecol-O-metiltransferasa Val158Met conduce a la aparición del virus del papiloma humano-Gueye, que se describe erróneamente como viruela del mono

Mosab Nouraldein Mohammed Hamad

Head of Parasitology and Medical Entomology Department, College of Health and Allied Sciences, St. Joseph University In Tanzania, Dar Es Salaam,Tanzania United Republic.

Corresponding author
Mosab Nouraldein Mohammed Hamad
E-mail: musab.noor13@gmail.com

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Abstract

A perspective study discussed how the epsilon variant of COVID-19 induced mutation to the existed human papilloma virus via mutagenic cadmium content of the COVID-19, and arsenic content of epsilon variant lead to appearance of new strain of human papilloma virus, we named it Human Papilloma Virus-Gueye. As this virus is most common among gay men, and due to the absence of infection with it among HIV-controlled patients. We suggest that this virus disturbs Catechol-O-Methyltransferase Val158Met which is the region which is responsible for male sexual orientation and has been linked to executive dysfunction, which might increase sexual risk behaviours favouring HIV transmission, which is damaged by mycotoxin of myecetoma fungal species and by cadmium contents of epsilon variant of COVID-19.

We conclude that COVID-19 is not hazardous just because of its severe symptoms , but also because of its action as a mutagen on other microbes that may be present in a subclinical state. Also, we suggest that immunization against COVID-19 may lead to unexpected complications, especially mutations in other microbes. Finally, we claim that the scientific community named it monkey pox. Even among individuals who do not travel to the endemic, it is just mutant form of Human Papilloma virus.

Key words: COVID-19, human papilloma virus, monkey pox, Catechol-O-Methyltransferase, heavy metals.

Resumen

En este estudio se discute cómo la variante épsilon de COVID-19 induce la mutación del virus del papiloma humano a través del contenido de cadmio mutagénico del COVID-19, y además como el contenido de arsénico de la variante épsilon conduce a la aparición de una nueva cepa del virus del papiloma humano, que denominamos Virus del Papiloma Humano-Gueye. Como este virus es más común entre los hombres homosexuales, y debido a la ausencia de infección entre los pacientes VIH controlados, se sugiere que este virus altera la Catecol-O-Metiltransferasa Val158Met, que es la región responsable de la orientación sexual masculina y que se ha relacionado con la disfunción ejecutiva, lo que podría aumentar las conductas sexuales de riesgo que favorecen la transmisión del VIH, que se ve dañada por la micotoxina de las especies de hongos del micetoma y por el contenido de cadmio de la variante épsilon de COVID-19.

Concluimos que el COVID-19 no es peligroso sólo por sus graves síntomas, sino también por su acción como mutágeno sobre otros gérmenes que pueden estar presentes en un estadio subclínico. Además, sugerimos que la inmunización contra la COVID-19 puede provocar complicaciones inesperadas, especialmente mutaciones en otros gérmenes. Por último, afirmamos que lo que la comunidad científica denomina viruela del mono, incluso entre los individuos que no viajan a la zona endémica, es sólo una forma mutante del virus del papiloma humano.

Palabras clave: COVID-19, virus del papiloma humano, viruela del mono.

Introduction

The World Health Organization (WHO) has currently confirmed nearly 100 cases of monkey pox in over a dozen countries, with the largest number of cases in the United Kingdom. As most cases so far are between gay and bisexual men, individuals with well-controlled HIV are not at augmented risk[1]. So we suggested that this new monkey pox infection is similar to myecetoma infection which has never been documented in association with HIV infection[2], and both those viral and fungal microbes affect he COMT Val158Met variant which is responsible for male sexual orientation, and declaration of the outbreak of new monkey pox infection among gays and during COVID-19 era, increase our attention to search for the presence of possible role of COVID-19.

The catechol-O-methyltransferase (COMT) gene, which contains a well-studied functional polymorphism (Val158Met), plays a critical role in central dopamine function through the degradation of the COMT enzyme[3].

Dopamine is a type of monoamine neurotransmitter. It's made in the brain and acts as a chemical messenger, communicating messages between nerve cells in the brain and brain and the rest of the body.

It plays a role as a "reward center" and in many body functions, including memory, movement, motivation, mood, attention, sleep and arousal, mood, learning, lactation, blood vessels relaxation, increases sodium and urine excretion, reduces insulin production, slows gastrointestinal content movement and protects gastrointestinal linings and reduces lymphocytes activity in immune system[4].

A functional polymorphism of the Catechol O-methyltransferase (COMT) gene, designated rs4680 or Val158Met, has been associated with anxiety-related behaviours and the so-called "worrier" phenotype. Met allele frequency was positively correlated with COVID-19 prevalence and mortality rate[5].

Discussion

COVID-19 infection

I hypothesized that COVID.19 resulted from mutation of influenza virus induced by cadmium and lead[6].

Cadmium reduced dopamine content in the median eminence, as amplified its content in the posterior pituitary and provoked a phase advanced peak at 20:00 h[7].

Low levels of dopamine have been linked to Parkinson's disease, restless legs syndrome and depression[4].

Some researchers believe that COVID-19 may make patients more likely to develop Parkinson's disease either sooner or later[8], Restless legs syndrome is associated with long-COVID in women[9]. A case presenting with restless anal syndrome following affection of COVID-19 as restless legs syndrome variant. That case fulfilled 4 essential features of RLS[10]. RLS was associated with increased odds of perceived olfactory and taste dysfunction[11].Patients with COVID-19 often complain of smell and taste disorders (STD)[12] and individuals who reported taste and smell dysfunction had higher concentrations of blood cadmium than those without perceived dysfunction[13].

In the first year of the COVID-19 pandemic, global prevalence of anxiety and depression increased by a massive 25%, according to a scientific brief released by the World Health Organization[14], and Individuals in the highest quartile of blood cadmium had higher odds of having depressive symptoms[15].

there is no significant differences in experiences of COVID-19 symptoms by sexual orientation and gender[16], but infection of Covid-19 can temporarily diminish male fertility[17].

Cadmium also disrupts the vascular system of the testis. It is a reactive oxygen species inducer and possibly induces DNA damage, thus epigenetically regulating somatic cell and germ cell function, leading to male subfertility/infertility[18].

New Strain of Human Papilloma virus (Human Papilloma virus-Gueye)

Since 13 May 2022, cases of monkey pox have been reported to WHO from 12 Member States that are not endemic for monkey pox virus, across three WHO regions. Epidemiological investigations are ongoing, however, reported cases thus far have no established travel links to endemic areas[19].

I hypothesized that the claim of the scientists on appearance of Monkey pox is not true, but this is mutant form of Human papilloma virus (HPV) resulted from COVID.19 infection, which is a viral infection that's passed between people through skin-to-skin contact[20].

Arsenic causes cancer in man through the activation of an oncogenic virus like the human papilloma virus[21], and as cadmium and lead are responsible for mutation of influenza virus into COVID-19[6], arsenic are responsible for appearance of epsilon variant of COVID-19[22].

Cutaneous abnormalities and lesions are the most common outcome and health effects from consumption of drinking-water containing arsenic[23]. Cadmium is strong mutagen that act by inhibiting mismatch repair[24] of influenza virus lead to COVID-19 and of human papilloma virus lead to development of new strain of human papilloma virus. This strengthens by latest data

demonstrates that the Epsilon variant "relies on an indirect and atypical neutralization-escape stratagem[25].

This supported by the study showed that Long noncoding RNA ENST00000455974 plays an oncogenic role through up-regulating JAG2 in human DNA mismatch repair-proficient colon cancer[26].

Many mismatch repair (MMR) gene disease-causing mutations identified in cancer patients result in aberrant messenger RNA (mRNA) splicing[27].

lncRNAs are emerging as important players in the regulation of virus-mediated infection and the subsequent disease status. Along with advancements in research tools and techniques, numerous lncRNAs have been found to be differentially expressed in COVID-19 patients, and key lncRNAs for virus-host interactions have also been identified[28]. A non-coding RNA (lncRNA) MT1DP, a pseudogene in the metallothionein (MT) family, promoted Cd-induced cell death through activating the RhoC-CCN1/2-AKT pathway and modulating MT1H induction[29].

Conclusion

We conclude that the newly emerged cases where scientists claim that the monkey pox, is a mutant form of human papilloma virus (human papilloma virus-Gueye), mutated by the action of cadmium content in Epsilon variant of COVID-19.

And we conclude that the dangerousness of COVID-19 is not just attributed to its severe symptoms, but also to its ability to mutate other RNA viruses and shape new strains of it. Lastly, we knock on the warning ring about the unexpected complications of COVID-19 infection and immunization , which is not only related to the unknown long term symptoms but mutations of subclinical viral infection.

Interests conflict

The researcher declare that he has no conflict of interest.

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ORIGINAL

Trastornos funcionales gastrointestinales en niños con obesidad en atención primaria

Functional gastrointestinal disorders in children with obesity in primary care

Brian González-Pérez[1], Melissa Muñoz-Rocha[1], Martín Segura-Chico[2], María Teresa Magaña-Torres[3], Liliana Aurora Carrillo-Aguiar [4], Ricardo Salas-Flores[5]

1. Instituto Mexicano del Seguro Social, Servicio de Atención Familiar. Unidad de Medicina Familiar No.38, Tampico, Tamaulipas, México 2. Instituto Mexicano del Seguro Social, Coordinación de Investigación en Salud. Órgano de operación administrativa desconcentrada - Tamaulipas, México. (OAAD-Tamaulipas) 3. Instituto Mexicano del Seguro Social, Centro de Investigación Biomédica de Occidente, División de Genética, Independencia Oriente, Guadalajara Jalisco, México 4. Instituto Mexicano del Seguro Social, Titular de la Residencia en Medicina Familiar. Unidad de Medicina Familiar No.77, Madero, Tamaulipas., México 5. Universidad Autónoma de Tamaulipas, Facultad de Medicina "Dr. Alberto Romo Caballero", Tampico, Tamaulipas, México

Corresponding author
Brian González-Pérez
E-mail: brian.gonzalez.perez@gmail.com

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Resumen

Objetivo: Evaluar la obesidad como factor de riesgo para la presencia de trastornos funcionales gastrointestinales (TFG) en niños con obesidad.
Material y métodos: Se realizó un estudio transversal, comparativo de casos y controles, en niños entre 5 y 12 años, seleccionados por la presencia o ausencia de obesidad; se obtuvieron datos antropométricos, sociodemográficos, antecedentes familiares de enfermedades endocrinológicas, antecedentes familiares de TFG, presencia de síntomas abdominales y tipo de TFG según criterios de Roma IV. El análisis estadístico fue de tipo descriptivo e inferencial utilizando la prueba χ^2. Se utilizó OR para calcular el riesgo entre los grupos.
Resultados: Se incluyeron 130 casos y 135 controles, dando un total de 265 participantes. Se encontraron asociaciones significativas únicamente en el grupo de los casos entre los antecedentes familiares de trastorno funcional gastrointestinal (p=0.034) y la obesidad (p=0.000) con la presencia de TFG. Asimismo, se determinó un riesgo de 8.16 para los niños con obesidad (OR=8.16; IC95%: 4.67 – 14.25) y en este mismo grupo, un riesgo de 2.53 en aquellos con antecedente familiar de trastorno funcional digestivo de manera individual (OR=2.53; IC95%: 1.05 – 6.1) de manifestar algún trastorno funcional gastrointestinal.
Conclusiones: la obesidad es un factor determinante para la aparición de trastornos funcionales gastrointestinales y que la presencia concomitante de antecedentes familiares de TFG incrementa aún más dicho riesgo.

Palabras clave: Obesidad infantil, trastorno funcional gastrointestinal, síndrome de intestino irritable, estreñimiento, náuseas.

Abstract

Objective: To evaluate obesity as a risk factor for the presence of functional gastrointestinal disorders (FGD) in children with obesity.
Material and methods: A cross-sectional study, comparative of cases and controls, was conducted in children aged between 5 and 12 years old, selected by the presence or absence of obesity; Anthropometric, sociodemographic data, family history of endocrinological diseases, family history of FGD, presence of abdominal symptoms and type of FGD according to Rome IV criteria were obtained. Statistical analysis was descriptive and inferential using the χ^2 test. OR was used to calculate the risk between groups.
Results: 130 cases and 135 controls were included, giving a total of 265 participants. Significant associations were found only in the case group between family history of functional gastrointestinal disorder (p=0.034) and obesity (p=0.000) with the presence of FGD. Likewise, a risk of 8.16 was determined for children with obesity (OR=8.16; CI95%: 4.67 - 14.25) and in this same group, a risk of 2.53 in those with a family history of functional digestive disorder individually (OR= 2.53; 95% CI: 1.05 – 6.1) of manifesting some functional gastrointestinal disorder.
Conclusions: obesity is a determining factor for the appearance of functional gastrointestinal disorders and that the concomitant presence of a family history of FGD increases this risk even more.

Key words: Child obesity, functional gastrointestinal disorders, irritable bowel syndrome, functional constipation, nausea.

Introducción

La obesidad infantil es uno de los problemas de salud pública mundial más importantes[1]. En México, la Encuesta Nacional de Salud y Nutrición de Medio Camino 2016 (ENSANUT MC 2016) refirió que 5 246 895 escolares (33.2%) y 6 713 282 adolescentes (36.3%) tienen sobrepeso y obesidad (SP+O). Estas cifras de aumento constante se han documentado durante los últimos 30 años, lo que ha ubicado a México como el país con la mayor prevalencia[2]. El sobrepeso y la obesidad infantil son reconocidos como un desafío importante en la salud pública en México y en el mundo[3], debido a su magnitud, rapidez de crecimiento y por su asociación con comorbilidades tanto a corto y a largo plazo como lo son psicosociales, cardiovasculares, endocrinológicas, ortopédicas, neurológicas, pulmonares y gastrointestinales[4,5].

Diferentes estudios recientes indican que la obesidad también está asociada con trastornos funcionales gastrointestinales (TFG)[6,7]. Los TFG son trastornos comunes en niños de todas las edades e incluyen una variedad de síntomas gastrointestinales crónicos o recurrentes que no pueden ser explicados por anormalidades estructurales o bioquímicas[8]. Estos trastornos son la causa más común en la práctica clínica y representan más del 50 % de las consultas de los gastroenterólogos pediátricos y del 2 al 4 % de todas las visitas al pediatra[9]. Los niños que presentan de TFG tienen bajo funcionamiento físico, social y emocional, así como bajo desempeño escolar, puntajes menores de calidad de vida en comparación con aquellos con enfermedades orgánicas, como la enfermedad intestinal inflamatoria[10].

La patogénesis de los TFG aún no está bien establecida y es probable que sea multifactorial[11]. Pocos estudios pediátricos han propuesto una asociación entre la obesidad y los trastornos funcionales gastrointestinales comunes, como el estreñimiento funcional, el síndrome del intestino irritable (SII) y el dolor abdominal[12]. Sin embargo, estos estudios tienen limitaciones en sus diseños de estudio[13]. Por lo anterior, la necesidad de identificar esta asociación en atención primaria será de gran beneficio para la creación de programas de prevención e identificación de grupos de riesgo. El objetivo principal del presente estudio es evaluar la obesidad como factor de riesgo para la presencia de TFG en niños con obesidad.

Material y método

Se realizó un estudio transversal analítico comparativo de casos y controles, autorizado por el Comité Local de Investigación en Salud 2801 del Instituto Mexicano del Seguro Social (IMSS), durante el periodo de enero 2019 a enero 2020, en la Unidad de Medicina Familiar No. 77 (UMF77); se realizó un cálculo de tamaño de muestra con la fórmula para el estudio de casos y controles, utilizando a todos los pacientes derechohabientes de la UMF77 con edad de 5 a 12 años, obteniendo un total de 125 casos y 125 controles mínimos requeridos para generar una significancia en los resultados, los cuales se seleccionaron de forma aleatoria simple. Los criterios de inclusión fueron niños de ambos sexos de cinco a doce años, los cuales decidieron participar previa firma del consentimiento y asentimiento informado. Por ser pacientes menores de edad, el familiar acompañante firmó la hoja de consentimiento informado estandarizado para proyectos de investigación en IMSS, el cual, expone los puntos de ética y confidencialidad de los datos proporcionados. Se recabaron datos sociodemográficos como sexo, edad, antecedentes heredofamiliares de enfermedad endocrinológica, antecedentes familiares de TFG; en antropometría y antecedente patológicos, en el cual se agrupan el peso, talla, IMC, perímetro abdominal, TGF, presencia de síntomas abdominales y tipo de TFG según criterios de Roma IV[14]. Para determinar a qué grupo corresponde cada uno de los participantes, se utilizó el IMC de los niños. El IMC se calculó como el peso (kg) dividido por la altura al cuadrado (m^2). De acuerdo con los criterios establecidos por la CDC, aquellos niños cuyo IMC se encuentra dentro de los percentiles 5 a 75 se incluyeron en el grupo de los controles (peso normal) mientras que aquellos en los percentiles ≥ 85 se consideraron como casos (sobrepeso u obesidad)[15]. Todas las mediciones fueron realizadas por el mismo médico familiar entrenado. Los criterios de exclusión fueron pacientes que no contestaron completamente los cuestionarios y que no completaron las mediciones antropométricas.

Se utilizaron medidas de tendencia central y de dispersión para describir las variables cuantitativas, y frecuencias y porcentajes para las variables cualitativas. Posteriormente se generaron tablas cruzadas para la relación entre variables dentro de cada grupo, obteniendo el valor *p* por medio de la χ^2 y para calcular el riesgo entre los grupos Odds Ratio (OR) en el programa estadístico SPSS (V.23; SPSS Inc, Chicago IL, USA). Se consideró una significancia estadística una *p* bilateral ≤ 0.05.

Resultados

La muestra estuvo conformada por 265 pacientes (130 casos y 135 controles), las características demográficas y clínicas de los participantes del estudio, según la presencia de obesidad, están presentes en la **tabla I**. En los casos, la edad promedio fue de 8.35 + 2.14 años y en los controles de 08.19 + 02.35 años. El 60% (n=78) de los casos son masculinos mientras que el 40% (n=52) son femeninos. Por otra parte, dentro del grupo de los niños con peso normal, el 54.1% (n=73) son femeninos y el 45.9% (n=62) son masculinos.

En lo que respecta a los antecedentes familiares de enfermedades endocrinológicas el 64.3% (n=84) de los casos posee por lo menos un familiar con alguna patología endocrinológica. En cambio, el 49.6% (n=67) de los niños con peso normal cuenta con algún familiar afectado por dichas enfermedades. A continuación, se procedió a determinar el antecedente familiar de trastorno funcional gastrointestinal. En los casos, el 60.5% (n=79) cuenta con algún familiar que sufre algún TFG y en los niños de peso normal el 30.4% (n=41). Se encontró que el antecedente familiar de TFG también se asocia significativamente con la aparición de la misma patología en los niños considerados como casos (p=0.034) con un riesgo 2.53 veces mayor (OR = 2.53; IC95%: 1.05 - 6.1) para aquellos que poseen dicho antecedente.

Ya adentrándose a los trastornos funcionales gastrointestinales, se identificó que el 79.3% (n=103) de los casos padece de algún TFG. En cambio, en los pacientes con peso normal únicamente el 31.9% (n=43) sufre dichos trastornos. Se comprobó que la obesidad tiene una asociación estadísticamente significativa con la aparición de TFG (p=0.000) y que poseen un riesgo 8 veces mayor de padecerla (OR=8.16; IC95%: 4.67 – 14.25). Respecto a la determinación del tipo de trastorno funcional gastrointestinal presentados por los participantes se detectó en los casos que el 48.6% (n=50) padece síndrome de intestino irritable, el 22.3% (n=23) estreñimiento funcional, el 16.5% (n=17) dispepsia funcional, el 7.8% (n=8) aerofagia, el 1.9% (n=2) náusea y vómito funcional, el 1.9% (n=2) dolo abdominal no funcional no especificado de otra forma y el 1% (n=1) restante incontinencia fecal no retentiva.

Además, acerca de los síntomas abdominales, se determinó que dentro del grupo de los casos el 80.8% (n=105) padece algún síntoma abdominal. Dentro de dicha proporción de sujetos afectados, se encontró que el 32.4% (n=34) padece distensión abdominal, el 31.4% (n=33) dolor abdominal no asociado a la defecación, el 16.2% (n=17) dolor en epigastrio, el 13.3% (n=14) dolor abdominal asociado a la defecación y el 6.7% (n=7) tenesmo rectal.

Discusión

En los últimos años, estudios realizados en adultos y niños han demostrado múltiples asociaciones

Tabla I: Características demográficas y clínicas de la población estudiada.

Estado nutricional / Características	Casos Obesidad (n=130)	Controles Normal (n=135)
Sexo		
Femenino (n, %)	52 (40)	73 (54.1)
Masculino (n, %)	78 (60)	62(45.9)
Antecedentes familiares de enfermedades endocrinológicas.		
Si (*n*, %)	84 (64.3)	67 (49.6)
No (*n*, %)	46 (35.7)	68 (50.4)
Antecedentes familiares de Trastorno funcional gastrointestinal *		
Si (*n*, %)	79 (60.5)	41 (30.4)
No (*n*, %)	51 (39.5)	94 (69.6)
Edad (años + DE)	8.35 + 2.14	08.19 + 02.35
Peso (kg + DE)	39.02 +11.85	27.58 + 07.82
Talla (m + DE)	01.30 + 00.12	01.28 + 00.13
IMC (kg/m^2 + DE)	22.57 + 03.14	16.36 + 01.51
Perímetro abdominal (cm + DE)	72.05 + 12.97	57.11 + 08.99
Trastorno funcional gastrointestinal *		
Si (*n*, %)	103 (79.3)	43 (31.9)
No (*n*, %)	27 (20.7)	92 (68.1)
Tipo de trastorno funcional gastrointestinal		
Náusea y vómito funcional (*n*, %)	2 (1.9)	1 (2.3)
Aerofagia (*n*, %)	8 (7.8)	2 (4.7)
Dispepsia funcional (*n*, %)	17 (16.5)	15 (34.8)
Síndrome de intestino irritable (*n*, %)	50 (48.6)	14 (32.6)
Estreñimiento funcional (*n*, %)	23 (22.3)	8 (18.6)
Incontinencia fecal no retentiva (*n*, %)	1 (1)	0 (0)
Dolor abdominal funcional no especificado de otra forma (*n*, %)	2 (1.9)	3 (7)
Presencia de síntomas abdominales		
Si (*n*, %)	105 (80.8)	47 (34.9)
No (*n*, %)	25 (19.2)	88 (65.1)
Síntomas abdominales		
Distensión abdominal (*n*, %)	34 (32.4)	12 (25.5)
Ardor en epigastrio (*n*, %)	17 (16.2)	13 (27.7)
Dolor abdominal no asociado a la defecación (*n*, %)	33 (31.4)	10 (21.3)
Dolor abdominal asociado a la defecación (*n*, %)	14 (13.3)	9 (19.1)
Tenesmo rectal (*n*, %)	7 (6.7)	2 (4.3)
Otros (*n*, %)	0 (0)	1 (2.1)

IMC= Índice de Masa Corporal, DE= Desviación estándar. * Estadísticamente significativo p < 0.05

entre los síntomas gastrointestinales como el reflujo gastroesofágico con la obesidad. Sin embargo, actualmente existen pocos estudios en población pediátrica donde se busque la existencia de una relación entre la obesidad y los trastornos funcionales digestivos. Por si no fuera poco, varios de dichas investigaciones tienen limitaciones en cuanto a los diseños retrospectivos de los estudios, los tamaños pequeños de las muestras y/o la falta de poblaciones de control adecuadas. Además, la mayoría de estos estudios han reportado que los niños con síntomas gastrointestinales padecen frecuentemente de obesidad[16].

Este es el primer estudio en nuestra comunidad en el que se recabó información respecto al riesgo que representa la obesidad en niños con la presencia de TFG según los criterios ROMA IV. Se comprobó que la obesidad es un factor determinante para considerar la aparición de TFG, los niños con obesidad presentaron un riesgo de 8 veces mayor a sufrir trastornos funcionales gastrointestinales (OR: 8.162, IC 95%: 4.674 – 14.251). Esta cifra supera por mucho a lo estimado por Michael Camilleri, et al[17] donde se encontró que los niños con obesidad tienen un riesgo de 1.6 veces mayor a sufrir TFG (OR, 1.60; IC 95%, 1.04–2.47). Esto quiere decir que la obesidad ejerce un mayor peso en la aparición de trastornos funcionales gastrointestinales en los niños con obesidad que reciben atención médica en la UMF77.

Por otra parte, se encontró que los antecedentes familiares de trastorno funcional gastrointestinal en el grupo de niños con obesidad son 2.5 veces (OR: 2.538, IC 95%; 1.056 – 6.101) más propensos de padecer algún TFG. Esta situación resalta debido a que es mayor el riesgo encontrado en nuestro estudio a lo reportado por Miguel Saps et al.[18], que fue de 1.2 veces mayor el riesgo. Aunque el diseño de este estudio no permite la determinación de la causalidad, los resultados se alinean con el modelo biopsicosocial que propone que los factores psicológicos y sociales juegan un papel en la patogénesis de los TFG. Según el modelo biopsicosocial, los síntomas resultan de la interacción de factores gastrointestinales y del sistema nervioso central[19].

En el presente estudio se pudo identificar mayor frecuencia de TFG en los niños con obesidad en comparación con los niños de peso normal. Resultados similares son reportados por Teitelbaum et al.[20] en el que se mostraron un mayor porcentaje de niños con obesidad y estreñimiento, enfermedad por reflujo gastroesofágico, síndrome de intestino irritable, encopresis y dolor abdominal en comparación con los niños de peso normal. Desde otro punto de vista, Bonilla et al.[21] describieron en una cohorte de 2007 a 2008 con una prevalencia de obesidad del 20.2 % en pacientes con TFG; sin embargo, no se realizó ninguna comparación con el grupo de control sano.

Desafortunadamente el panorama se desfavorable para los niños que son atendidos en la UMF77 y que padecen obesidad, puesto a que la mayoría de ellos, tienen antecedentes familiares de TFG, por lo que la obesidad generó un importante efecto acumulativo en dicha población y esto se ve reflejado en la altísima frecuencia de trastornos funcionales gastrointestinales en la población pediátrica con obesidad la cual casi alcanzó el 80%. Es por ello por lo que, para la atención primaria de trastornos funcionales digestivos en los niños de 5-12 años, es de suma importancia abordar conjuntamente el problema de la obesidad y vigilar cuidadosamente a aquellos niños que además cuentan antecedentes familiares de trastornos funcionales gastrointestinales.

Se concluye que la obesidad representa un factor de riesgo a padecer trastornos funcionales gastrointestinales y que la presencia concomitante de antecedentes familiares de TFG incrementa aún más dicho riesgo.

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Conflicto de intereses
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Protección de personas y animales
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Confidencialidad de los datos
Los autores declaran que han seguido los protocolos de su centro de trabajo sobre la publicación de datos de pacientes.

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ORIGINAL

Estimation of hepatic repercussion in obesity and cardiometabolic risk

Estimación de repercusión hepática en obesidad y riesgo cardiometabólico

Mª Teófila Vicente-Herrero, MD, PhD[1], Mª Victoria Ramírez-Iñiguez de la Torre, MD, PhD[2], Luisa Capdevila García, MD, PhD[3], Ana Victoria Bueno Atkinson[4], Ángel Arturo López González, MD, PhD[5]

1. Obesity and work group-Asociación Española de especialistas en Medicina del Trabajo-AEEMT. ADEMA-HEALTH Group of the University Institute of Health Sciences-IUNICS Illes Balears (Spain) 2. Occupational Health and safety Services of Correos, Albacete (Spain). Obesity and work group-Asociación Española de especialistas en Medicina del Trabajo-AEEMT 3. Occupational Health and safety Services MAPFRE, Valencia (Spain). Obesity and work group-Asociación Española de especialistas en Medicina del Trabajo-AEEMT 4. Occupational Health Nurse. MAPFRE-UBS Majadahonda. Madrid (Spain). 5. Occupational Health and safety Services Servei de Salut de les Illes Balears. University School ADEMA, Palma de Mallorca (Spain). ADEMA-HEALTH Group of the University Institute of Health Sciences-IUNICS Illes Balears (Spain).

Corresponding author
Mª Teófila Vicente-Herrero
E-mail: vicenteherreromt@gmail.com

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Abstract

Introduction: Obesity is a global pandemic with cardiometabolic repercussions and increased risk in the development of non-alcoholic liver disease. The objective of this work is to relate the cardiometabolic risk in obesity with the risk of hepatic repercussion in the working population.
Method: Cross-sectional descriptive study in 815 workers between March 2020-June 2021. The FLI-fatty liver index and FIB-4 Index for liver fibrosis calculators and their relationship with body mass index and cardiometabolic risk are used.
Results: A greater presence of high FLI and FIB-4 values was found in groups with a higher level of cardiometabolic risk and with BMI at levels of overweight/obesity, with more unfavorable results in men.
Conclusions: In workers with obesity and cardiovascular risk or metabolic syndrome, a higher risk of hepatic repercussion quantified with FLI and FIB-4 is detected.

Key words: FLI index; FIB index 4; cardiometabolic risk, obesity; nonalcoholic liver disease, occupational health.

Resumen

Introducción: La obesidad es una pandemia mundial con repercusión cardiometabólica y riesgo aumentado en el desarrollo de enfermedad hepática no alcohólica. Es objetivo de este trabajo relacionar el riesgo cardiometabólico en obesidad con el riego de repercusión hepática en población trabajadora.
Método: Estudio descriptivo transversal en 815 trabajadores entre marzo de 2020- junio de 2021. Se utilizan las calculadoras FLI- fatty liver index y FIB-4 Index for liver fibrosis y su relación con el índice de masa corporal y el riesgo cardiometabólico.
Resultados: Se encontró una mayor presencia de valores altos de FLI y FIB-4 en los grupos con mayor nivel de riesgo cardiometabólico y con IMC en niveles de sobrepeso/obesidad, con resultados más desfavorables en hombres.
Conclusiones: En trabajadores con obesidad y riesgo cardiovascular o síndrome metabólico se detecta mayor riesgo de repercusión hepática cuantificada con FLI y FIB-4.

Palabras clave: índice FLI; índice FIB 4; riesgo cardiometabólico, obesidad; enfermedad hepatica no alcohólica, salud laboral.

Introduction

Obesity continues to be a public health problem throughout the world and has a demonstrated association with health behaviors and outcomes. Over the last 2 decades, obesity has increased worldwide, so it is essential to act in prevention and reduce its impact on health[1]. Programs such as Healthy people 2030 have encouraged interventions that make it easier for people to be more physically active, eat a balanced diet, and maintain a healthy weight[2].

BMI is typically used to define overweight and obesity in epidemiological studies. However, it has low sensitivity

and there is a large interindividual variability in body fat percentage for any BMI value[3]. Some authors propose reviewing the prevalence and possible causes and comorbidities associated with obesity[4].

Current clinical and epidemiological evidence has linked obesity to a wide spectrum of cardiovascular diseases (CVD) and it is assumed that it can directly and indirectly increase CVD morbidity and mortality[5,6]. Similarly, the finding that obesity and metabolic disorders are accompanied by low-grade chronic inflammation has changed the view of underlying causes and their health consequences[7]. This concept has been useful as a screening approach to better identify subgroups of high-risk people who would benefit from clinical and population approaches aimed primarily at their lifestyle[8].

In obesity, adipose tissue and the liver play an important role in regulating whole-body energy homeostasis, and prolonged metabolic stress leads to adipose tissue dysfunction, inflammation, and adipokine release resulting in increased blood flow lipids to the liver[9]. Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in the world and its presentation varies from simple steatosis to non-alcoholic steatohepatitis. It is a hepatic manifestation of the metabolic syndrome that includes central abdominal obesity along with other components[10].

The objective of this work is to estimate the relationship between the cardiometabolic risk associated with obesity and the risk of developing non-alcoholic liver disease using the FLI and FIB-4 questionnaires.

Method

Cross-sectional descriptive study in a sample of the Spanish working population of 815 workers (481 men and 334 women), aged between 18 and 66 years in a total population of 1028, of which 76 workers were excluded because they did not meet criteria and 137 refused to participate. Data collected by the occupational physician during the periodic health surveillance examinations of the participating companies in the service sector of the Balearic Islands from March 2020 to June 2021, with voluntary participation and informed consent for the epidemiological use of the results obtained. The inclusion criteria are: being active in the company and not being treated for previous cardiovascular disease or having uncontrolled or compensated cardiovascular risk factors.

The study was approved by the Clinical Research Ethics Committee of the Balearic Health Area (IB 4383/20).

BMI was calculated as weight in kg divided by the square of height in meters. The ranges for BMI considered by the WHO and included in this study are: normal weight <25; overweight >25-<30; grade 1 obesity >30-<40; grade 2 obesity >40[11].

To calculate the Cardiometabolic Risk Level (NR), the presence or absence of: Metabolic Syndrome (MetS), high cardiovascular risk (CVR) (Score or Regicor) and abnormal values in 2 or more of the adiposity indicators (AI) are assessed. These values were independently related to the BMI value classified by the WHO with the aforementioned parameters[12].

Cardiovascular risk has been calculated with the Score and Regicor calculators,[13,14,15] which are the two available in Spain, although the REGICOR function is the only one validated in our population. Score estimates the risk of death in 10 years and includes: sex, age, tobacco use, systolic blood pressure and total cholesterol. Regicor includes: age, gender, basal blood glucose, tobacco use, systolic and diastolic blood pressure, total and HDL cholesterol.

Metabolic syndrome has been calculated with the application available online based on the ATP-III definition and validated in Spanish patients, which includes: sex, abdominal circumference, triglycerides, maximum and minimum blood pressure, and basal glycaemia[16].

Body composition was determined with the TANITABC-420MA analyzer, estimating the percentage of body fat and visceral fat. The following have been calculated as adiposity indicators (AI):[17,18] Waist circumference (WCI): considering a value <94 cm normal in men and <80 cm in women waist/hip ratio (WHR): it is considered normal in men if it is <0.94 and in women if it is <0.84 waist-to-height ratio (WHR): it is considered normal if it is <0.5 for both men and women. Body fat percentage (BF): it is considered normal in men if it is <10 and in women if it is <20. Visceral fat (VF): considered normal if it is <10 for both men and women.

Four levels of Cardiometabolic Risk are established based on the presence of none, 1, 2 or 3 altered aspects: NR 0= none of the altered aspects assessed; NR1= 1 of the 3 aspects evaluated in non-normal limits; NR 2= 2 of the 3 aspects assessed within non-normal limits and NR 3= the 3 aspects assessed within non-normal limits[19].

To estimate Fatty Liver, the fatty liver index-FLI calculator was used, an algorithm based on waist circumference, BMI, and triglyceride and γ-glutamyltransferase levels, available at: https://www.mdapp.co/fatty-liver -index-fli-calculator-356/ and validated for the general population. A value <30 is considered low risk of fatty liver and rules out steatosis with a sensitivity of 87% and a negative predictive value of 0.2, while a score >60 is considered indicative of the presence of steatosis with a specificity of 86% and a positive predictive value of 4.3. Between 30-59 is considered an intermediate zone, ultrasound

is required and for liver fibrosis estimation the FIB 4 Index for liver fibrosis calculator validated algorithm based on age, platelet count and glutamic oxaloacetic transaminase (GOT) or levels of γ-glutamyltransferase (GGT). In non-alcoholic steatohepatitis, using the lower cut-off value of 1.45, a FIB-4 score <1.45 has a negative predictive value of 90% for advanced fibrosis (Ishak fibrosis score 4 to 6, which includes early bridging fibrosis to cirrhosis). In contrast, an FIB-4 >3.25 would have a specificity of 97% and a positive predictive value of 65% for advanced fibrosis[20,21].

The validated PREDIMED survey of adherence to the Mediterranean diet, available at: https://dietamediterranea.com/test-de-la-dieta-mediterranea/ qualifies adherence to the Mediterranean diet (MedDiet) with the score: < 9 low adherence >= 9 good adherence[22,23].

For the assessment of healthy lifestyle habits in physical activity, the IPAQ-reduced validated survey with self-registration from the last week was used. It collects the following score: moderate physical activity of at least 600 METs and high, at least 3000 METs7. In both cases, the self-administered survey was conducted through a face-to-face interview[24,25].

Statistical analysis

A descriptive analysis of the categorical variables was performed, calculating the frequency and distribution of responses for each of them. For quantitative variables, the mean and standard deviation were calculated, and for qualitative variables, the percentage. A bivariate association analysis was performed using the 2 test (with a correction with Fisher's exact statistical test, when the conditions required it) and a Student's t-test for independent samples. To assess the concordance between the different scales, Cohen's Kappa test is applied. Statistical analysis was performed with the SPSS 27.0 program and a p value of <0.05 was considered statistically significant.

Results

The characteristics of the population sample show higher mean BMI values in men (27.49) than in women (26.33) and significant differences between both (p_0.001) (**Figure 1**). Greater adherence to the Mediterranean diet is observed in women and without significant differences in physical activity between men and women, both at moderate/high levels (**Table I**).

Figure 1: Percentage results of Prevalence. Overweight / Obesity according to BMI. Gender differences.

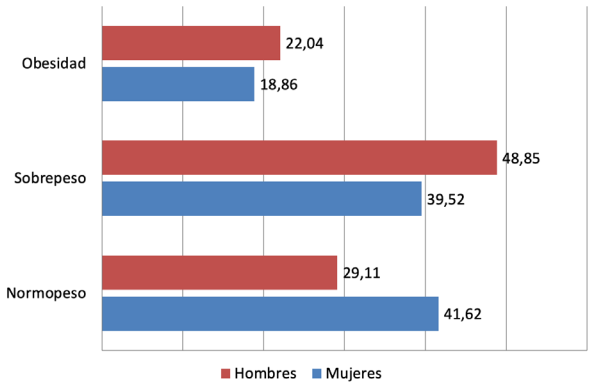


Table I: Population characteristics. Comparison between genders.

Variables analyzed		Male (N = 481)		Female (N = 334)		Value_p
		Mean	(SD)	Mean	(SD)	
Age		48.25	8.35	48.89	8.16	0.277
Anthropometric variables: mean (SD)	Weight Height BMI	82.79 173.42 27.49	13.93 6.81 4.01	67.97 160.72 26.33	11.98 5.98 4.47	<0.0001 <0.0001 <0.0001
Adiposity variables mean (SD	Waist Waist/height Hip Waist/Hip Total body fat Visceral fat	94.61 0.55 106.22 0.92 24.70 11.35	10.96 0.06 58.83 0.07 6.58 4.53	84.35 0.53 99.00 0.85 36.08 7.53	11.43 0.07 10.13 (0.06 7.78 2.65	<0.0001 <0.0001 0.027 <0.0001 <0.0001 <0.0001
BMI classification	Normal weight Overweight Obesity	29.11 48.86 22.04		41.62 39.52 18.86		0.001
Life habits: adherence to the Mediterranean Diet-PREDIMED	Hight Adherence MedD	43.87		56.89		<0.0001
Life habits: Physical Activity-IPAQ	Low physical activity Moderate physical activity High physical activity	1.87 40.33 57.80		3.29 47.31 49.40		0.041

ST= standard deviation ; p value lower than 0.05 was considered statistically significant (p<0,05)

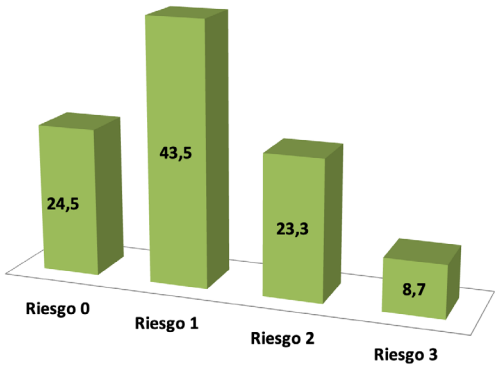
More than 75% of the population studied presented some degree of cardiometabolic risk, although the most prevalent level was NR-1 (**Figure 2**) (43.5% had at least 1 of the 3 factors studied altered). The estimated level of risk shows a statistically significant relationship between high BMI and the risk increases as obesity increases, the relationship being significant. The prevalence of NR 1 stands out in people with overweight or type 1 obesity.

In all the parameters included in the risk estimation, higher percentages of altered values are observed in men with statistical significance, this difference being especially wide in high CVR (41.85% in men versus 11.34% in women) (**Table II**).

The presence of hepatic steatosis estimated with FLI in medium and high values increases as the level of cardiometabolic risk increases, with statistically significant results (p<0.0001). It is especially significant that 47.62% of workers with NR 2 and 66.20% of those with NR 3 present high FLI.

The risk of liver fibrosis, estimated with FIB-4, increases according to the level of cardiometabolic risk, although with little difference between the highest levels[2-3] (p<0.0001) (**Table III**).

Figure 2: Percentage distribution of Estimated Cardiometabolic Risk Level.



Discussion

Monitoring the prevalence of obesity and overweight is important to assess interventions aimed at preventing or reducing the burden of obesity. According to a 2014 study in 20 European countries, more than half of the European population is overweight and obese (53.1%), more men than women are overweight (44.7% compared to 30.5%) (26) and this coincides with our results. In our study, the BMI values correspond to pre-obesity/overweight and are higher in men (27.49% vs. 26.33%).

The scientific literature is consistent on the risks associated with obesity. The metabolic syndrome, which includes abdominal obesity, dyslipidemia, hyperglycemia and hypertension, is a major challenge for public health and its average prevalence is 31% of the population and is associated with a double risk of coronary heart disease, cerebrovascular disease, and a 1.5-fold

Table II: Percentage distribution of the assessment included factors to estimated liver risk. Relationship with BMI and the risk factors included.

Percentage distribution of the factors included in the liver risk evaluation							
Gender differences			**Male %**		**Female %**		**Value_P**
MetS Presence			20.88		16,82		<0.0001
CVR Presence- Score/Regicor			41,85		11,34		<0.0001
Adiposity indicators (AI) ≥ 2 IA out of normal values			75,05		68.26		0.001
Relationship between the estimated cardiometabolic risk level and BMI.							
LR estimated	**Normal weight**		**Overweight**		**Obesity (I and II)**		**Value_P**
	n	**%**	**n**	**%**	**n**	**%**	
LR 0	173	62.0	26	7.1	0	0	<0.0001
LR 1	89	31.9	207	56.9	57	33.9	<0.0001
LR 2	16	5.7	100	27.5	72	42.9	<0.0001
LR 3	1	0,4	31	8,5	39	23.2	<0.0001

Table III: FLI fatty liver and FIB-4 fibrosis liver. Relationship with the estimated cardiometabolic risk level.

FLI	**Cardiometabolic risk level classification**								**Value_P**
	RL0		**RL1**		**RL2**		**RL3**		
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
FLI- low	188	94,47	189	53,54	34	17,99	1	1,41	<0.0001
FLI - medium	11	5,53	105	29,75	65	34,39	23	32,39	<0.0001
FLI high	0	0	59	16,71	90	47,62	47	66,20	<0.0001
FIB-4	**Cardiometabolic risk level classification**								**Value_P**
	RL0		**RL1**		**RL2**		**RL3**		
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
Normal	175	87,94	292	82,72	138	71,88	52	73,24	<0.0001
Intermediate	24	12,06	61	17,28	54	28,12	19	26,76	<0.0001

Fatty liver estimate =fatty liver index-FLI; Liver fibrosis estimate = FIB 4 Index for liver fibrosis; p value lower than 0.05 was considered statistically significant (p<0,05)

increased risk of all-cause mortality[27]. In our work, risk levels are established by combining both the presence of metabolic syndrome and CVR calculated by Score or Regicor, and it shows that more than 75% of the population studied has some degree of cardiometabolic risk, with the results, in all cases, being more unfavorable in men (20.88% vs. 16.82% in MetS and 41.85% vs. 11.34% in CVR), although it must be considered as a bias in the calculation of CVR in workers under the age of 40 years.

Currently, it is still a matter of discussion that individuals with a similar body mass index may have different metabolic and cardiovascular risk profiles. It is recognized that susceptibility to obesity-related cardiometabolic complications is not mediated solely by total body fat, but is largely dependent on individual differences in the regional distribution of body fat and the expandability of subcutaneous adipose tissue, which is considered one of the key clinical variables that explain the metabolic heterogeneity of obesity and the associated cardiovascular risk[28]. In our work, both men and women present at least two indicators of adiposity outside the normal ranges, this being the most outstanding aspect of the three included in the estimation of the level of risk (body fat, visceral fat, waist/height ratio, waist-hip ratio or waist circumference) is the most prominent aspect of the three included in the estimation of the level of risk and is more prevalent in men than in women (75.05% vs. 68.26%) and with statistical significance.

An outstanding aspect in our study is the estimation of hepatic repercussion both in estimated risk of steatosis (with the FLI calculator) and fibrosis (with the FIB-4 calculator).

Non-alcoholic fatty liver disease (NAFLD) is a disorder of excessive accumulation of fat in the liver, it can manifest as simple steatosis or as steatohepatitis, known as non-alcoholic steatohepatitis (NASH), which is accompanied by inflammation and possibly fibrosis. The pathophysiology of NAFLD and NASH is not fully elucidated, but it is known that it involves the complex interaction between different metabolic, environmental, and genetic factors, among which obesity is one of the most prominent. Despite its growing prevalence throughout the world, to date there is no treatment approved by the FDA, so its prevention and early action on modifiable risk factors is of special importance[29].

Although the gold standard for the diagnosis of NASH is liver biopsy, other non-invasive methods have been developed: FibroTest, ELF, Hepascore, FIB-4, NFS, FLI and ION (biochemical panels), but they lack specificity to detect the mild fibrosis[30]. However, these estimation calculation methods are easily accessible at basic levels such as occupational medicine and allow preventive action to be taken, anticipating liver damage or delaying its evolution.
In our work we have used FLI as a method of estimating the risk of hepatic steatosis and FIB-4 for the case of hepatic fibrosis, in both related to obesity and its cardiometabolic repercussion, and concluded with both methods that the highest values of hepatic repercussion (steatosis or fibrosis) are significantly associated with high cardiometabolic risk (NR2 and NR3) and increase as these risk levels rise.

Assuming the high rate of unreliable results with these predictive tools and, given their easy use and accessibility and the high prevalence of NAFLD in the general population, these non-invasive methods could be used in clinical practice as first-line tools for early detection in patients with NAFLD, in order to help determine who might need a liver biopsy or other interventional or expensive methods not accessible in occupational medicine[31].

Conclusion

The cardiometabolic risk is significantly related to the estimation of hepatic repercussion obtained with the FLI indicators of steatosis and FIB-4 of fibrosis in patients with obesity or overweight. The results obtained with the FLI and FIB-4 indicators increase with the level of cardiometabolic risk obtained.

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Conflict of interest

The authors declare that they have no conflict of interest.

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ORIGINAL

Single session osteopathic manipulative treatment in Parkinson's disease: a randomized clinical trial protocol

Tratamiento de manipulación osteopática en una sola sesión en la enfermedad de Parkinson: un protocolo de ensayo clínico aleatorizado

Guilherme Machado Pulcherio, Leonardo Santos Lobo, Larissa Bastos Tavares, Vera Lúcia Santos de Britto, Thiago da Silva Rocha Paz, Clynton Lourenço Correa

Faculty of Physical Therapy. Federal University of Rio de Janeiro | UFRJ
Graduate Program of Physical Education

Corresponding author
Clynton Lourenço Correa
E-mail: clyntoncorrea@gmail.com

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Abstract

The aim of the study is to evaluate the influence of a single session of OMT in individuals with PD based on ICF domains. Randomized clinical trial protocol available at the link: https://ensaiosclinicos.gov.br/rg/RBR-7pkypg3, in which 60 individuals diagnosed with PD are randomly allocated to one of two groups (Control, n=30 and OMT, n=30). Participants will be evaluated in 2 moments (baseline and post-treatment). The control group will not undergo any intervention and remains lying for 30 minutes. Protocol will be applied to the OMT group. The following outcomes will be compared: TUG (G-Walk®), gait speed (G-Walk®), C7 measurement test for the wall of the flexed trunk posture, evaluation of the range of motion of ankle dorsiflexion and MiniBESTest. A descriptive analysis of sociodemographic variables will be carried out. The statistical analysis will consider data distribution for the statistical test selection. The dependent T-test will be used to compare baseline and post-measurements for variables with normal distribution. For variables with non-normal distribution, the Wilcoxon signed rank test will be adopted. The effect size will be evaluated through the Pearson coefficient in which 0 (no effect) and (perfect effect). A confidence interval of 95% will be adopted and statistical significance $p<0.05$ will be considered. We hypothesized that the use of OMT could bring positive effects in relation to the improvement of gait, posture, balance, dorsiflexion ROM and general mobility. OMT may be a therapeutic approach to consider for individuals with PD.

Key words: Parkinson's disease, osteopathic manipulative treatment, ICF, gait, balance.

Resumen

El objetivo del estudio es evaluar la influencia de una sola sesión del Tratamiento Manipulativo Osteopático (TMO) en personas con Enfermedad de Parkinson (EP), en función de los dominios de la CIF. El protocolo de ensayo clínico aleatorizado está disponible en el enlace: https://ensaiosclinicos.gov.br/rg/RBR-7pkypg3, en dicho estudio, participaron 60 personas diagnosticadas con EP y se asignaron aleatoriamente a uno de dos grupos (Control, n=30 y TMO, n=30). Los participantes serán evaluados en 2 momentos (línea base y postratamiento). El grupo control no se someterá a ninguna intervención y permanecerá tumbado durante 30 minutos. Se le aplicará el protocolo al grupo TMO. Se compararán los siguientes resultados: TUG (G-Walk®), la velocidad de la marcha (G-Walk®), la prueba de medición C7 para la pared de la postura del tronco flexionado, la evaluación del rango de movimiento de la dorsiflexión del tobillo y el MiniBESTest. También se llevará a cabo un análisis descriptivo de las variables sociodemográficas. El análisis estadístico, considerará la distribución de datos para la selección de la prueba estadística. La prueba T dependiente se utilizará para comparar las mediciones iniciales y posteriores de las variables con distribución normal. Para las variables con distribución anormal, se adoptará la prueba de los rangos con signo de Wilcoxon. El tamaño del efecto se evaluará a través de Pearson, el coeficiente en el que 0 (sin efecto) y (efecto perfecto). Se adoptará un intervalo de confianza del 95% y la significación estadística $p<0,05$ será considerada. Presumimos que el uso de TMO podría traer efectos positivos en la relación con la mejora de la marcha, la postura, el equilibrio, el rango de movimiento de dorsiflexión y la movilidad general. TMO puede ser un enfoque terapéutico a considerar para personas con EP.

Palabras clave: Enfermedad de Parkinson, tratamiento manipulativo osteopático, CIF, marcha, equilibrio

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease in the world[1]. It is a disease that affects the central nervous system. The most characteristic motor signs of the disease are rigidity, bradykinesia, resting tremor and postural instability, constituting the parkinsonian tetrad[2]. Due to motor signs and the evolution of PD, people affected by the disease may present a flexed posture, which worsens gait performance, balance, and mobility[3,4]. Other factors, such as degenerative disc disease, weakness of the extensor muscles of the spine, vertebral fractures and postural habits are associated with postural alteration[5].

Physical exercise is a type of non-pharmacological treatment indicated for patients with PD due to the motor impairments caused by the disease[6]. Among the possible approaches to physical exercise, there is scientific evidence indicating that osteopathic manipulative treatment (OMT) can positively influence both postural instability in elderly people with vertigo, and gait in PD[7,8]. OMT emphasizes the central role of the musculoskeletal system, which could be ideal for addressing somatic dysfunction associated with rigidity in people with PD[9]. In published studies, patients with PD improved gait parameters (increased step length and gait speed) after OMT, while healthy people did not show significant changes. These findings suggest a positive effect in patients with PD after OMT regarding gait and dynamic mobility of the lower limbs[7,8].

There is still a lack of studies that address the effects of a therapeutic program based on Osteopathy in individuals with PD, and there is a lack of knowledge on the subject. To date, the possible influence of OMT on the range of motion (ROM) of ankle dorsiflexion, balance, and spatiotemporal gait variables (stride length, swing phase, single stance phase and double stance phase of the lower limbs) has not been evaluated in patients with PD. In studies, it was not clear which protocols were used, and each study evaluated only one variable, that were balance or gait. Based on clinical reasoning, OMT can improve the biomechanical functions of joints and muscles. For this reason, allied health professionals who work to promote physical activity can consider OMT as a possibility to manage musculoskeletal symptoms of PD[10].

Our study aims to evaluate different variables based on the ICF and single-session application of a OMT protocol. Therefore, the problem question presented in this article is: Can OMT acutely influence lower limb mobility, balance, and gait in patients with PD?

Methods

Experimental design

This is a randomized controlled clinical trial approved by the Ethics Committee and registered in the Brazilian Registry of Clinical Trials under the number RBR-7pkypg3, available at the link: https://ensaiosclinicos.gov.br/rg/RBR-7pkypg3. The study will be carried out in a Physical therapy Service. All participants will sign a Free and Informed Consent Term (FIC), based on the Helsinki Resolution.

Population and sample size

The formula below was used to determine the sample size (n) based on the estimation of Brazilian population proportion:

$$n = \frac{(N \cdot p \cdot q \cdot (Z\ \alpha/(2))}{p \cdot q \cdot (Z\ \alpha/2)^2 + (N-1) \cdot E^2}$$

Where:
N = Brazilian population according to 2010 Census (190.755.799 people).
p = prevalence Parkinson's Disease – 2% average of the elderly population (0.02).
q = 1 - p (0.98)
Z α/2 = critical value associated with a confidence level of 95% (1.96).
E = 5% sample error (0.05).

From the formula above, the result obtained by the sample calculation is 30 participants. Sixty individuals of both sexes with a diagnosis of idiopathic PD will be allocated in the Control (n=30) and Osteopathic Manipulative Treatment (OMT) (n=30) groups. All assessments and treatment protocol will be performed in the "on" phase of medication (period of drug action, from 30 minutes to 2 hours after the last dose) where patients are able to move more freely when antiparkinsonian drugs are working well. Volunteers can only be included in the research after understanding and consenting to participate in the research by signing the FIC.

Inclusion criteria

Adults with idiopathic PD diagnosed by a neurologist, classified in stages 1 to 3 of disability on the Modified Hoehn & Yahr scale, being on stable antiparkinsonian medication; participants' ability to obey verbal commands analyzed by the Montreal Cognitive Assessment (MoCA).

Exclusion criteria

Presence of other associated neurological diseases; severe osteoporosis, significant change in the ability to understand and perform tasks according to MoCA, acute rheumatologic diseases, previous history of spinal surgery using osteosynthesis and arthrodesis-type procedure, individuals classified in stages 4 and 5 of the Modified Hoehn & Yahr.

This study will be carried out according to the phases of randomized trial of two groups (enrollment, intervention allocation and data analysis).

ICF-based clinical tools

The assessment based on the ICF domains comprises body function and structure, activities, participation and contextual factors (environmental and personal). These domains cover aspects of functionality and disability. In the domain "body function and structure" the following assessment instruments/tests will be adopted: the MoCA scale for cognition assess; the Modified H&Y staging scale to assess PD clinical staging; section I of the Unified Parkinson's Disease Rating Scale (UPDRS) for the assessment of mental activity, behavior and mood in PD; the C7 measurement test to verify the flexed posture; the evaluation of ankle dorsiflexion ROM and the MiniBESTest for the analysis of static and dynamic balance. In the "activities" domain, the following assessment instruments/tests will be adopted: freezing of gait questionnaire (FOGQ); Timed up and go (TUG) using G-Walk® to assess the dynamic mobility of the lower limbs; 7-meter walk test that will also use the G-Walk®; section II of the UPDRS to analyze activities of daily living and section III of the UPDRS to assess motor impairment stage. Contextual factors will be addressed through anamnesis and verification of the equivalent daily dose of patient's levodopa.

ICF - Body function and structure domain

Cognitive Assessment - Montreal Cognitive Assessment (MoCA)

The MoCA is a brief global cognitive scale useful in detecting mild cognitive impairment in patients with PD. In MoCA, different cognitive domains are evaluated, such as visuospatial and executive functions as memory, attention, language, abstraction, delayed recall, concentration and calculation, repetition and orientation[11].

Modified Hoehn & Yahr Staging Scale (H&Y)

The modified Hoehn and Yahr scale assesses disease staging in individuals with PD[12,13], including postural instability. To assess postural stability, the patient is pulled back abruptly from the shoulders[12]. In addition to sample characterization, H&Y will be used as an important tool included in exclusion criteria of the study, excluding individuals with stages 4 and 5.

Measurement of C7 trunk flexion to wall distance

The flexed posture of the trunk in individuals with PD is associated with a general worsening of the disease. It can have, in particular, a negative effect when it comes to mobility and balance, becoming a compensatory mechanism that increases risk of falls[14]. To perform the test, patients will be instructed to stand up against the wall in their usual posture. Their feet should be shoulder-width apart and slightly away from the wall. Then, the evaluator measures the distance, in centimeters, between the seventh cervical vertebra and the wall, in a horizontal direction[14].

Assessment of ankle dorsiflexion range of motion

The assessment of ankle dorsiflexion ROM in closed kinetic chain (CKC) is used to assess joint mobility. The test consists of placing the foot to be evaluated on a measuring tape on the floor in a straight line from a wall. Patients in an orthostatic position keep the hallux on the tape. Then, patients are instructed to perform the dorsiflexion movement in CKC, placing the foot as far as possible, keeping the knee in contact with the wall. Patients' heels must also maintain contact with the ground. When the patients reach the maximum amplitude, the evaluator performs the measurement of the distance between the wall and the hallux[15].

Subjective assessment of postural balance – Mini BESTest

The Mini BESTest assesses dynamic balance in individuals with PD. Anticipatory postural adjustments; reactive postural control; sensory orientation, and gait stability are covered in this test[16].

ICF - Body function and structure /Activities domains

Clinical assessment of PD - Unified Parkinson's Disease Rating Scale (UPDRS)

The UPDRS determines, through self-report and clinical observation, the disease progression and the effectiveness of the treatment evaluating signs, symptoms and certain activities of the patients[17,18,19]. Composed of 42 items, the scale is divided in 4 parts, namely: 1) mental activity, behavior and mood, 2) activities of daily living, 3) motor exploration and 4) complications of drug therapy. The maximum value indicates more severe impairment, while the minimum value indicates mild impairment from PD[19].

ICF - Activities domain

Assessment of dynamic mobility of lower limbs, using the Timed up and go test (TUG) through G-WALK®

The Timed Up and Go test consists of measuring, in seconds, the time in which the individual stands up from a chair, walks a 3 meters distance in a safe and comfortable way, turns 180 degrees, walks towards the chair again and sits down[20]. The longer the time, the greater the association with fall risk. During the test, participants can use, if necessary, walking aids, but without any physical assistance from the evaluator. Subjects are instructed to perform the test once to become familiar with the movements[20,21]. The test will be performed with the triaxial G-WALK® sensor positioned in the lumbosacral region. The sensor transmits the information, via bluetooth, to a computer with GStudio software for data storage[22]. G-WALK® sensor makes it possible to determine the time in the test 5 phases, namely: transition from sitting

to standing, forward walking, pivoting, back walking and transition from standing to sitting.

Evaluation of freezing of gait phenomenon – Freezing of Gait Questionnaire (FOGQ)

The freezing of gait (FOG) is described as a sudden inability to start or continue walking and usually lasts less than 10 seconds, reaching 30 seconds as the disease progresses, increasing the risk of falls[23]. Individuals with PD report having their feet glued to the ground sensation, especially when starting to walk, changing direction, passing through narrow places, immediately before reaching a destination and when trying to avoid objects[24]. The Freezing of Gait Questionnaire (FOGQ) has 6 items, 4 of which are used to assess the severity of FOG, and the other 2 items are used to assess gait. The application of the questionnaire is indicated during the ON phase of medication. All questions, with the exception of question 3, are based on events of the last week or general presence of the phenomenon. Question 3, "Do you feel like your feet are glued to the floor as you walk, turn around, or when you try to start walking (freezing)?" it is extremely important since the answer "no" considers the individual to be non-freezing, and the assessment is completed. The evaluator must demonstrate what an episode of FOG would be like to the individual[24]. FOGQ will be used for sample characterization.

Assessment of gait speed through the 7-meter walk test using the G-WALK

The 7-meter walk test with the G-WALK® consists of analyzing the gait phases, speed (m/sec), cadence (steps/min), stride length (m), step length and number of steps. Moreover, propulsion and symmetry are analyzed. Propulsion describes the ability to adapt total load in relation to body weight in one of the lower limbs after the deceleration phase, and to push the center of mass forward in the opposite lower limb. Symmetry provides information about the patient's ability to similarly maintain the acceleration of the center of mass during right and left step cycles. All analyses will be performed for both sides. Patients will be instructed to walk 7 meters comfortably. If assistance is needed, it should be provided as little as possible, just so patients can perform the test. This assistance must be documented to reflect the highest level of assistance offered[25].

ICF Contextual factors

Identification form - anamnesis

Patients will fill in the identification forms with socio-demographic and clinical data that include: patient's name, date of birth, age, gender, height, body mass, education level, profession, address, contact phone, Parkinson's disease diagnosis time.

Calculation of the Levodopa equivalent daily dose

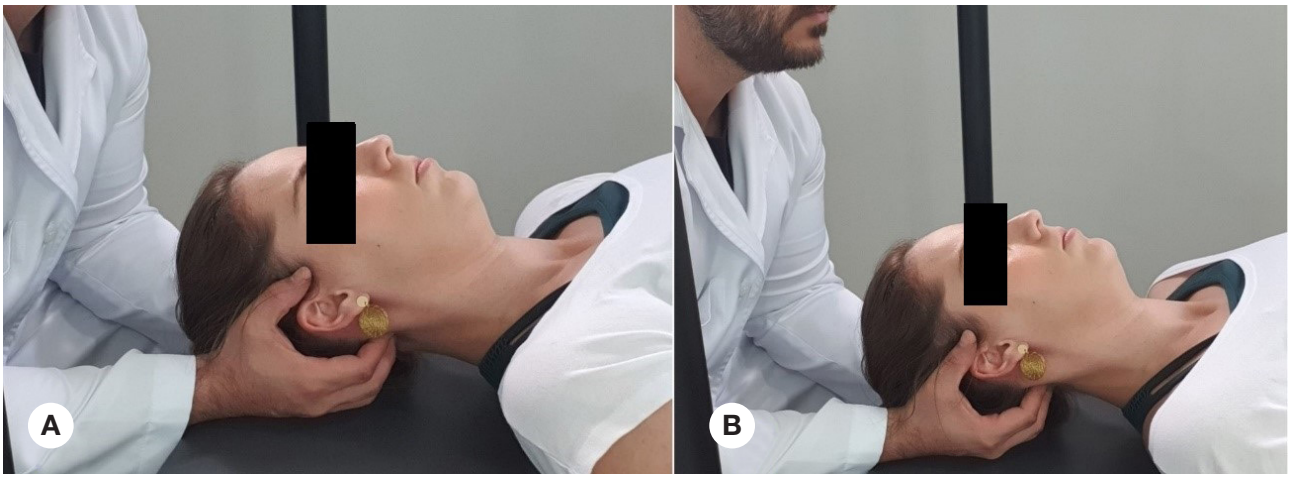
The levodopa equivalent daily dose (LEDD) will be calculated to verify the amount of the study patients' ingestion of equivalent daily dose of Levodopa. The literature suggests that high doses of levodopa can influence directly the functional status of patients with PD[26,27].

For this purpose, the formula used to calculate the LEDD is as follows: 100 mg of levodopa = 130 mg of controlled-release levodopa = 70 mg of levodopa + catechol -O-methyl-transferase inhibitor = 1 mg of pergolide = 1 mg pramipexole = 5 mg ropinirole[28,29].

Description of OMT protocol

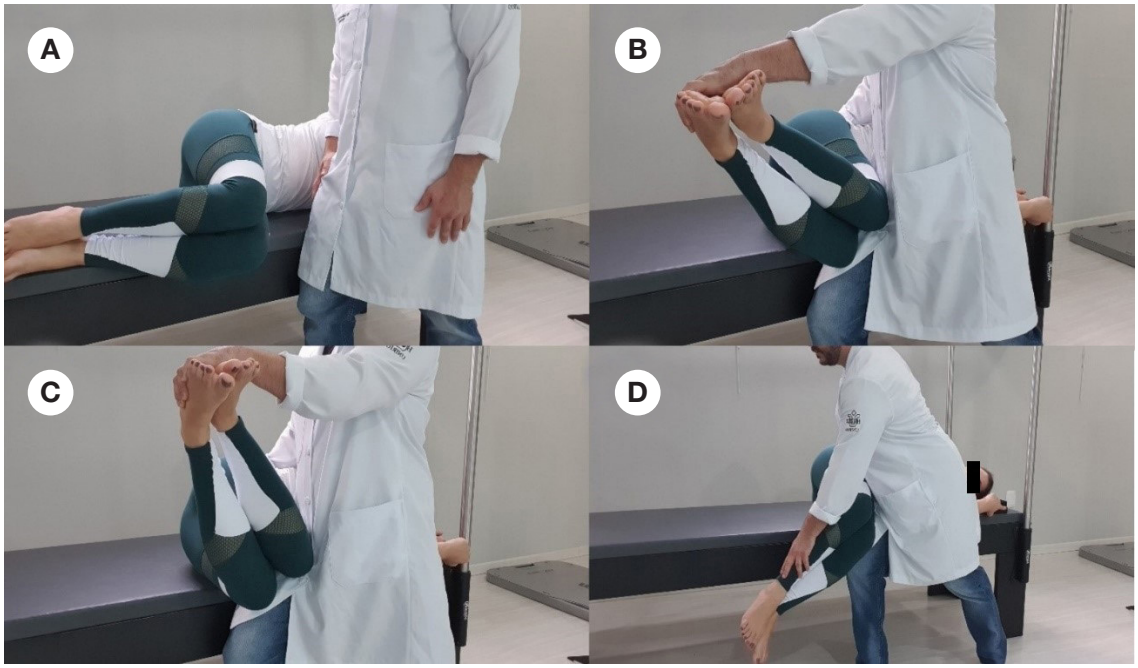
Patients randomly allocated to the OMT group will receive a protocol containing 13 specific osteopathic techniques lasting approximately 30 minutes. Specific techniques are described below.

1. Suboccipital muscles inhibition technique with the patient in supine position[30]
A: The technique starts with the patient relaxed in the supine position.
B: Progression to therapist's fingers tension increase towards ceiling. Source: Own authorship.



2. Cervical vertebrae articulation technique in dorsal decubitus[31]
A: The technique starts with the patient in the supine position, head in flexion and resting on the therapist's abdomen. Therapist contacts the articular facets of the atlas and axis region.
B: Therapist articulates the region in 8.
C: Technique continues the for the opposite side.

3. Stretching technique for iliolumbar ligaments, in lateral decubitus
A: The technique starts with the patient in lateral decubitus.
B: Support of the patient's lower limbs on the therapist's knee and abdomen.
C: Tension increase towards the ceiling.
D: Tension increase towards the ground.

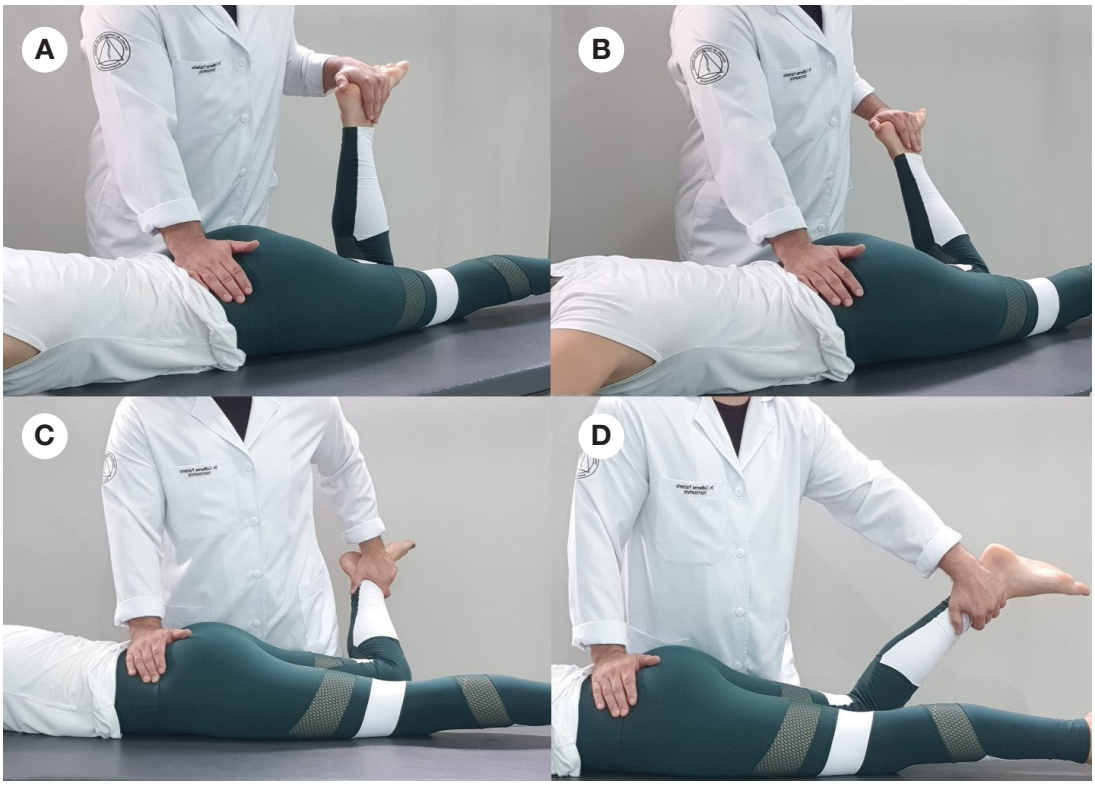


Contact in the iliolumbar ligaments' region.

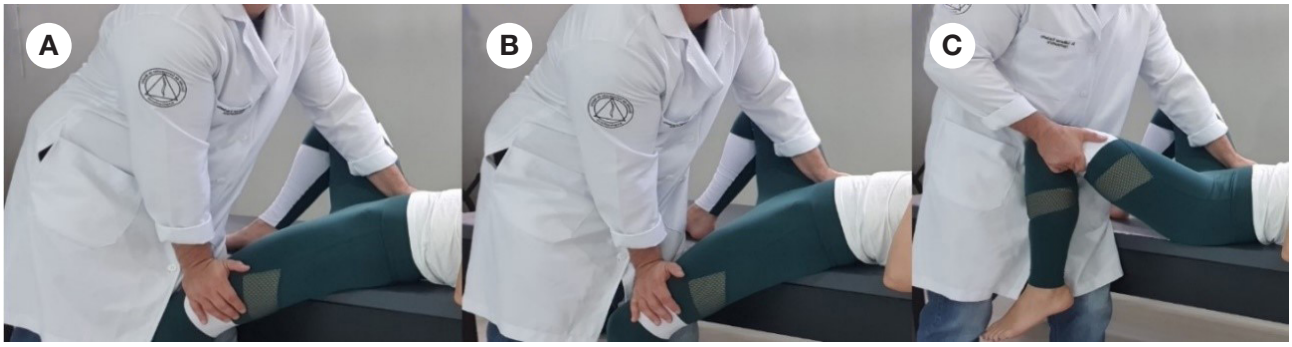
4. Articulatory technique with crossed pisiforms for the thoracic spine
A: Contact with crossed pisiforms in the upper thoracic spine, inner hand with finger in cephalic direction and external hand with fingers in caudal direction.
B: Contact with the mid thoracic spine.
C: Contact with the lower thoracic spine.

5. Articulation technique for the lumbar spine in prone position
A. Contact with crossed pisiforms in the patient's lumbar region.
B. Start of rotation movement associated with light pressure towards the ground.
C. Increased rotation and compression.

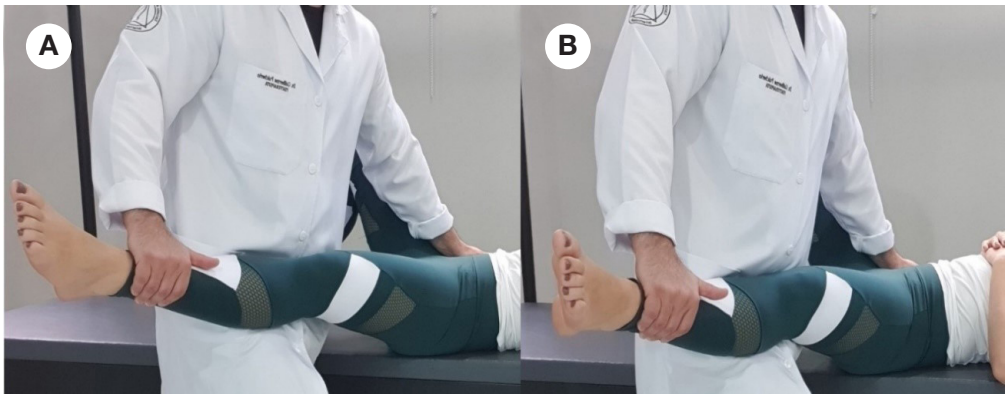
6. Articulation technique in ventral decubitus for sacroiliac[32]
A: The technique starts with the patient in prone position, contact of the cephalic hand with the contralateral sacroiliac, stabilizing the region. Caudal hand in contact with the patient's ankle.
B: Internal rotation of the coxofemoral.
C: In a rhythmic and continuous way, the tension is increased.
D: Return to the starting position.



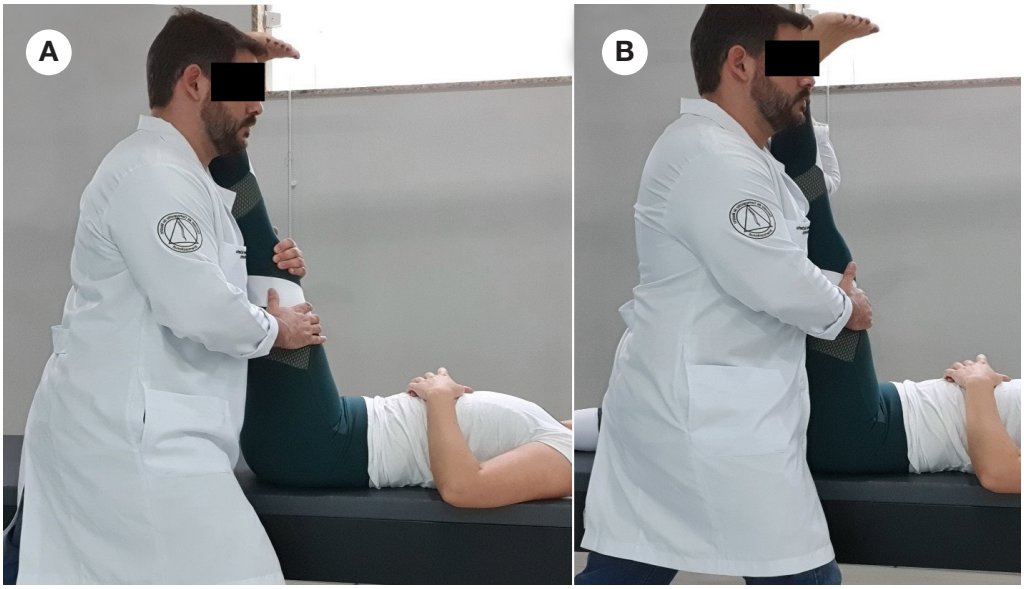
7. Muscle energy technique for psoas[33]
A: The technique starts with the patient on the edge of the stretcher, in dorsal decubitus and lower limb out.
B: Isometric contractions begin.
C: Passive return to the starting position.



8. Muscle energy technique for adductor muscles
A: The technique starts with the patient in dorsal decubitus, with the first lower limb motor barrier in abduction. Isometric contractions starts.
B: Take the new motor barrier so that in the end of the technique, passively return to the starting position.



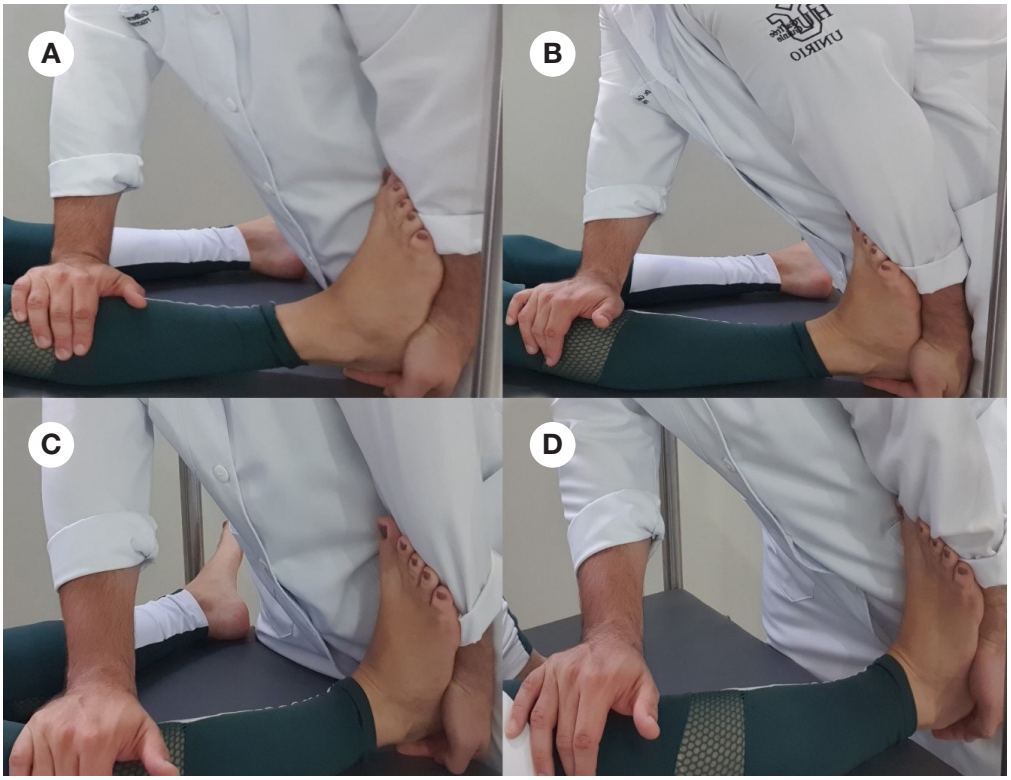
9. Muscle energy technique for hamstring muscles
A: The technique starts with the patient in dorsal decubitus, hip flexion and knee extension.
B: Begin isometric contraction cycles and at the end of the technique, passively return to the starting position.



10. Popliteal release technique
The technique starts with the patient in the supine position. Therapist contacts the lower hand on the distal part of the tibia on the side to be treated. Upper hand in contact with the popliteus muscle region. The technique is performed dynamically, in lateral rotation of the tibia and extension.

11. Cuneiform articulation technique in 8
A: The technique starts with the patient in dorsal decubitus, therapist in abdominal contact at the metatarsals base and hands under the plantar surface, with thumbs in the cuneiform region.
B: Articulatory movement starts in "8".
C: Movement development.

12. Muscle energy technique for ankle plantarflexion muscles
A: Patient in dorsal decubitus, therapist in contact with the caudal hand on the calcaneus and forearm on the patient's plantar surface.
B: Isometric contraction cycle begins.
C: Gain of new motor barrier.
D: End of technique passively returning to starting position.



13. Diaphragm release with seated patient associated with trunk extension[34]
A. Knee supported on the patient's side, stabilizing the trunk.
B. Therapist's hands on the costal margin with posterior glide.
C. Trunk and cervical flexion in the expiratory phase and increase of diaphragm contact.
D. Trunk and neck extension in inspiratory phase.
E. Relaxation of therapist's hands.
F. Cycle repetition.

Source figures: Own authorship

Control group procedures

After performing the initial assessments, patients of control group will be directed to a room where the evaluator will ask them to lie down in a comfortable position, being able to change decubitus, lasting as the OMT group protocol, 30 minutes. After this period, patients will be reassessed.

Statistical analysis

The SPSS 23.0 statistical program will be adopted as a tool for statistical analysis. Descriptive analysis of socio-demographic variables will be performed. Numerical variables will be presented as mean and standard deviation. Nominal variables will be presented in frequency and percentage. Levene's test will be adopted to analyze the homogeneity of variances. The Shapiro-Wilk test will verify the distribution of variables regarding normality. T-test for independent samples will be adopted to compare measurements between groups at baseline and post-treatment, in normal distribution. For non-normal distribution, the non-parametric Mann-Whitney test will be adopted. Dependent T test will be used to compare baseline and post measurements for normally distributed variables. For variables with non-normal distribution, the Wilcoxon signed rank test will be adopted. The effect size will be evaluated through the Pearson coefficient where 0 (no effect) and 1 (a perfect effect). R = 0.10 (small effect), r = 0.30 (medium effect); r = 0.50 (large effect). A confidence interval of 95% will be adopted, considering statistical significance through $p<0.05$. Intention-to-treat analysis will also be considered for individuals who for some reason do not complete integrally the study[35]

Discussion

The present article is a randomized clinical trial protocol study with the objective of knowing the effects of an OMT session through studied outcomes based on ICF domains. The OMT intends to provide greater mobility in structures such as joints and muscles to improve the individual's functionality[7,8]. This protocol study used as a basis a previous study on OMT in patients with PD and healthy subjects that demonstrated an improvement in length, step cadence, and lower limb speed after performing OMT session in patients with PD, which did not occur in the control group participants[7]. The WELLS study[7] was also used as a basis for another study[8] that discussed the effects of a protocol on motor function, balance and gait stability. The results demonstrated a significant improvement in motor function, in addition to a significant clinical improvement in gait, balance and motor function.

In the present protocol study, some techniques were included in order to address different structures that influence the outcomes to be studied (cervical mobility, ankle mobility, balance, temporo-spatial gait variables). The diaphragm release technique aims to improve its function. The diaphragm is an extremely important muscle for breathing, and it also contributes to the maintenance of posture and postural changes[35]. Therefore, the technique for its release in the sitting position was included. The iliofemoral ligaments are important for the union between the lumbar spine and the pelvis, and their function is to limit the movements of lateral inclination, flexion (superior fasciculus) and extension (inferior fasciculus[36]. Patients with PD have a decrease in ankle ROM, which can impair the activity of climbing a ladder[37,38] and, therefore, impair quality of life. Thus, a therapeutic approach emphasizing the ankles was included in the protocol, specifically, muscle energy for the plantarflexor muscles and articulatory mobilization for the cuneiform muscles. Postural disorders are also common, which also increases the risk of falling, immobility, and loss of independence[39]. Therefore, articulatory and muscle energy mobilizations will be carried out in order to optimize the structures functions related to posture.

The ICF domains will be considered in the participants evaluation in order to favor the integral view of each individual. The domain "body function and structure" will be evaluated using the following parameters: MoCA, Modified H&Y staging scale, UPDRS I, the C7 measurement test, the assessment of ankle dorsiflexion ROM and the MiniBESTest. In the "activities" domain, the following will be used: The Freezing of Gait Questionnaire (FOGQ), the G-Walk® in the Timed up and go (TUG) and in the 7-meter walk test. Furthermore, UPDRS II and III will also be used in ICF domain. Contextual factors will also be addressed through anamnesis and verification of Levodopa daily dose. The choice of ICF aims to identify how the same health condition (in this case, PD) can influence and be influenced by the domains of ICF and, consequently, the functioning in different ways in PD patients.

PD courses with motor signs and symptoms such as: bradykinesia, muscle rigidity and postural instability[2], leading to changes in gait and general mobility, including dynamic mobility of the lower limbs[7,40], which can impair activities of daily living performance. There is a knowledge gap in the acute effects of OMT in patients with PD based on the outcomes presented here. The studies found in the literature do not have a statistical importance, since presented a small number of patients[7,8]. In this work will be used the formula based on the population where the study will be carried out and on the prevalence of PD to set the number of patients in each group (OMT =30, Control =30). To date, there are no studies that use the ICF domains to study the functioning of people with PD after OMT. Most studies were not detailed in describing the osteopathic techniques used in people with PD, which make dificult their reproducibility. From a scientific point of view, it is important to detail the techniques/interventions adopted in scientific reports to confirm that the studied clinical outcomes are potentially influenced by the available treatment of experimental groups. The

hypothesis of the present study is that positive effects are found in the OMT group regarding improvement of dorsiflexion ROM, posture, balance, as well as general mobility compared to participants in the control group. Thus, further studies are needed to evaluate OMT as a complementary therapy in PD.

Conflict of interest

The authors declare that they have no conflict of interest.

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ORIGINAL

Gene expression of *COX-2*, *MLH1* and *MSH2* in papillary thyroid carcinoma: a retrospective analysis

Expresión génica de COX-2, MLH1 y MSH2 en carcinoma papilar de tiroides: un análisis retrospectivo

Edgar García-Torres[1], Graciela Zambrano- Galván[2], Juan Carlos Cuevas- González[3], Víctor Hiram Barajas Pérez[1]

Research professors

1. Faculty of Dentistry. Juarez University of the State of Durango

2. Nutriepigenomics and Clinical Nutrition Laboratory, Faculty of Medicine and Nutrition. Juarez University of the State of Durango

3. Department of Stomatology, Institute of Biomedical Sciences, Autonomous University of Ciudad Juárez

Corresponding author
Dra. Graciela Zambrano- Galván
E-mail: gzambrano@ujed.mx

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Abstract

Objetives: To determine the mRNA expression of the *COX-2, MLH1* and *MSH2* genes in Papillary Thyroid Carcinoma.
Methods: This is comparative cross-sectional clinical molecular study. The study was constituted by 26 biopsies with histopathological diagnosis of Papillary Thyroid Carcinoma, from the 450 General Hospital of Durango State. The relative gene expression of the *COX-2, MLH1* and *MSH2* was performed by qPCR.
Results: The mean age of patients was 46 ± 15.22. They were observed differences in the gene expression of *COX-2* ($p = 0.001$), *MLH1* ($p = 0.06$) and *MSH2* ($p = 0.09$) in the total Papillary Thyroid Carcinoma sample. The correlation between gene expression and patient age was $r^2 = 0.441$ ($p = 0.024$) for the *MSH2* gene. The correlation of mRNA expression between *COX-2* and *MLH1* was $r^2 = 0.69$ ($p = 0.001$); for *COX-2* and *MSH2* of $r^2 = 0.47$ ($p = 0.01$), while for *MSH1* and *MSH2* of $r^2 = 0.94$ ($p = 0.001$).
Conclusions: The results obtained in the present study showing the presence of gene expression of molecular targets such as the *COX-2, MLH1* and *MSH2* genes, contributing to the understanding of the molecular physiopathology of the Papillary Thyroid Carcinoma.

Key words: Papillary thyroid carcinoma, gene, expression.

Resumen

Objetivos: Determinar la expresión del mRNA de los genes *COX-2*, *MLH1* y *MSH2* en Carcinoma Papilar de Tiroides.
Métodos: Se trata de un estudio clínico- molecular transversal comparativo. El estudio estuvo constituido por 26 biopsias con diagnóstico histopatológico de Carcinoma Papilar de Tiroides, del Hospital General 450 del Estado de Durango. La expresión génica relativa de *COX-2*, *MLH1* y *MSH2* se realizó mediante qPCR.
Resultados: La edad media de los pacientes fue de 46 ± 15,22 años. Se observaron diferencias en la expresión génica de *COX-2* ($p = 0,001$), *MLH1* ($p = 0,06$) y *MSH2* ($p = 0,09$) en la muestra total de Carcinoma Papilar de Tiroides. La correlación entre la expresión génica y la edad del paciente fue de $r^2 = 0,441$ ($p = 0,02$) para el gen *MSH2*. La correlación de la expresión de ARNm entre *COX-2* y *MLH1* fue $r^2 = 0,69$ ($p = 0,001$); para *COX-2* y *MSH2* de $r^2 = 0,47$ ($p = 0,01$), mientras que para *MSH1* y *MSH2* de $r^2 = 0,94$ ($p = 0,001$).
Conclusiones: los resultados obtenidos en el presente estudio muestran la presencia de expresión génica de dianas moleculares como los genes *COX-2*, *MLH1* y *MSH2*, contribuyendo al conocimiento de la fisiopatología molecular del Carcinoma Papilar de Tiroides.

Palabras clave: Carcinoma papilar de tiroides, gen, expresión

Introducction

Thyroid cancer (TC) is the main malignant neoplasm of the endocrine system, which in the United States accounts for 6% of tumors in general[1], of which 80% corresponds to papillary thyroid carcinoma (PTC)[2], and of which it has manifested greater incidence in the last decades in different populations around the world[3-6]. It affects men and women, predominating in the female sex[7]. The PTC belongs to the well-differentiated TC originated from follicular cells of the thyroid gland[8], usually follows a slow and non-aggressive behavior that generally shows a low mortality; however[9],; there is knowledge of variants with different morphological and molecular manifestations that confer a high potential for aggressiveness[10]. There are risk factors such as age, sex, exposure to ionizing radiation and gene alterations so its clinical manifestation[11-13], approach and prognosis depends largely on the histopathological variants, which are identified using hematoxylin and eosin staining[10,14]. It should be mentioned that although histopathological assessment is the gold standard for diagnosis, the implementation of molecular tools has become important in recent years, since previous studies have shown the relationship between altered levels of gene expression with the manifestation and development of several types of cancer including PTC[15-17].

In this regard, it has been proposed that cyclooxygenases belonging to the family of enzymes that catalyze arachidonic acid resulting in prostaglandins have pain and inflammation regulatory functions, there are two isozymes *COX-1* and *COX-2*, of these the *COX-2* (cyclooxygenase 2) represents an inducible inflammatory initiating enzyme that is mediated under normal conditions, but under pathological stimuli such as inflammatory mediators and kinases shows an increased activity. Different studies have shown an overexpression of this protein in a large variety of tumors in humans, and its altered presence suggests an important action on progression, transformation and even tumor angiogenesis[18-22].

Similarly, the alterations that the repair mechanism of the DNA called Reparative System or Mismatch Repair[23] controlled by the *MLH1, MSH2, MSH6* and *PMS2* genes can undergo mainly[24]. When there is damage to the DNA, the reparative system acts by activating the cell cycle, stopping it or sending the cell to a programmed death. However, it has been observed that the inactivation or alteration of this system is related to the presence of hereditary or spontaneous cancer[25] because the main function of *MLH1* is to form a ternary complex with DNA in mismatch and the MutSα complex, increasing discrimination between heteroduplexes and homoduplexes, which also works in meiotic recombination; whereas *MSH2* recognizes the mismatches between base-base and the insertion-deletion loops[26]. It is for all of the above that in the present study the objective was to determine the mRNA expression of the *COX-2, MLH1* and *MSH2* genes in papillary thyroid carcinoma.

Methods

A comparative cross-sectional study was carried out, in which a total of 26 samples included in paraffin blocks (previous signature of informed consent and biopsy), corresponding to patients with a histopathological diagnosis of PTC in the period 2007-2014 were included. Those samples included in paraffin that did not present a complete clinical file were excluded. From the clinical files, sociodemographic data were collected such as age, sex, place of birth and residence, the definitive diagnosis of PTC, time of evolution, type of biopsy used, size of the lesion and its statification according to the tumor- nodule-metástasis system (TNM). This work was approved by the ethics committee of the General Hospital 450 of the Health Services of the State of Durango with a unique registration number assigned 405/014.

Procedures

Tissue Obtention

A histological cut was made with a thickness of 4 µm which was placed on a slide to proceed with the mRNA extraction.

mRNA extraction

To obtain the mRNA, the QuickExtract ™ FFPE RNA Extraction Kit mRNA extraction kit from EPICENTRE (Madison, WI, USA) was used according to the manufacturer's instructions.

Synthesis of cDNA.

The cDNA has obtained by the iScript ™ cDNA Synthesis Kit from BIO-RAD (Hercules, CA, USA), following the manufacturer's instructions.

Analysis of COX-2, MLH1 and MSH2 gene expression

The sense and antisense primers were designed in the PRIMER BLAST program of NCBI (Bethesda, MD, USA), and were synthesized by Integrated DNA Technologies (Coralville, IA, USA). The sequence and the size of the product for each gene are shown in **table I**. The PPIA gene was applied as a normalizing gene. The intercalating dye used was QuantiFast SYBR Green PCR Kit from BIO-RAD (Hercules, CA, USA) according to the manufacturer's instructions. The evaluation of the relative quantification of gene expression was carried out in an Eco Real-Time PCR System of Illlumina (San Diego, CA, USA). The polymerase activation it started at 95ºC for 15 min, followed for the initial denaturalization at 95ºC for 15s, and anneling-extension at 65ºC for 15s for 40 qPCR cycles.

Table I: The sequence and the amplicon size of the product of *COX-2, MLH1, MSH2* genes.

GENE	MOLECULAR LOCUS	EXÓN	OLIGONUCLEÓTID SECUENCE	AMPLICON SIZE
COX-2	1 q25.2-q25.3	10	F'TCT CAG ACG CTC AGG AAA TAG A-3' R'GTC GTT GAC CTC GTC TGT TAT G-3'	113 bp
MLH1	3p21.3	21	F'GTC CAC TGT AAC CTG CCT AAT C-3' R'CCA GCC CAA GAT GTC TCT TAA C-3'	99 bp
MSH2	2 p21	19	F'GAA GAT GGT GAG TGA GGA TAG G-3' R'GTG GAC TGA AAC TGT GCT AAT G-3'	94 bp

Statistical analysis.

Frequencies and central tendency measures were used for the analysis of the descriptive data. To determine the differences between means, the relationship and correlation between variables, the Student's t-test, Chi-square test, and Pearson's correlation were used, respectively. The statistically significant differences were estimated with a p <0.05 value. The statistical program IBM SPSS version 22 (Chicago, Inc.) was used. For the analysis of relative expression, the REST program of QIAGEN v.2009 was used.

Results

Twenty six samples of PTC were analyzed. The mean age in patients was 46.1 ± 15.52, being the youngest of 22 and the oldest of 82 years; 63% of the patients were born in the capital of the State of Durango, Mexico; of which 81% had a permanent residence in the mentioned location. The clinical manifestations of PTC in patients younger than 45 years of age are shown in **table II**. It is important to mention that the approach for biopsy was 46% thyroidectomy, 31% hemi-thyroidectomy, 19% excisional approach and only 4% incisional.

The reference *PPIA* gene allowed to observe differences in the expression of mRNA of *COX-2* (p = 0.001), *MLH1* (p = 0.06) and (p = 0.09) in CPT, presented in **figure 1**.

A statistically non significant correlation was observed (r^2 = 0.037, p = 0.85) between the expression of *COX-2* mRNA and the age of the patient at the time of

Table II: Clinical manifestation of the papillary thyroid cancer in patients younger than 45 years of age.

CPT Clinical Manifestatión	<45 years %(n=13)	>45 years %(n=13)	Total %(n=26)	P≤ 0.05*
Tumor Clinical Extention				
≤ 1cm	---	---	---	---
> 1- ≤ 4cm	30(4)	70(9)	50(13)	0.05
> 4cm	70(9)	30(4)	50(13)	
Diameter of CPT				
< 1cm	15(2)	15(2)	16(4)	0.67
1-2cm	47(6)	62(8)	54(14)	
> 2 - ≤4cm	38(5)	23(3)	30(8)	
> 4cm	---	---	---	
Metastasis to lymph nodes				
Present	23(3)	8(1)	16(4)	0.27
Ausent	77(10)	92(12)	84(22)	
TNM Estadificacion**				
TNM I	77(10)	8(1)	42(11)	0.001
TNM II	23(3)	62(8)	42(11)	
TNM III	---	30(4)	16(4)	
TNM IV	---	---	---	

*Fisher´s exact test for statistical analysis. **Tumor-nodule- metastasis.

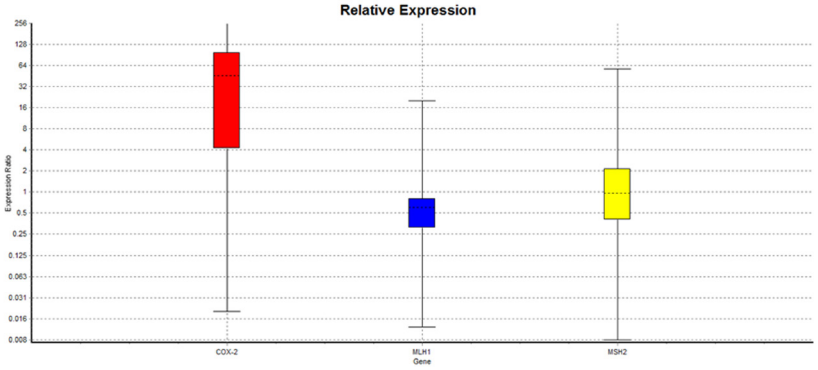
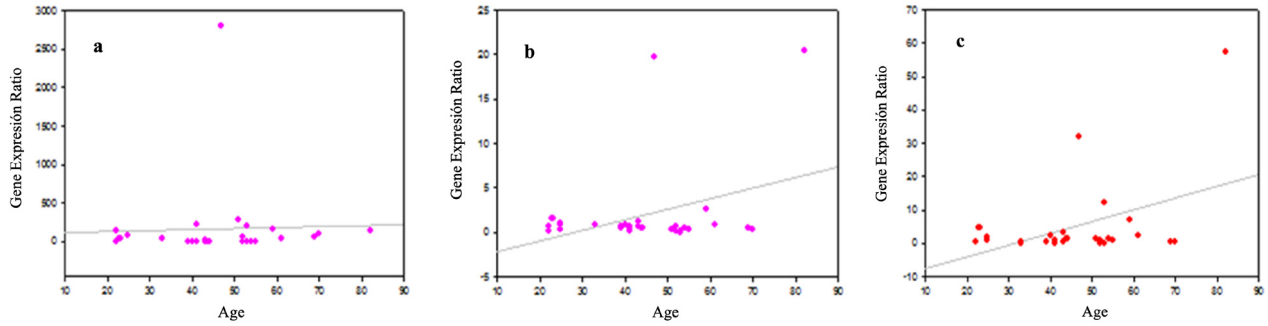


Figure 1: Results of the mRNA expression of *COX-2, MLH1, MSH2; PPIA** mRNA expression was used to reference gene.

*The results are calculated according to the average of the Ct values. Whiskers represent mean ± standard deviation for each group. Boxes represent mean ± SEM (standard error of mean). ǂT-Student test.

Figure 2: Correlational analysis between the age patient's and gene expression of (a) *COX-2* (r2= 0.037, p=0.85*), (b) *MLH1* (r2= 0.34, p=0.08) and (c) *MLH2* (r^2=0.441, p= 0.02).



diagnosis (**Figure 2a**), while the expression of *MLH1* mRNA and age of the patient at the time of diagnosis shows a statistically non significant correlation (r^2 = 0.34, p = 0.08) as seen in **figure 2b**. On the other hand, the expression of *MSH2* mRNA against the age of the patient at the time of diagnosis shows a mean and statistically significant correlation (r^2 = 0.44, p = 0.02), which is observed in **figure 2c**.

When the age was evaluated based on the clinical extension of the PTC, a statistically significant inverse correlation was found, since the patient's older age showed a smaller clinical lesion size (r^2 = -0.393, p = 0.04).); otherwise, when evaluating the age and diameter of PTC (r^2 = 0.08, p = 0.67).

Statistically significant difference was found between the clinical extension of the PTC and the age groups (p=0.05), **table II**. On the other hand, the diameter of the PTC was not statistically different between patients older and younger than 45 years (p= 0.67); **table II**. A correlation of r^2= 0.69 (p = 0.001) was obtained between the expression of mRNA of *COX-2* and *MLH1*; for *COX-2* and *MSH2* of r^2= 0.47 (p = 0.01), and for *MSH1* and *MSH2* of r^2= 0.94 (p = 0.001).

Discussion

The papillary thyroid carcinoma (PTC) is the most frequent malignancy of the thyroid gland, in general it tends to have a good biological behavior, however it is a disease that has a wide range of histological variants which confers changes in the prognosis of the lesion and it is important to focus your study with a molecular point of view. There are limitations for early diagnosis of PTC, which makes it difficult to understand how the lesion is differentiated in histological variants, resulting in late and radical treatments that compromise the patient's health.

The results found in this study show that the average age of the patients is consistent with the results shown in other studies where they are 45 years old[27], as the most frequent at the time of diagnosis compared to the one found in this study that was 46 years old. The age of the patient at the time of diagnosis has been established by the scientific literature as a risk factor for the development of thyroid carcinoma and in the same way as a prognostic factor, within the risk factor the presence of thyroid nodules is frequent in individuals that exceed the fourth decade of life and shows an increase in the incidence in patients within 40-50 years, it is worth mentioning that there have been cases in patients under the age of 16 years[28,29]. As a prognostic factor, age is used by the TNM system to stage the lesion solely and exclusively in thyroid carcinoma, and it is known that after 45 years, local aggressiveness and metastatic capacity increase at a distance[11,30,31]. Some studies conducted in the United States show that women are mostly affected by PTC at a female: male ratio that ranges from 2: 1 to 4: 1[28], while in Mexico the ratio is 4: 1 as reported by the National Institute of Cancerology[27]. In addition to being the most frequent PCT in women, they also have a better prognosis compared to men[17,32,33]. It should be mentioned that the literature reports that ethnicity plays an important role as a risk factor, in the United States the white race has greater affectation than the black race at a ratio of 11: 5 respectively[34]. In Hispanic, Hawaiian, Chinese and Japanese populations, women are more affected, and such differences can be attributed to genetic factors or to the type of diet without being completely clear[32,35]. In the present study, 63% of the patients affected with PTC were born in the capital of the State of Durango, Mexico; and that 81% had a permanent residence in the mentioned location. The importance of the *COX-2* gene in the development of malignant neoplasms is well established and its presence promotes cell invasion and growth. It can be present in many cancers such as colon, pancreas, stomach, cervix, esophagus, breast, lung and melanoma; some studies mention a high expression of *COX-2* in thyroid carcinomas compared with thyroid adenomas, similarly there was greater expression in undifferentiated thyroid carcinomas than in CPT in a study conducted in the Chinese population[36]. Regarding the results obtained in this study, they indicate that there is an overexpression of *COX-2* in 77%. Likewise, the presence of an increase in the *COX-2* gene has been reported in patients aged>

50 years suffering from papillary thyroid carcinoma[37]. DNA repair genes are important in the prevention of genetic instability, *MLH1* and *MSH2* have been detected with over expression in neoplasms with a tendency to malignancy more than in benign neoplasms[38]. The results of this study show that only about *MLH1* expression was found in only 15% while *MSH2* was present in 35% of the analyzed samples, In addition, this study allows us to identify the behavior of this disease in the population of Durango, Mexico, which will lead to future studies for a better understanding and management of the lesion in patients susceptible to this susceptible to this condition[39]. That is why the use of molecular tools that serve for the identification, diagnosis and monitoring of patients with susceptibility to the development of PTC will allow a timely and appropriate intervention in order to offer the best prognosis and provide quality care[40]. Despite the size of the small sample used in the present study, we were able to identify gene expression levels of importance for the development of the disease. The results obtained coincide with what is reported in the scientific literature, which is extremely important. The behavior of the disease in the population of Durango, Dgo. Mexico, which will allow future studies for a better understanding and management of the lesion in patients susceptible to this condition.

Conclusions

The results obtained in the present study show that gene expression of molecular targets regulating inflammation and DNA repair, such as *COX-2, MLH1* and *MSH2* genes, are involved in thyroid tumor development, which allows us to contribute to the understanding of the molecular pathophysiology of PTC.

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Conflict of interest

The authors declare that they have no conflict of interest.

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ORIGINAL

Factor associated with snoring and sleep disturbance among students of Majmaah University

Factor asociado a los ronquidos y a los trastornos del sueño entre los estudiantes de la Universidad de Majmaah

Raed Eid Alzahrani[1], Riyaz Ahamed Shaik[2], Mohammad Shakil Ahmad[2], Abdulaziz Badar Almutairi[3], Waleed Khalid Z Alghuyaythat[3], Abdalah Emad Almhmd[3], Abdulrahman Ghayeb Alrashidi[3], Shouq Yaseen Alaoufi[3], Alanoud Mohammad Altheiaib[3], Rand Muslat Alanazi[3], Raghad Ali Alharbi[3]

1. Department of Basic Medical Sciences, College of Medicine, Majmaah University, Majmaah, Saudi Arabia
2. Department of Family and Community Medicine, College of Medicine, Majmaah University, Majmaah, Saudi Arabia.
3. Medical student, College of Medicine, Majmaah University, Majmaah, Saudi Arabia.

Corresponding author
Riyaz Ahamed Shaik
E-mail: r.shaik@edu.sa

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Abstract

Background: Sleep apnea is the medical condition related to sleep of the individual. It is considered as one of the serious disorder where the person's breathing is interrupted during sleep. According to numerous studies it is seen that prevalence of sleep apnea is more among medical students as compared to other students. This study has aimed to know about factors of sleep apnea on the basis of the occurrence of snoring and sleep disturbance among the medical student of various colleges under Majmaah University.
Material and method: It is a cross-sectional study conducted among 298 students aged 18-25 years studying in various colleges under Majmaah University. The sample was randomly selected using Simple random sampling method. Data collection was done using questionnaire based on Epworth-sleepiness scale and analyzed using SPSS version 18. Both descriptive and inferential statistics were used to obtain the required results.
Results: In this study the mean age of the students was 21.9, while the mean height and weight of the student were 165.25 cm and 64.74 kg, respectively. The prevalence of snoring among the respondents was 14%. There is significant association between the sex of the respondent and forgetfulness in the daytime (P=0.027) reportedly more in female compared to male. Disorientation of time, place and time person (p=0.028) was statistically significant with the age group. Almost half (43.3%) of the 18-20 reported feeling disoriented, while only 4.3% of age 23 and more reported disorientation. Similarly, a significant association was seen between the respondent's frustration during routine activities and their age group (p=0.008), where 70% of the students of age group 18-20 reported feeling frustrated during routine activities.
Conclusion: This study concludes that there is prevalence of sleep apnea among the medical student where snoring is one of the major issue in which due to the sleep disorder individual are usually frustrated and disoriented. Maintaining healthy lifestyle could be the solution but if condition worsens seeking medical help is must.

Key words: Sleep Apnea, snoring, sleep disturbances, medical students.

Resumen

Antecedentes: La apnea del sueño es una condición médica relacionada con el sueño del individuo. Se considera uno de los trastornos graves en los que la respiración de la persona se interrumpe durante el sueño. Según numerosos estudios, se observa que la prevalencia de la apnea del sueño es mayor entre los estudiantes de medicina en comparación con otros estudiantes. El objetivo de este estudio es conocer los factores de la apnea del sueño en función de la incidencia de los ronquidos y las alteraciones del sueño entre los estudiantes de medicina de varias facultades de la Universidad de Majmaah.
Material y método: Se trata de un estudio transversal realizado entre 298 estudiantes de 18 a 25 años que estudian en varias facultades de la Universidad de Majmaah. La muestra se seleccionó aleatoriamente mediante el método de muestreo aleatorio simple. Los datos se recogieron mediante un cuestionario basado en la escala de somnolencia de Epworth y se analizaron con el programa SPSS versión 18. Se utilizaron técnicas estadísticas descriptivas e inferenciales para obtener los resultados requeridos.
Resultados: En este estudio la edad media de los estudiantes fue de 21,9 años, mientras que la altura y el peso medios del estudiante fueron de 165,25 cm y 64,74 kg, respectivamente. La prevalencia del ronquido entre los encuestados fue del 14%. Existe una asociación significativa entre el sexo del encuestado y el olvido durante el día (P=0,027), que se registra más en las mujeres que en los hombres. La desorientación de tiempo, lugar y persona (p=0,028) fue estadísticamente significativa con la edad. Casi la mitad (43,3%) de los de 18 a 20 años informaron de que se sentían desorientados, mientras que sólo el 4,3% de los de 23 años o más informaron de desorientación. Del mismo modo, se observó una asociación significativa entre la frustración de los encuestados durante las actividades rutinarias y su grupo de edad (p=0,008), donde el 70% de los estudiantes del grupo de edad de 18 a 20 años declararon sentirse frustrados durante las actividades rutinarias.
Conclusiones: Este estudio concluye que existe una alta prevalencia de la apnea del sueño entre los estudiantes de medicina y que los ronquidos son uno de los principales problemas que provocan frustración y desorientación. Mantener un estilo de vida saludable podría ser la solución, pero si la condición empeora, es necesario buscar ayuda médica.

Palabras clave: Apnea del sueño, ronquidos, trastornos del sueño, estudiantes de medicina.

Introduction

Sleep disorders is the problems which is related to irregularity of sleep which include the quality, timing, the amount, and which also results in daytime distress and functional impairment. There are different types of sleep- disorders among which the most conjoint disorders include narcolepsy, restless leg-syndrome, insomnia, and obstructive sleep apnea. Sleep disorders are usually linked with either some medical conditions or various mental issues, such as depression, anxiety or any other cognitive disorders[1]. Sleep apnea is a considered as one of the serious sleep disorder that happens when a person's breathing is interrupted during sleep. It occurs if the upper airway becomes repeatedly blocked during their sleep which reduces or stoops the airflow. The most common symptoms are excessive daytime sleepiness, fatigue, decreases in attention, alertness, concentration, decreased motor & verbal skill, visual-spatial memory, dry mouth, and headache and some other symptoms such as sexual dysfunction creating decreased sexuality, more urination during night are some additional[2].

According to Hypopnea Index (AHI), Globally, the prevalence of sleep apnea ranged from 9% to 38% and was higher in men, likewise it is also found increased to 90% in men and 78% in women. The prevalence is the condition is seen more in obese population[2]. In the Western world, the prevalence is associated "EDS (excessive daytime sleepiness)", ranging from 3%-7% in men and 2%-5% in women which is similar in "middle east and Asian nations"[4].

There are various studies conducted among university students which highlight the risk of sleep apnea and its association with their decreased academic performance. The major challenges seen among college student includes the sleep deprivation and daytime sleepiness which further results for their lower grades, academic failure, learning compromise, mood impairment, and motor vehicle accident risk[5].

The overall objective of this study is to know about sleep apnea on the basis of the occurrence of snoring and sleep disturbance among the medical student of various colleges under Majmaah University. Besides the study also aims to find out its association with the socio-demographic profile of the students and also assess the responsible factors.

Research Methodology

It is a cross-sectional study conducted among 298 students aged 18-25 years studying in various colleges under Majmaah University. In this study simple random sampling method was used where the required sample were randomly selected through excel generated random number.

For the collection of data questionnaire relating to Epworth, sleepiness scale (ESS) was used. The ESS is kind of self-administered questionnaire having total of eight questions relating with eight different activities engaged for falling asleep[6]. The scoring and rating was done to obtain the required results. Besides, an anthropometric measurement for neck circumference was also performed as the part of data collection of the study. The collected data were analyzed using SPSS version 18. For the data analysis, both descriptive and inferential statistics were used wherein interpretation of association was based on the obtained p-value. Before every data collection, participants were informed about the procedure and purpose of the study, followed by obtaining written consent where confidentiality of participants' identity and information were highly ensured.

Results

Among the 298 respondents selected for the study, sixty percent were aged 21-23, followed by the age group 18-20(30%). Less than 10% of the respondent were aged 23 and above. The mean age of the students was 21.9, while the mean height and weight of the student were 165.25 cm and 64.74 kg, respectively. Among 205 students whose data was available, the mean neck circumference of the respondent was 20.45.

Snoring:

In this study snoring among the total respondents was found to be 14%. Detail of snoring among those who snore is given in the **table I**.

According to the **table I** among the respondents who snored, 67% of respondents snored slightly louder than breathing, while 14% responded that they snored as loud as talking. Moreover, 28% of the respondents snored 1-2 times a month, followed by 23% who snored 1-2 times a week, 21% nearly every day. More than half of the respondents (55.8%) reported that changing position actually helps to get relive from snoring, 4.7% who were not relieved of snoring by changing position. Almost two-thirds (72%) of respondents reported that they have not noticed that they quit breathing during their sleep, while 7% of the respondent have noticed that they quit breathing during their sleep nearly every day and 1-2 times a week each. Furthermore, more than half of the respondents (58%) have never woken up in the night due to nasal congestion, followed by 18.6% who woke 1-2 times a month, 9.3% that woke 3-4 times a week, and 7% who woke 1-2 time and 7% nearly every day. Similarly, about half of the respondents (48.8%) have never woken up in the night with sudden breath-holding, gasping, or choking sensation, followed by 32.6% who woke 1-2

times a month, 9.3% that woke 1-2 times a week and 9.3% who woke nearly every day. Among the respondent who reported snoring, one-third of them (74.4%) reported having someone in their family that snored.

Sleep disturbances

According to **table II**, 23.5% of the respondents reported that they feel tired or fatigued after sleep 1-2 times a week, followed by 1-2 times a month (21.8%), nearly never or never (21.8%), 3-4 times a week (16.8%) and nearly every day (16.1%). Similarly, one-fourth of the respondents reported that they nearly never feel tired or fatigued at their waking time while 25.2% reported that they feel tired or fatigued at their waking time 1-2 times a month (25.5%), followed by nearly every day (22.5%), 1-2 times a month (15.4%), and 3-4 times a week (11.4%). About 21.5% of the respondent have nodded off or fallen asleep while driving a vehicle. Among them, 53% reported that this occurs 1-2 times a month, while 32.8% reported nearly never. Approximately 6% of these respondents reported nodding off while driving 1-2 times a week, followed by 4.7% 3-4 times a week, while 3.1% reported nodding off nearly every day.

Table I: Detail of snoring.

Categories	Frequency (n-43)	Percent (%)
Kind of Snoring		
As loud as talking	6	14.0
Louder than talking	2	4.7
Slightly louder than breathing	29	67.4
Very loud - can be heard in adjacent rooms	3	7.0
Not applicable	3	7.0
Frequency of snoring		
Nearly every day	9	20.9
1-2 times a week	10	23.3
3-4 times a week	3	7.0
1-2 times a month	12	27.9
Never or nearly never	9	20.9
Change in the position to relive snoring		
Yes	24	55.8
No	2	4.7
Don't know	17	39.5
Frequency of nasal congestion during sleep		
Nearly every day	3	7.0
1-2 times a week	3	7.0
3-4 times a week	4	9.3
1-2 times a month	8	18.6
Never or nearly never	25	58.1
Frequency of waking up in the night with sudden breath holding ,gasping or choking sensation		
Nearly every day	4	9.3
1-2 times a week	4	9.3
1-2 times a month	14	32.6
Never or nearly never	21	48.8

Table II: Detail of Sleep Disturbance.

Categories	Frequency (n-298)	Percent (%)
Tired or fatigued after your sleep		
Nearly every day	48	16.1
1-2 times a week	70	23.5
3-4 times a week	50	16.8
1-2 times a month	65	21.8
Never or nearly never	65	21.8
Feeling tired and fatigued while waking up		
Nearly every day	67	22.5
1-2 times a week	46	15.4
3-4 times a week	34	11.4
1-2 times a month	76	25.5
Never or nearly never	75	25.2
Fallen asleep while driving a vehicle		
No	234	78.5
Yes	64	21.5
If yes, frequency of its occurrence		
Nearly every day	2	3.1
1-2 times a week	4	6.3
3-4 times a week	3	4.7
1-2 times a month	34	53.1
Never or nearly never	21	32.8

Other Comorbidities

The majority of the respondent did not have high blood pressure, while 6% had high blood pressure and 13.8% did not know. Similar results were seen in Diabetes mellitus, where 92.3% of respondents did not have diabetes mellitus while 2% had Diabetes mellitus and 5.7% did not know. Furthermore, 90% of the respondents had never suffered from cardiac diseases while 2% had and 8.1% did not know.

Factors associated with sleep apnea

The association of factor between the sex of the respondent is shown in above **table III** where significant association was seen between the sex of the respondent and forgetfulness in the daytime (P=0.027). About 41% of female respondents reported forgetfulness in the daytime, while 32.8% of the male respondents reported forgetfulness. The statistical association was also seen between the sex of the respondent and having difficulty in concentrating or focusing on your routine activities (P=0.002). About half of the female respondents (50.5%) reported that they feel forgetful in the daytime, while 35.3% of the male respondent reported the same. Similarly, a significant association was seen between the sex of the respondent and feeling of disorientation with time, place, and person(p=<0.001), where 45.6% of the female respondent reported feeling disoriented on contrary to 23% of male respondents. Association was also seen between the sex of the respondent and feeling of sudden blanking out (p=<0.001). About 60% of female respondents reported that they suddenly blank out, while 36.2% of the

Table III: Association of factors with sex.

Factors	Sex		Total	Chi-Square	P-value
	Male	Female			
Forgetfulness in the daytime					
No	35 (30.2%)	31 (17.0%)	66 (22.1%)		
Yes	38 (32.8%)	75 (41.2%)	113 (37.9%)	7.247	**0.027**
Maybe	43 (37.1%)	76 (41.8%)	119 (39.9%)		
Difficulty concentrating or focusing on your routine activities					
No	44 (37.9%)	36 (19.8%)	80 (26.8%)		
Yes	41 (35.3%)	92 (50.5%)	133 (44.6%)	12.580	**0.002**
Maybe	31 (26.7%)	54 (29.7%)	85 (28.5%)		
Disoriented with time, place, and person					
No	48 (41.4%)	42 (23.1%)	90 (30.2%)		
Yes	27 (23.3%)	83 (45.6%)	110 (36.9%)	17.776	**<0.001**
Maybe	41 (35.3%)	57 (31.3%)	98 (32.9%)		
Sudden blanking out					
No	43 (37.1%)	26 (14.3%)	69 (23.2%)		
Yes	42 (36.2%)	109 (59.9%)	151 (50.7%)	23.746	**<0.001**
Maybe	31 (26.7%)	47 (25.8%)	78 (26.2%)		
Frustrated at a time during your routine activities					
No	34 (29.3%)	14 (7.7%)	48 (16.1%)		
Yes	55 (47.4%)	128 (70.3%)	183 (61.4%)	26.667	**<0.001**
Maybe	27 (23.3%)	40 (22.0%)	67 (22.5%)		

Table IV: Association of factors between Age groups.

Factors	Age			Total	Chi-Square	P-value
	18-20	21-23	>23			
Forgetfulness in the daytime						
No	13 (14.4%)	42 (23.3%)	11 (39.3%)	66 (22.1%)		
Yes	38 (42.2%)	66 (36.7%)	9 (32.1%)	113 (37.9%)	8.165	0.086
Maybe	39 (43.3%)	72 (40.0%)	8 (28.6%)	119 (39.9%)		
Difficulty concentrating or focusing on your routine activities						
No	19 (21.1%)	48 (26.7%)	13 (46.4%)	80 (26.8%)		
Yes	44 (48.9%)	80 (44.4%)	9 (32.1%)	133 (44.6%)	7.021	0.135
Maybe	27 (30.0%)	52 (28.9%)	6 (21.4%)	85 (28.5%)		
Disoriented with time, place, and person						
No	19 (21.1%)	58 (32.2%)	13 (46.4%)	90 (30.2%)		
Yes	39 (43.3%)	67 (37.2%)	4 (14.3%)	110 (36.9%)	10.882	**0.028**
Maybe	32 (35.6%)	55 (30.6%)	11 (39.3%)	98 (32.9%)		
Sudden blanking out						
No	11 (12.2%)	50 (27.8%)	8 (28.6%)	69 (23.2%)		
Yes	54 (60.0%)	85 (47.2%)	12 (42.9%)	151 (50.7%)	9.212	0.056
Maybe	25 (27.8%)	45 (25.0%)	8 (28.6%)	78 (26.2%)		
Frustrated at a time during your routine activities						
No	5 (5.6%)	34 (18.9%)	9 (32.1%)	48 (16.1%)		
Yes	63 (70.0%)	106 (58.9%)	14 (50.0%)	183 (61.4%)	13.843	**0.008**
Maybe	22 (24.4%)	40 (22.2%)	5 (17.9%)	67 (22.5%)		

male respondent reported sudden blank-outs. Moreover, a significant association was seen between the sex of the respondent and feeling of frustration at times during your routine activities (p=<0.001), where 70.3.% of the female respondents and 47.4% of the male respondents reported feeling frustrated during routine activity.

The association of factors and age groups among the student's members of Majmaah University is shown in above **table IV**. Here, disorientation of time, place and time person (p=0.028) was statistically significant with the age group. Almost half (43.3%) of the 18-20 reported feeling disoriented, while only 4.3% of age 23 and more reported disorientation. Similarly, a significant association was seen between the respondent's frustration during routine activities and their age group (p=0.008), where 70% of the students of age group 18-20 reported feeling frustrated during routine activities. Among the ages 21-23, 59% reported feeling frustrated. Similar results were seen in students aged 23 and more, where 50% reported of feeling frustrated during routine activity.

Discussion

In the current study, sleep apnea was seen more in aged group 21-23 years which is also similar as to other study conducted in medical students. Female students are more prone to this condition as compared to male students which are shown similar in other study. In the study conducted in medical Yarmouk University, the height of students 156-165 cm which was not more different than this current study. Similarly height of students who were suffering from disease was 51-60 kg which was different from others[8]. Neck circumstance had significant role in sleep apnea so above 17 inches for a male or 16 inches for a female recommending visit examination[9].

Snoring is the common factor in sleep apnea as reported by several studies. Most of the students snore little more than normal breathing where only 1-2 times in a month snoring happened which disturbed others as reported in similar studies[10]. More than half of the respondent has reported as they change the position of the pillow which also showed that position therapy is good for snoring[11]. As shown is several studies that episodic breathing during sleep is common in sleep apnea which lasts between 10-20 seconds and can happen from 5 to over 100 times per hour[12]. This current study presents that 1-2 times a month people have noticed about the quietness due to breathing but they never wake up due to difficult in nasal congestion during sleep. And also (48.8%) respondent reported that they have never wake up in the night with sudden breath-holding, gasping, or choking sensation. While one-third of the participants told that they have someone in their family that snored.

In this present study the respondents has reported that they are tired or fatigued after sleep 1-2 times per week as well as during waking time, they feel tired, fatigued almost every day which is also similar compare with other studies. Compare to other study they had reported that at least once in their lifetime they had nodded off to sleep while driving while our study population respond they most of them did not experience such thing[10].

One of the study shows that changing in Blood Pressure may likely to contribute in cardiovascular risk in sleep apnea[13] which is seen contrasting in our study. The relationship between OSA and type 2 diabetes may be bidirectional in nature given that diabetic neuropathy can affect central control of respiration and upper airway neural reflexes, promoting sleep-disordered breathing as mentioned in some article but is also not similar in this current study[14]. People with sleep apnea have lower levels of GABA and abnormally high levels of glutamate, according to the study published on 2016[15]. Some researcher found that while comparing mammillary bodies' structure in brain of healthy and sleep apnea patient nearly 20% smaller than in their untroubled counterparts resulting in forgetfulness[16]. These GABA are responsible for person's thinking skill, mood and concentration. Due to imbalance of these chemical in brain people with sleep apnea face problems. Here in this current study female are facing more problem of forgetting, lack of concentration, mood disorder as compared to male which is significant association was seen between the respondent's frustration during routine activities and their age group (p=0.008).

Conclusion

This study concludes that there is prevalence of sleep apnea among the medical student where snoring is one of the major issue. The study also reflected that sleep apnea is not only related to age group but also differs with the sex and due to the sleep disorder individual are usually frustrated and disoriented. So as to improve the physical and mental health regular and timely sleep is highly required for not only medical students but also to every individual. As medical students are seen usually stressed out already due to their academic demands they are more the sufferer. Maintaining healthy lifestyle which includes regular meditation, yoga, exercise, adoption of comfortable sleep position, keeping the sleeping room humid and fresh and avoidance of addictive substances can naturally help to overcome the problem of sleep apnea. Seeking medical help can be the next level solution if the condition worsens.

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Conflict of interest
The authors declare that they have no conflict of interest.

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ORIGINAL

Tuberculosis infection trend over 6 years. A retrospective analysis from 2011 to 2016

Tendencia de la infección por tuberculosis a lo largo de 6 años. Un análisis retrospectivo de 2011 a 2016

Inês Rego de Figueiredo[1], Joana Branco Ferrão[2], Sara Dias[1], Rita Vieira Alves[1], Diogo Drummond Borges[1], Margarida Torres[3], Sara Guerreiro Castro[1], Filipa Lourenço[1], Ana Margarida Antunes[1], Heidi Gruner[1], António Panarra[1]

1. Medicina 7.2, Hospital Curry Cabral, Centro Hospitalar Universitário Lisboa Central (CHULC)
2. Medicina 2.3, Hospital de Santo António dos Capuchos, Centro Hospitalar Universitário Lisboa Central (CHULC)
3. Serviço de Doenças Infecciosas, Hospital Curry Cabral, Centro Hospitalar Universitário Lisboa Central (CHULC)

Corresponding author
Inês Rego de Figueiredo
E-mail: inesregofigueiredo@gmail.com

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Abstract

Introduction: Tuberculosis (TB) remains the leading cause of death from a single infectious agent and a major public health problem in Europe and worldwide. The present study pretends to characterize and evaluate the tendency of TB infections over a 6-year period.
Methods: We performed a retrospective study on patients admitted to a tertiary hospital with tuberculosis, from 2011 to 2016, through electronic medical files' data collection.
Results: We included 591 patients with a peak in 2013, as well as a slight increase in male gender prevalence and length of stay over the 6 years. There was a spike of comorbidities in 2012. A decrease in prevalence in white patients, due to increase in African and Asian was also reported, besides a decline in HIV status, homelessness and IV drugs use. This coincided with an increase in laboratory changes and radiological changes, along with a rise in microbiological resistance.
Discussion: Our data is in line with current health policy reports. It is of utmost importance the effort towards control and elimination of TB, through rapid diagnosis, prompt report and complete treatment.

Key words: Tuberculosis, risk factors, mortality.

Resumen

Introducción: La tuberculosis (TB) sigue siendo la principal causa de muerte por un único agente infeccioso y un importante problema de salud pública en Europa y en todo el mundo. El presente estudio pretende caracterizar y evaluar la tendencia de las infecciones de TB en un período de 6 años.
Metodología: Realizamos un estudio retrospectivo de pacientes ingresados en un hospital de tercer nivel con tuberculosis, desde 2011 hasta 2016, a través de la recolección de datos de historias clínicas electrónicas.
Resultados: Se incluyeron 591 pacientes con un pico en 2013, así como un ligero aumento en la prevalencia de género masculino y la duración de la estancia durante los 6 años. Hubo un pico de comorbilidades en 2012. También se informó una disminución en la prevalencia en pacientes blancos, debido al aumento en africanos y asiáticos, además de una disminución en el estado del VIH, la falta de vivienda y el uso de drogas intravenosas. Esto coincidió con un aumento en los cambios de laboratorio y cambios radiológicos, junto con un aumento en la resistencia microbiológica.
Conclusión: Nuestros datos están en línea con los informes de política de salud actuales. Es de suma importancia el esfuerzo por el control y eliminación de la TB, a través del diagnóstico rápido, el reporte oportuno y el tratamiento completo.

Palabras clave: Tuberculosis, factores de riesgo, mortalidad.

Introduction

Tuberculosis (TB) is an infectious-contagious disease, transmitted between humans through the respiratory route whose etiological agent is *Mycobacterium tuberculosis*[1]. Pulmonary tuberculosis is the most frequent manifestation (~70%) and extrapulmonary TB occurs less frequently[2,3].

Despite misconceptions that TB is a disease of the past it continues to represent a public health threat even though there is an effective/curative treatment. TB is still the leading cause of death from a single infectious agent worldwide since 2007 and was responsible for 1.18 million deaths in 2017[2-4].

It is a major public health problem in Europe and worldwide with a well-established association between public assistance spending, failure of antibiotic treatment and the rise of multidrug TB resistance and mortality. Despite implementation of control measures, active immunization and improvement in the socioeconomic state of the population in the last century have been achieved[3-7].

In Portugal, the incidence in 2018 was 16.6 cases per 100.000 inhabitants, higher in Lisbon (23,7 cases/100.000 inhabitants)[8]. It has been reported an increase in the age of the TB patients, resulting in a reduction of community transmission[8]. Even though in Portugal, unlike other European countries, the majority of cases occurs in native population, the proportion of cases in people born outside of Portugal has increased (19,2% in 2017 and 20,2% in 2018)[8].

The present study pretends, therefore, to characterize and evaluate the tendency in demographic, clinical and radiological features, treatment outcomes and mortality over a period of six years.

Methods

A retrospective study on patients admitted to a tertiary hospital from 2011 to 2016, with a tuberculosis (TB) infection diagnosis, was performed. Inclusion criteria were age over 18 years old and an ICD-9 code for TB (010-018). Considering the retrospective nature of the work, ethical approval was waivered.

A revision of the electronic medical record was performed to obtain demographic data, length of stay, comorbidities (according to the Charlson Index), race (white, African and Asian) and risk factors for TB (HIV infection, immunosuppression, direct contact with patient with TB, homeless status or resident in a health care facility, intravenous drug use and health care professional status). TB was characterized according to site (lung, disseminated, etc), previous infection and clinical (local and systemic symptoms), analytical (leucocytes values higher than $11x10^9$/L and below $4,5x10^9$/L, and C-reactive protein (CRP)>5mg/mL, erythrocyte sedimentation rate (ESR)>16mm/h and hyponatremia<135mmoL) and radiological features (any of the TB radiological presentations was considered), microbiological isolate (and which), as dichotomous variables (presence/absence). Outcomes were in-hospital mortality, antibiotic complications and microbiologic resistance and were assessed for each year (2011-2016).

Data was analyzed as non-normal with median and Interquartile range (IQR). Trends throughout the years were evaluated by linear regression for continuous normal outcomes, test for trend for continuous non-normal variables, and standard correlation for the binary outcomes. A p-value of <0.05 was considered to be significant. Analysis was conducted in Stata (StataCorp. Stata statistical software: release 14. College Station, TX: StataCorp LP).

Results

A total of 591 patients were included, with a significant peak in 2013 (min 15- max 20%, p-value=0.001). Age was apparent stable over the years (42-48 median age, p-value=0.7). Although not statistically significant, there was a slight increase in male gender prevalence (65-79%, p-value=0.09), and length of stay (23-29 days, p-value=0.07). There was a trend with a peak of comorbidities by Charlson index score in 2012 (2-6, p-value=0.01) as well as a significant decrease in prevalence in white patients (from 80% to 52%) due to an increase in African (16%-38%) and Asian (3%-10%) (p-value=0.001). (**Table I**)

Regarding risk factors, there was a decrease in frequency regarding HIV status (from 34% to 23%, p-value=0.02), homelessness state (from 15% to 3%, p-value=0.005) and the use of IV drugs (from 19% to 3%, p-value=0.02). No tendency was observed in health care facility users or workers, direct contact with Tb patient or immunosuppression, regardless of the cause. (**Table I**)

Considering TB infection characteristics, there was an increase in laboratory changes detected (from 51% up to 98%, p-value=0.001) and in radiological changes (from 85% up to 99%, p-value<0.001). There was no difference regarding TB site, previous infection status, systemic or local symptoms or specimen positivity. (**Table II**)

As for clinical outcomes, there was a trend noticed, only in microbiological resistance with a significant increase from 5% up to 19% (p-value=0.02). No trend in treatment complications or mortality was found. (**Table III**).

Discussion

Mycobacterial infections have co-evolved with humans for thousands of years.

Table I: Demographic data and risk factor distribution: A total of 591 patients were included, which had a significant peak in. Age was apparent stable over the years. Although not statistically significant, there was a slight increase in male gender prevalence, and in length of stay. There was a trend with a peak of comorbidities by Charlson index score in) as well as a significant decrease in prevalence in white patients due to an increase in African and Asian patients. It was observed a decrease in frequency regarding HIV status, homelessness state and the use of IV drugs. No tendency was observed in health care facility users or workers, direct contact with TB patient or immunosuppression, regardless of the cause.

Demographics	2011	2012	2013	2014	2015	2016	Total	p-value
Age (median, IQR)	43 (34-52)	48 (38-58)	43 (36-55)	44,5 (32-56)	42 (34-56)	44,5 (34-57,5)	44 (35-56)	0.7
Gender (male)	62 (65%)	66 (72%)	90 (74%)	82 (75%)	67 (79%)	65 (74%)	432 (73%)	0.09
Lenght of stay (median, IQR)	23 (13-38)	28,5 (15,5-43)	28 (14-48)	28 (16-48)	29 (16-52)	27 (16-50)	27 (15-47)	0.07
Chalrson index (median; IQR)	3 (0-7)	6 (1,5-8)	5 (1-6)	2 (0-6)	3 (0-8)	2 (0-6)	3 (0-6)	0.01
Race								
White	73 (80%)	61 (66%)	88 (74%)	80 (73%)	48 (64%)	41 (52%)	391 (69%)	0.001
African	15 (16%)	25 (27%)	28 (24%)	24 (22%)	21 (28%)	30 (38%)	143 (25%)	
Asian	3 (3%)	6 (7%)	3 (2,5%)	6 (5%)	6 (8%)	8 (10%)	32 (6%)	
Risk factors	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**Total**	**p-value**
HIV status	32 (34%)	38 (41%)	44 (36%)	23 (21%)	30 (35%)	20 (23%)	187 (32%)	0.023
Homelessness status	14 (15%)	8 (9%)	12 (10%)	6 (5%)	7 (8%)	2 (3%)	49 (8%)	0.005
Health care facility user	1 (1%)	4 (4%)	6 (5%)	0 (0%)	4 (5%)	0 (0%)	15 (2,5%)	0.4
IV drugs user	18 (19%)	10 (11%)	28 (23%)	15(14%)	15 (18%)	3 (3%)	89 (15%)	0.02
Health care worker	2 (2%)	1 (1%)	0 (0%)	1 (1%)	1 (1%)	1 (1%)	6 (1%)	0.6
Direct contact	6 (6%)	7 (8%)	14 (12%)	18 (16%)	9 (11%)	10 (11%)	64 (11%)	0.1
Immunosuppression	18 (19%)	19 (21%)	32 (26%)	25 (23%)	13 (15%)	14 (16%)	121 (21%)	0.3
Immunosuppresion cause								0.9
Autoimmune Disease	3 (18%)	0 (0%)	2 (6%)	0 (0%)	0 (0%)	0 (0%)	5 (4%)	
Immunosuppressive drugs	1 (6%)	0 (0%)	1 (3%)	0 (0%)	1 (8%)	0 (0%)	3 (2%)	
Diabetes	5 (29%)	10 (53%)	10 (31%)	12(46%)	7 (54%)	7 (50%)	51 (42%)	
Cancer	5 (29%)	4 (21%)	14 (44%)	9 (34%)	3 (23%)	6 (43%)	41 (34%)	
Hemodialysis	1 (6%)	1 (5%)	4 (13%)	0 (0%)	2 (15%)	0 (0%)	8(7%)	
Solid organ transplant status	2 (12%)	4 (21%)	1 (3%)	5(19%)	0(0%)	1(7%)	13(11%)	
Total	95 (16%)	92 (16%)	121 (20%)	110 (19%)	85 (14%)	88 (15%)	591	0.001

Table II: TB infection characteristics: There was an increase in and in radiologic changes. There was no difference in TB site, previous infection status, systemic or local symptoms or specimen positivity.

TB infection	2011	2012	2013	2014	2015	2016	Total	p-value
TB site								
Lung	67 (70%)	68 (74%)	86 (71%)	79 (72%)	68 (80%)	69 (78%)	437 (74%)	0.1
Other	28 (30%)	24 (26%)	35 (29%)	31 (28%)	17 (20%)	19 (22%)	154 (26%)	
Previous infection	12 (13%)	17 (18%)	27 (22%)	28 (25%)	15 (18%)	9 (9%)	107 (18%)	0.6
Systemic symptoms	79 (83%)	69 (76%)	117 (97%)	91 (83%)	66 (79%)	83(94%)	505 (85%)	0.1
Local symptoms	84 (88%)	68 (75%)	117 (97%)	98 (89%)	69 (82%)	81 (92%)	517 (88%)	0.2
Laboratory changes	71 (76%)	46 (51%)	117 (98%)	92 (84%)	54 (65%)	83 (94%)	463 (79%)	0.001
Radiological changes	85 (89%)	78 (85%)	117 (98%)	109 (99%)	78 (93%)	87 (99%)	554 (94%)	<0.0001
Specimen positivity	81 (85%)	87 (95%)	101 (83%)	100 (91%)	76 (90%)	84 (95%)	529 (90%)	0.07

Table III: Clinical outcomes: Only in microbiological resistance was a trend observed with a significant increase. No trend in treatment complications or mortality was noted.

Outcomes	2011	2012	2013	2014	2015	2016	Total	p-value
Microbiological resistance	5 (5%)	8 (9%)	8 (7%)	8 (7%)	14 (19%)	15 (17%)	58 (10%)	0.002
Treatment complications	8 (8%)	14 (15%)	23 (19%)	13 (12%)	20 (24%)	12 (14%)	90 (15%)	0.1
In-admission mortality	8 (8%)	4 (4%)	13 (11%)	7 (6%)	2 (2%)	5 (6%)	39(7%)	0.2

This infectious disease is generally transmitted through aerosols, although preventable and curable, remains to date a major public health problem and is one of the most common opportunistic infections in people living with HIV (PLHIV)[9,10].

Tuberculosis disease is a contagious infection that untreated or improperly treated has a significant fatality. WHO estimated that, in the last two decades, there has been a progressive increase in the number of cases of tuberculosis across the globe, due to an increase in incidence of human immunodeficiency virus (HIV), low economic status of nations, migration and emergence of resistant strains of tuberculosis bacillus[11]. 8-9 million people develop the disease per year, and approximately two million people die[10,11].

Since TB resurgence peaked in the 90s, our data shows a steady number of reported cases although following a downward slope trend throughout the years.

This decrease in reports can be explained by the impact of financial and clinical resources to assist national and local TB control efforts, wider screening, and preventive therapy for high-risk populations and growing support for TB prevention programs among HIV-infected persons[9].

Comparing to the WHO Global TB report, we confirm the same increase in the number of cases in foreign born populations[8,9], with significant decrease in prevalence in white patients (from 80% to 52%) due to an increase in African (16%-38%) and Asian (3%-10%). Migrants have several risk factors that make them more susceptible to

this disease. The migration process itself is complex, and a constant changing social phenomenon that can generate new social scenarios making the chains of transmission less predictable. The data analysis tends to reflect the sub-lineages prevalent in the patients' home countries, which suggests that they either brought their strains with them as latent infections, or acquired them in Portugal through social contact with people from their native country[12,13]. It is important to see that the increase in the influx of immigrants into Portugal from high TB incidence countries may be a determinant for the persistence of TB locally[13].

Taking in consideration widely known risk factors for TB, our study reported only a decrease in frequency regarding HIV status, homelessness state and the use of IV drugs. These data may reflect as stated previously the political, financial and social efforts in place in our country to reduce poverty, improve access to medical care and screening programs and also the national program against drug use.

TB as a clinical entity is the result of an immune imbalance. Immunological insufficiency may depend on different clinical factors, namely the presence of comorbidities such as diabetes mellitus[10]. We do report a trend with a peak of comorbidities by Charlson index score in 2012, reflecting the wider range of population affected by this disease and the need for proper screening programs amongst those with chronic diseases who have an increased risk for immunological insufficiency.

The increasing load of comorbidities is not only conditioning the tuberculous infection but it may also impact the morbidity and mortality amongst those infected.

Taking in consideration TB infection characteristics, there was an increase in laboratory changes detected (from 51% up to 98%) and in radiological changes (from 85% up to 99%), reflecting the raised suspicion for the diagnosis in an earlier stage and a more accurate use of adequate diagnostic tests.

In line with the decline of HIV positive patients and immune compromised patients in our sample, there was no difference in TB site with a higher prevalence of pulmonary forms of disease. The same trend was noticeable in the inaugural symptoms and systemic manifestations which didn't differ from previous data collected in other studies at our center.

While analyzing clinical outcomes, the noteworthy data goes to the increase in microbiological resistance (from 5% up to 19%), keeping in mind the previous data about immigration and resurgence of cases in foreign born patients, this can be an explanation for the emerging number of resistant strains among the population of our study.

Maintaining the decline in TB morbidity and aiming towards the goal of eliminating TB requires sustained prevention and control efforts, especially rapid diagnosis, ensured completion of treatment, and prompt and complete reporting. Furthermore, establishing tuberculin-screening programs that target patients at higher risk may ensure the appropriate use of preventive therapy.

Disclosures

The paper authors have no actual or potential conflict of interests.

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Conflict of interest

The authors declare that they have no conflict of interest.

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ORIGINAL

Examining the effect of the dimensions of Islamic management on clinical care

Examinar el efecto de las dimensiones de la gestión islámica en la atención clínica

Fatemeh Mirparsa[1], Abasat Mirzaei[2,3]

1. Midwifery undergraduate and master student of Health Services Management, Department of Health Services Management, Faculty of Health, Tehran, Medical Sciences, Islamic Azad University, Tehran, Iran 2. Associate professor, Department of Health Care Management, Faculty of Health, Tehran Medical Science, Islamic Azad University, Tehran, Iran 3. Farhikhtegan Medical Convergence sciences Research Center , Farhikhtegan Hospital Tehran Medical sciences ,Islamic Azad University,Tehran,Iran

Corresponding author
Abasat Mirzaei
E-mail: amacademic@yahoo.com

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Abstract

Background: The complete patient care approach refers to providing services for all the needs of patients, including physical, mental, social, and spiritual needs, which means total patient management. The present study aimed to examine the effect of dimensions of Islamic management on patients' clinical care by nurses.
Methods: This study was conducted in hospitals of Sistan and Baluchestan provinces. The research sample was selected using the census technique, with the sample size being as large as the 2859 Nurse individuals. The data collection tool had three main components: managers' faith, knowledge, adequacy, and ability with 40 indices.
Results: The findings showed that the effect of the components mentioned above, i.e., managers' faith, knowledge, adequacy, and ability in the clinical care of patients, were statistically significant (P <0.001). In prioritizing the impact of the manager's faith in the patients' clinical care, the participants prioritized righteousness and piety based on the p-value (0.99). Also, among the indicators of managers' knowledge, they chose managers' familiarity with motivation and leadership as the first priority (0.95). Finally, about the component of managers' adequacy and ability, they prioritized the managers' decision-making ability based on the p-value (0.88).
Conclusion: Implementing the dimensions of Islamic management has a positive influence on patients' clinical care. Hospital managers must employ different dimensions of Islamic management to improve clinical care in the health care system.

Key words: Hospital management, clinical care, islamic management.

Resumen

Antecedentes: El enfoque de atención completa al paciente se refiere a la prestación de servicios para todas las necesidades de los pacientes, incluidas las físicas, mentales, sociales y espirituales, lo que significa una gestión total del paciente. El presente estudio tenía como objetivo examinar el efecto de las dimensiones de la gestión islámica en la atención clínica de los pacientes por parte de las enfermeras.
Métodos: Este estudio se realizó en hospitales de las provincias de Sistán y Baluchistán. La muestra de la investigación se seleccionó mediante la técnica del censo, y el tamaño de la muestra fue de 2859 enfermeras. El instrumento de recogida de datos tenía tres componentes principales: la fe de los gestores, los conocimientos, la adecuación y la capacidad con 40 índices.
Resultados: Los resultados mostraron que el efecto de los componentes mencionados anteriormente, es decir, la fe, el conocimiento, la adecuación y la capacidad de los gestores en la atención clínica de los pacientes, eran estadísticamente significativos (P <0,001). Al priorizar el impacto de la fe del gestor en la atención clínica de los pacientes, los participantes priorizaron la rectitud y la piedad, según el valor p (0,99). Asimismo, entre los indicadores de los conocimientos de los gestores, eligieron como primera prioridad la familiaridad de los gestores con la motivación y el liderazgo (0,95). Por último, sobre el componente de adecuación y capacidad de los directivos, priorizaron la capacidad de decisión de los directivos en base al valor p (0,88).
Conclusión: La aplicación de las dimensiones de la gestión islámica influye positivamente en la atención clínica de los pacientes. Los gestores de los hospitales deben emplear las distintas dimensiones de la gestión islámica para mejorar la atención clínica en el sistema sanitario.

Palabras clave: Gestión hospitalaria, atención clínica, gestión islámica.

Introduction

Islamic management is the science and art of properly using individuals and facilities to fulfill organizational goals that do not contradict religious standards[1].Given this definition, the word Islam in the term "Islamic management" is a structure that combined a single concept called "Islam" and a less complex structure called "management"[2]. The combination of management and Islam highlights the difference between this type of management and other types of management specifications. The science of management is a reality that is realized at a certain time and place. The objective realization of this knowledge is related to its time properties and culture. Although management, in its general sense, has a long history at this age, management is a product of the increasing post-WWII awareness on the importance of quality of management and its impact on the modern lives of human beings. Due to this significance, management has been widely analyzed and studied, and its environment and techniques have been examined in detail[3]. Islamic management has long attracted the attention of those who whole-heartedly believe in Islam. Accordingly, many have attempted to recognize and introduce this crucial phenomenon[4]. Islamic management is a set of interrelated precise and accurate propositions or concepts derived from Islamic sources concerning managing people and resources in a society or an organization to meet predetermined goals. This definition aims to develop an Islamic management ethical system based on propositions carrying cohesive and accurate meanings and concepts. Such propositions guide and determine the quality of employing humans as the most important element and using other material facilities in achieving specific goals[5]. An important point about Islamic management is that the essential existence of this structure must be different from other structures. This type of management is not called Islamic management due to its similarities with other types of management. Still, its differences make it unique and give it a special and distinctive nature[2]. One of the most important Islamic teachings that have been mentioned in the Hadith of Shorine is that the moral principles of Islam must be taken into account in all stages of making and implementing decisions. Islamic teachings must be used to complement the science of Islamic value management and extract Islamic management in its truest form[6]. By considering Islamic moral principles, management can decide what is right and wrong, who moves towards the organization's goals, and who is not. Thus, managers cannot act with certainty in performing their tasks, such as decision making, evaluation, monitoring, encouraging, and punishing their employees[7]. In this regard, many people have tried to look at Islamic management issues from their point of view[4]. For this reason, there are many approaches to addressing Islamic management. In the holy religion of Islam, providing health services to patients is a kind of humanitarian duty, and Muslims shall never be indifferent to it[8]. They must know that this is one of their obligations as a servant of God to preserve the integrity and value of other human beings. Protecting the human personality of patients in terms of faith, culture, moral standards, and beliefs is quite important when it comes to their recovery[9]. In regards to medical law, Imam Ali (AS) states: "Whoever deals with medical services shall have faith in God and do their best to serve and teach others to do so as well"[10]. In addition, Imam Sadegh (AS) says: "There are two kinds of people, those who are suffering from an illness and those who are completely healthy. Hence, the latter must be kind to the former, treat them with compassion, and thank God for their health"[11]. Nowadays, addressing quality and assessing it has attracted much attention in health care and nursing systems[12]. Furthermore, nursing is the most crucial issue in the health care systems[13]. Patients' satisfaction with care services is one of the most important factors to consider when assessing the quality of clinical care and its implementation[14]. Given the fact that nurses provide the most significant health care services to patients[15], the ultimate goal of nursing services is providing high-quality care to improve the outcomes of the care both for patients and society[16]. They believe that factors such as lack of access to resources, shortage of knowledge, and lack of adequate support for managers prevent evidence-based performance[17]. Additionally, a qualitative study has examined the nurse's viewpoint regarding the conditions that strengthen or prohibit evidence-based care. According to the findings of this study, there were four main obstacles when it came to providing evidence-based care, including non-applicable studies on nursing, nurses' inability to obtain and assess research evidence, lack of time, and lack of support from the organization[18]. However, according to previous studies in the field of quality of nursing services and patients' satisfaction, this goal has yet to be met despite the many attempts that have been made[19]. Therefore, it is necessary to examine the effective factors and the obstacles faced by nurses to achieve evidence-based performance to be able to provide effective solutions for such problems that are compatible with the local conditions. In recent years, various questionnaires have been designed to investigate the perceptions of the health care system employees of evidence-based care and the factors affecting them[20-22]. However, low levels of responsiveness, the inability of these questionnaires to explore the issue deeply and examine some of these concepts, and the artificiality of these obtained data have been the reasons why the findings of such studies have not been comprehensive[23]. Besides, nurses face complex situations when it comes to health care services resulting from complicated illnesses and changes in ethical and cultural factors. Accurate clinical decision-making regarding nurses' practices leads to a logical development of health care services that are most likely to succeed[24]. In this respect, the importance of spirituality in the physical life of humans has grabbed the attention of many health care experts over the past decades. They have realized that using modern methods and

technologies that have become known as the traditional tools of the science of medicine alone does not respond to all aspects of caring for patients, preventing illnesses, and patients' recovery. For this reason, nowadays, one of the most important discussions in health care studies is the scientific examination of the role of spiritual health[25]. Medical errors and safety failures in the intensive care unit are doubled when the illness is chronic and when there is an improper interaction between clinical groups. Lack of effective communication and organized coordination between members of the clinical group of the ICU can lead to serious and harmful errors in the treatment process of patients. Such errors are usually difficult to identify and extract since the patients are unconscious[26]. There has yet to be a study on the impact of Islamic management on clinical care from the perspective of nurses. Also, due to clinical problems, the importance of this issue and the serious responsibility of managers and nurses in proper clinical care is known now more than ever. Thus, the present study aims to investigate the effect of Islamic management dimensions on clinical care from nurses' viewpoint. Therefore, this research seeks to answer the following question: from the perspective of nurses, does Islamic management impact clinical care?

Materials and methods

This research was a descriptive-analytical study, an applied study regarding its objective, and cross-sectional research in terms of the research implementation time. This study was conducted in hospitals of Sistan and Balouchestan province in 2020. Totally, 2859 nurses were working at these hospitals. They were undergraduates and graduates working at different departments of the said hospitals. The statistical population of this study consisted of these nurses (2895), all of whom were selected as the research sample size using the census technique. The surveyed nurses had different backgrounds, educations, and occupations. All of them could participate in the study knowing that their information would remain confidential. They were also asked to express their consent concerning their participation in this study. As for the inclusion criteria, the participants had to have worked at a hospital for over a year and must fill out and sign a consent form. The gender of the nurses was not important. Regardless of gender, those nurses that did not qualify or were not present in their working shifts were excluded from the study. As a result, 317 nurses were eliminated from the sample, and ultimately, 2542 nurses took part in the study. A researcher-designed questionnaire was used to collect the necessary data. The said questionnaire aimed to examine the effect of different dimensions of Islamic management on clinical care from the perspective of nurses. It was scored using the five-point Likert scale, had forty indicators and three components. There were nineteen, ten, and eleven indicators associated with managers' faith, knowledge, and adequacy and ability, respectively. This questionnaire contained a primary part associated with demographic specifications, such as age, gender, education, occupational history, and work shift of the participants.

There is also some information regarding the objectives of the study and the confidentiality of the information provided by the respondents on the initial pages of the distributed questionnaires. It should be noted that Cronbach's alpha coefficient for the questionnaire was 0.879. The validity of the said questionnaire was measured using face and content validity, meaning that various information sources were studied, and the supervisor and some other professors and experts were asked to comment on this instrument. Descriptive and inferential statistics were used to analyze the collected data. Descriptive statistics were used to examine the condition of the research sample and describing it. Also, parameters such as percentage of frequency, mean, and mode were used in different tables and the Kruskal Wallis test to determine the p-value and prioritization of the research variables. Moreover, SPSS software version 25 was used to analyze the collected data.

Results

In the present study, to examine the effect of different dimensions of Islamic management in clinical care from the perspective of nurses, three components of Islamic management were studied, including managers' faith, managers' knowledge, and managers' adequacy and ability. Eleven, ten, and nineteen indicators were included in the questionnaire to represent each of these components, respectively. Then, the effect of each of these indicators on clinical care was reviewed from the viewpoint of nurses. Out of the 2859 nurses working at the Sistan and Balouchestan province hospitals, who initially composed our sample size, 2542 nurses (88.91%) filled out the questionnaire. The mean and standard deviation of the age of the participants was 37.5±6.2 years, and the mean of their occupational history was 21.8 years. Most of the surveyed individuals were female. Out of the participants, 91.3% had a bachelor's degree, 55.6% worked shifts, and 47.3% had between 10 and 20 years of work experience. **Table I** showed basic information about the participants.

The results obtained from the Kruskal Wallis test suggested a significant relationship between the component of managers' faith and patients' clinical care from the perspective of nurses ($P<0.001$). In prioritizing the impact of the manager's faith in the patients' clinical care, the participants prioritized righteousness and virtue based on the p-value (0.99). **Table II** showed the effect of managers' faith on clinical care from the viewpoint of nurses.

Table I: Basic information about research participants.

Variable	Item	Frequency	Percentage of frequency	mean	Mode
Age	To 30 years old 31 to 40 years old Over 40 years old	511 1060 971	20.1 41.7 38.2	37.5	-
Gender	Men Women	819 1723	32.2 67.7	-	Women
Education Level	Associate Undergraduate Graduate	0 2321 221	0 91.3 8.7	-	Undergraduate
Experience	Below 5 years 5 to 10 years 10 to 20 years Over 20 years	307.5 683.7 1202.6 348.2	12.1 26.9 47.3 13.7	21.8	-
Shift Schedule	Rotating Morning Evening Night	1413.5 882.0 73.7 172.8	55.6 34.7 2.9 6.8	-	Rotating

Table II: P-value and prioritization of the effect of managers' faith on clinical care from the viewpoint of nurses.

Managers' faith	p-value (priority)	Kruskal-Wallis Test (p<0.001)
Righteousness and virtue	0.99 (1)	p<0.001
Paying attention to prayer	0.98 (2)	P=0.410
Godliness	0.96 (3)	P=0.420
Trust in God	0.95 (4)	P=0.180
Justice and fairness	0.93 (5)	P=0.025
Respecting the rights of other religions	0.91 (6)	P=0.032
Respecting the rights of others	0.90 (7)	P=0.036
Generosity	0.88 (8)	P=0.028
Responsibility and accountability	0.85 (9)	P=0.210
Commitment to responsibilities	0.84 (10)	P=0.156
Hoping for divine reward and fearing divine punishment	0.82 (11)	P=0.030
Benevolence	0.81 (12)	P=0.035
Good history	0.79 (13)	P=0.018
Controlling anger	0.77 (14)	P=0.024
Humility	0.76 (15)	P=0.015
Authoritarianism and kindness	0.75 (16)	P=0.175
Moderation	0.74 (17)	P=0.155
Trust and confidentiality	0.72 (18)	P=0.133
Ambition	0.71 (19)	P=0.015

Table III: P-value and prioritization of the effect of managers' knowledge on clinical cares from the viewpoint of nurses.

Managers' knowledge	p-value (priority)	Kruskal-Wallis Test (p<0.001)
Familiarity with the science of motivation and leadership	0.95 (1)	P<0.001
Knowledge and awareness of divine commands	0.93 (2)	P=0.330
Familiarity with specialized knowledge	0.92 (3)	P=0.410
Familiarity with technical skills	0.90 (4)	P=0.180
Familiarity with perceptual skills	0.87 (5)	P=0.165
Familiarity with expertise in human and communication skills	0.85 (6)	P=0.200
Familiarity with the science of planning (operational and strategic)	0.83 (7)	P=0.045
Familiarity with the skill of problem diagnosis and analysis	0.81 (8)	P=0.155
Familiarity with the science of controlling the situation (monitoring and evaluation)	0.79 (9)	P=0.015
Familiarity with the science of organization	0.76 (10)	P=0.020

Table IV: P-value and prioritization of the effect of managers' adequacy and ability on clinical care from the viewpoint of nurses.

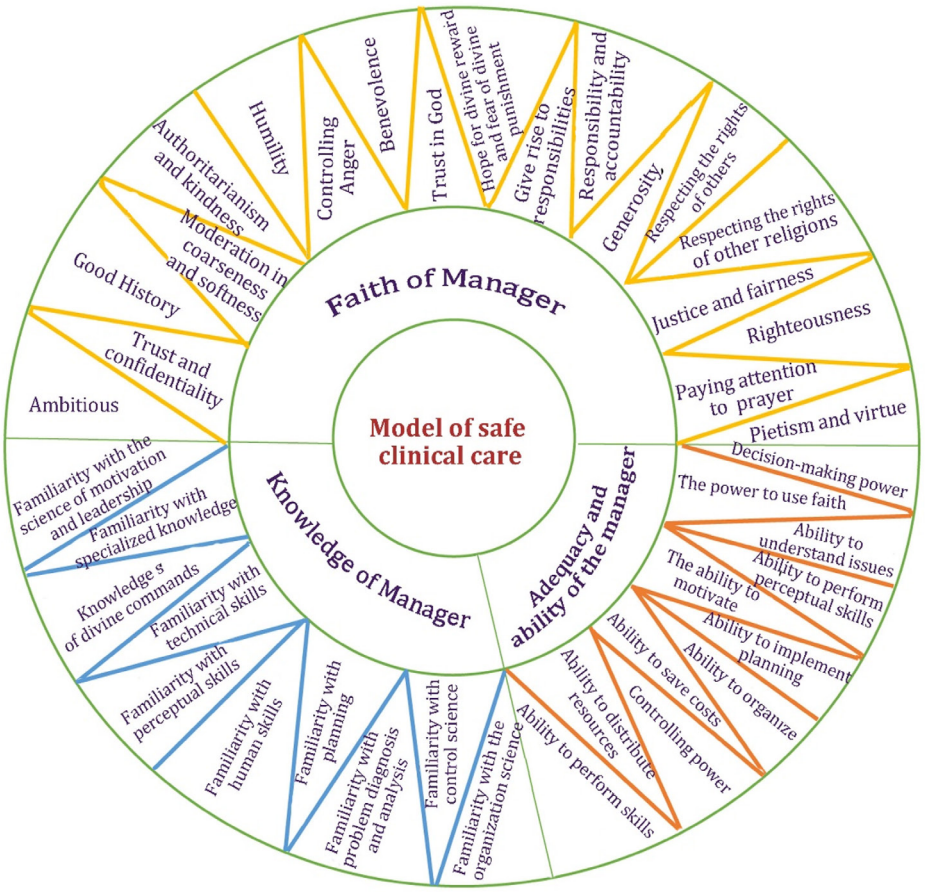
Adequacy and ability of the manager	p-value (priority)	Kruskal-Wallis Test (p<0.001)
The ability to make decisions about responsibilities	0.88 (1)	P<0.001
The executive managers' ability to utilize their faith and skills	0.86 (2)	P=0.342
The ability to understand issues and problems associated with responsibilities	0.84 (3)	P=0.200
The ability to implement perceptual skills	0.83 (4)	P=0.065
The ability to motivate people	0.81 (5)	P=0.410
The ability to implement plans (operational and strategic)	0.79 (6)	P=0.143
The ability to organize and coordinate responsibilities	0.78 (7)	P=0.165
The ability to enhance cost-effectiveness	0.76 (8)	P=0.025
The ability to control (monitoring and evaluation)	0.75 (9)	P=0.030
The ability to distribute resources (human and equipment)	0.72 (10)	P=0.055
The ability to execute human skills	0.70 (11)	P=0.157

The surveyed nurses' prioritization of the effect of managers' knowledge on patients' clinical care based on the p-value was as follows: familiarity with the science of motivation and leadership, knowledge and awareness of Islamic teachings and principles, specialized knowledge of their occupation, familiarity with technical skills and expertise, familiarity with perceptional skills, expertise in the field of human and communication skills, familiarity with planning, expertise in diagnosis and analysis of situations, ability to control, and organizational skills. Therefore, among the indicators of managers' knowledge, they chose managers' familiarity with motivation and leadership as the priority (0.95). It was also found that the component of managers' knowledge had a positive and significant effect on patients' clinical care (P<0.001). **Table III** showed the p-value and prioritization of the effect of managers' knowledge on clinical care from the viewpoint of nurses.

The surveyed nurses' prioritization of the effect of managers' adequacy and ability on patients' clinical care based on the p-value was as follows: the ability to make decisions regarding tasks, the ability of executive managers to use faith and expertise, the ability in understanding the issues and problems associated with the responsibilities, the ability to execute perceptional skills, the ability to motivate people, the ability to execute the set plans, the ability to organize and coordinate affairs associated with the responsibilities, the ability to reduce the expenses, the ability to control, the ability to distribute the resources, and the ability to execute human skills. Among the indicators of managers' adequacy and ability, the nurses chose managers' ability to prioritize the responsibilities (0.88). It was also found that the component of managers' adequacy and ability had a positive and significant effect on patients' clinical care (P<0.001). **Table IV** showed the p-value and prioritization of the effect of managers' adequacy and ability on clinical care from the viewpoint of nurses.

Figure 1 showed the secure clinical care model. This model provides a framework of skills and behaviors that could affect the quality of the nurses' performance in providing safe and secure clinical care to patients. In this article, the model mentioned above was introduced, which would suggest several ways to provide safe and secure clinical care services to patients.

Figure 1: Model of Safe clinical care.



Discussion

Hospitals are among the organizations with the most specialized employees. Therefore, identifying the dimensions of Islamic management and employing them in the patients' clinical care could enhance the success of this organization. Thus, the present study aimed to examine and discuss the components of managers' faith, knowledge, and adequacy and ability as various dimensions of Islamic management.

The component of managers' faith:
The first component was the managers' faith which was divided into 19 indicators. All of the indicators were effective in the clinical care provided for the patients by nurses. According to the research findings, the component of managers' faith had the greatest impact on the patients' clinical care. Therefore, it must be the priority as far as a manager's characteristics are concerned. Other studies showed that an Islamic manager's first and most important characteristic must be faith and belief in God[27]. Research showed that faith guaranteed a manager's success whenever faced with complicated situations as it affected other indicators. This characteristic could reduce the managers' efficiency and productivity. However, it might also have completely different results and lead to the desired result[28]. The latter was consistent with the findings of the present study. In terms of managers' faith, nurses found righteousness and virtue (0.99) priority. This variable had a positive and significant impact on the patients' clinical care. Righteousness is one of the most important components of value in the Holy Quran[29]. The holy Prophet said: divine piety shall be above all[30], if we practice righteousness, God will be with us above all else[31], and we will be saved[32], our journey to heaven is paved by righteousness[33], and God will light our way to righteousness[34], and we will find our way out of problems and complications[35], and we can get through anything[35]. Shafiee et al. have mentioned piety as one of the features of successful and effective leaders in discussing leadership in their book organizational behavior with an Islamic approach[36]. Studies have also shown that piety impacted the management style employed by the managers the increase of employees' efficiency[37]. These findings are consistent with the findings of the present study.

The second component was the managers' knowledge which was divided into ten indicators. In the study by Barati et al., the manager's knowledge was one of the most mentioned concepts in most interviews, and people believed that a hospital manager must be aware of current scientific issues and have sufficient knowledge in all areas and domains related to hospitals[38]. Indeed, God almighty forbade his servants from doing work they have no knowledge of in Surah Asra, verse 36. The necessity of such a principle is even more apparent and significant for a profession like medical workers, as they work with human lives[39]. The study of Rivkani in this field showed that although 70% of hospital managers had passed the training course for administrating hospital affairs, not all had adequate management experience and knowledge[40]. In terms of the component of manager's knowledge, the highest priority was familiarity with the science of motivation and leadership (0.95). Nurses believed that this variable had a positive and significant effect on the patients' clinical care (P<0.001). Mohsen Adib Haj Bagheri et al. also reported that lack of motivation hindered applying the theoretical knowledge of nurses in clinical care[41]. These findings complied with the quotations from studies conducted in various countries[42,43]. In Bass's opinion, a transformational leader was someone who motivated his/her employees to do something in a better way than they would normally do[44]. The present study showed that motivation led to safe and secure clinical care. Another study showed that reinforcing the motivation of employees and physicians pushed them towards fulfilling the predetermined goals[43].

The third component was the adequacy and ability of the manager, which was divided into 11 indicators. A study by Spritzer and Donson showed that empowering managers improved their performance, effectiveness, commitment to the organization, effective problem solving, and greater coordination of tasks[45]. Besides, in a study conducted by Blanchard and Zigarmi, managers' empowerment has been introduced as a strategy to affect the performance and improvement of human resources[46]. In a study by Kongor and Kanongo, it was shown that there were some organizations whose present and future depend on having committed and specialized human resources. Such organizations required competent enough managers, possessed the essential characteristics for a manager, and were able to enhance the efficacy and efficiency of their organization and human resources[47]. In terms of the manager's adequacy and ability, the highest priority was given to the manager's decision-making ability (0.88). Nurses believed that this variable significantly affected the patients' clinical care (P<0.001). In the study by Bowen et al., it was found that effectively and efficiently surviving in an organization depended entirely on the managers' principled and accurate decision-making[48]. The adequate style of decision-making employed by the manager was a crucial factor in the success of the manager and the organization's effectiveness[49]. Research has shown that making wrong decisions could irreparably destroy an occupation or an organization[50]. In this study, each of the components mentioned above and indicators was related and connected. Therefore, all of them must be taken into consideration altogether.

Given the three components of Islamic management, it could be concluded that managers that had faith in God considered themselves in the presence of God at all times and treated others fairly. The second component of Islamic management was the knowledge of the manager. Based on Islamic principles, the individuals who take on managing

an organization must be simultaneously faithful and knowledgeable. Knowledge and science were the tried and true experiences. Hence, managers' performance must not be just experience-based. For instance, the hospital personnel, including nurses, were expected to update their knowledge and utilize it in clinical care; otherwise, their skills in providing safe and secure clinical care would be gradually weakened. The Prophet also said in this regard: Whoever does something without knowledge, he will be more corrupted than fruitful[51]. In Islamic management, in addition to faith and knowledge, the adequacy and ability of the manager in managing the organization were also required. Adequacy refers to a special ability and prominence that combines faith and knowledge outside the mind and turns into something objective[52].

Conclusion

Therefore, hospital managers are expected to improve the clinical care of patients in the health system by using the dimensions of Islamic management. In this regard, it is suggested to explain the importance of applying various dimensions of Islamic management in clinical care and holding educational training for senior, line, and operational managers and employees.

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Conflict of interest
The authors declare that they have no conflict of interest.

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ORIGINAL

Hyponatremia in patients with aneurysmal subarachnoid hemorrhage: a literature review

Hiponatremia en pacientes con hemorragia subaracnoidea aneurismática: una revisión de la literatura

Paulo João Ferreira de Almeida[1,2], **Aldair Epalanga Cristóvão**[1,2]

1. Faculty of Medicine, Agostinho Neto University, Luanda, Angola;
2. Nucleus for Scientific Research of Health Students, Angola (NICESA)

Corresponding author
Paulo João Ferreira de Almeida
E-mail: ao.paulojoao@gmail.com

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Abstract

Introduction and objective: Hyponatremia is the most common electrolyte disturbance among patients with aneurysmal subarachnoid hemorrhage (aSAH). In these patients, the diagnosis must be early and the correction of hyponatremia is essential to avoid serious neurological complications and/or death. The objective of this work was to accomplish a bibliographical revision of the literature concerning the hyponatremia in patients with aSAH.
Methods: Using the PRISMA protocol, we performed a literature review through the Medical Literature Analysis and Retrieval System Online (MEDLINE) database. An association between the medical subject headings (MeSH) and the keywords was made using booleans operators, and additionally, a randomized search of clinical guidelines relevant to the study were performed.
Results: Initially, 55 articles were found, and after applying filters, 19 articles were considered eligible for the study.
Conclusion: We conclude that the early approach of patients with aneurysmal subarachnoid hemorrhage is crucial, in the way that late intervention can be associated with adverse outcomes.

Key words: Hyponatremia, aneurysmal subarachnoid hemorrhage, subarachnoid hemorrhage, approach.

Resumen

Introducción y objetivo: La hiponatremia es la alteración hidroelectrolítica más frecuente en pacientes con hemorragia subaracnoidea aneurismática (HSAa). En estos pacientes, el diagnóstico debe ser precoz y la corrección de la hiponatremia es fundamental para evitar complicaciones neurológicas graves y/o la muerte. El objetivo de este trabajo fue realizar una revisión bibliográfica de la literatura referente a la hiponatremia en pacientes con HAAa.
Métodos: Usando el protocolo PRISMA, realizamos una revisión de la literatura a través de la base de datos Medical Literature Analysis and Retrieval System Online (MEDLINE). Se realizó una asociación entre los encabezados de materias médicas (MeSH) y las palabras clave mediante operadores booleanos y, además, se realizó una búsqueda aleatoria de guías clínicas relevantes para el estudio.
Resultados: Inicialmente se encontraron 55 artículos y luego de aplicar filtros se consideraron elegibles para el estudio 19 artículos.
Conclusión: Concluimos que el abordaje temprano de pacientes con hemorragia subaracnoidea aneurismática es crucial, en la medida en que una intervención tardía puede estar asociada con resultados adversos.

Palabras clave: Hiponatremia, hemorragia subaracnoidea aneurismática, hemorragia subaracnoidea, Acercarse.

Introduction

The estimated mortality rate for aneurysmal subarachnoid hemorrhage (aSAH) in patients with hyponatremia is considerably high, and has been associated with high morbidity among survivors. In a patient with aSAH, timely diagnosis and aggressive hyponatremia correction are essential. Studies have shown that aneurysmal subarachnoid hemorrhage is more common in females, and factors such increasing age, smoking and alcoholic habits, hypertension, use of certain drugs and some genetic conditions are associated with these condition[1,2].

Cerebral salt wasting syndrome (CSWS) and syndrome of inappropriate antidiuretic hormone (SIADH) correspond to the main causes of hyponatremia in patients with Ahsa[3]. but it may occurs in patients with traumatic brain injury[4], hypopituitarism and inadequate dietary intake of salt[5,6].

Formulating a correct diagnosis is not always straightforward, as hyponatremia is often multifactorial and there are multiple confounding factors which make diagnosis complex. 1,3,7

When left untreated, hyponatremia in patients with aHSA can lead to serious neurological complications and adverse outcomes, including death[3,8-11]. We performed a literature review about hyponatremia in patients with aneurysmal subarachnoid hemorrhage.

Methods

A descriptive and qualitative literature review was performed using the MEDLINE search engine. As inclusion criteria, we consider full-text articles, articles published in the last 10 years, all types of studies where included, and we did not discriminate the language of publication. The exclusion criteria were duplicate articles.

We used the following search terms and Boolean combination:

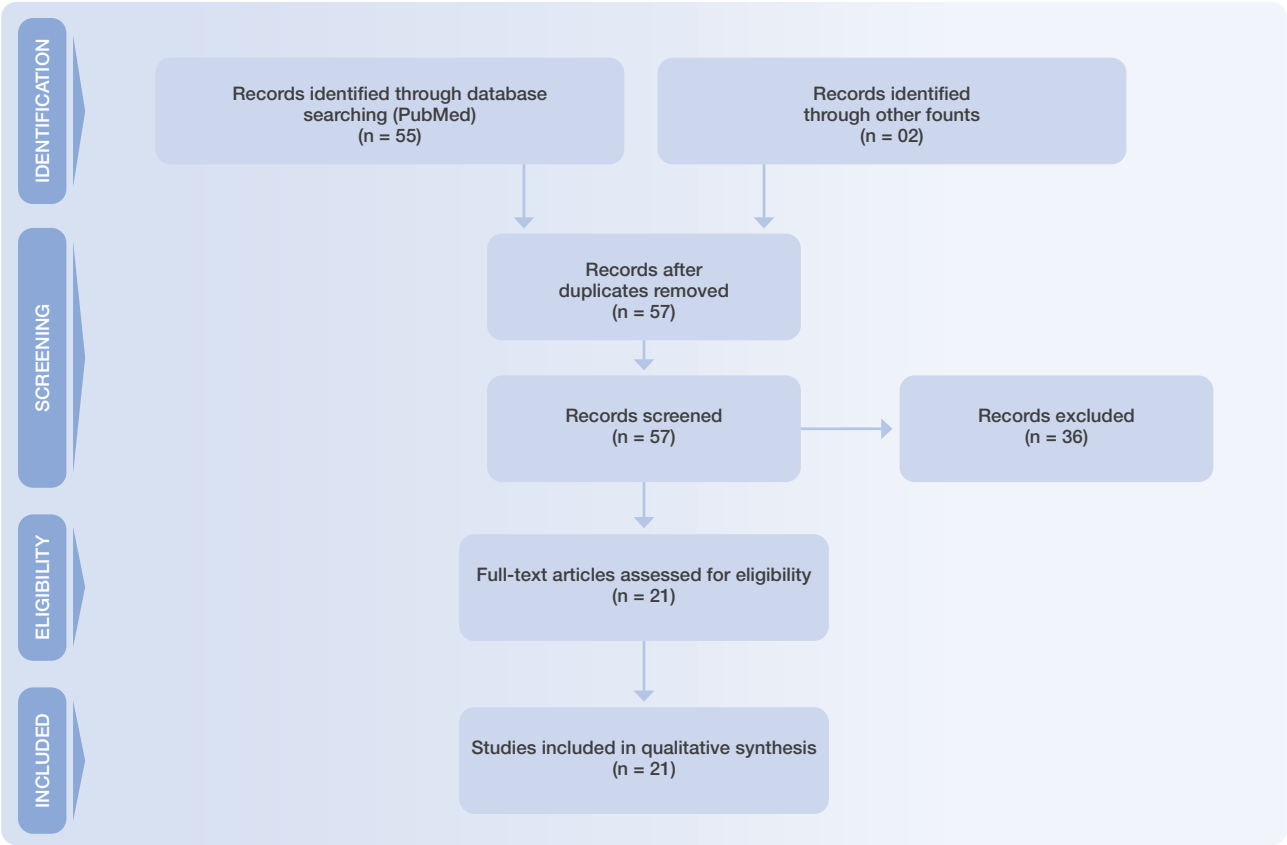
"Symptom Assessment"[Mesh] OR "treatment"[tw] OR "approach"[tw]" AND "hyponatremia""[MeSH] OR "severe hyponatremia"[tw] OR " severe acute hyponatremia"[tw] OR "symptomatic hyponatremia"[tw] AND "Subarachnoid Hemorrhage"[Mesh] OR "Aneurysmal Subarachnoid Hemorrhage"[tw] OR "SAH"[tw] OR "SAHs"[tw]".

Additionally, random searches of clinical guidelines relevant to the study were performed.

Results

Initially, 55 articles were found, and after applying the filters, 19 articles were retrieved, and these, the eligible for the study, as shown in the **figure 1**.

Figure 1: Flow search diagram.



Discussion

Hyponatremia, a serious problem in critically ill patients

Aneurysmal subarachnoid hemorrhage (SAH) has remained one of the most challenging neurosurgical emergencies with continued high mortality[12]. Hyponatremia can be considered an independent risk factor for poor clinical outcomes in patients with SAH2. It is known Hyponatremia is an electrolyte disturbance with a large proportion present in patients with subarachnoid hemorrhage (SAH), and in these patients, has been associated with increased morbidity, including cerebral edema, mental status changes, symptomatic cerebral vasospasm, late cerebral ischemia, representing longer hospital stay and most importantly, resulting in death[1,3,14].

The true contribution of cerebral salt waste (CSW) and syndrome of inappropriate antidiuretic hormone to hyponatremia is unknown, with CSW prevalence estimates ranging from 6% to 75%[3]. Patients with aneurysmal subarachnoid hemorrhage (aSAH) have an estimated 30-day mortality rate of around 35%, with great morbidity among the survivors (a third of whom require full care, and a third are not able to return to work). However, as 15%-30% of deaths occur before hospital admission, the actual incidence of aSAH is likely higher[3].

Risk factors

Some studies have shown that aSAH is more common in females[1,3]. Other factors include increasing age (peaking around 50 years old), hypertension, smoking, alcohol abuse, use of sympathomimetic drugs, family history of aneurysm or subarachnoid hemorrhage (more than two first-degree relatives), and certain conditions genetic (autosomal dominant polycystic kidney disease and Ehlers-Danlos syndrome type IV)[1,2]. As showing in **table I**, formulating a correct diagnosis is not always straightforward, as hyponatremia is often multifactorial and there are multiple confounding factors which make diagnosis complex[7].

Table I: Causes of hyponatremia in neurosurgical patients.

Hypovolemic	Diuretics Insufficient intravenous fluids Cerebral salt wasting
Euvolemic	SIADH Acute adrenocorticotrophic/cortisol deficiency Drugs (e.g., carbamazepine, desmopressin)
Hypervolemic	Excess of IV fluid

Adapted from Cuesta et al., 2016.

Etiology

Hyponatremia often occurs in patients with traumatic brain injury (TBI)4 and the main causes are cerebral salt wasting syndrome (CSW) characterized by depleted intravascular volume, syndrome of inappropriate antidiuretic hormone (SIADH), which occurs with normal intravascular volume, hypopituitarism and inadequate dietary intake of salt[5,6]. Of these, inadequate salt intake can be diagnosed with reasonable certainty if the urine spot sodium is low (below 20 - 40mEq/L) and hypopituitarism can be diagnosed by biochemical evaluation of pituitary hormones. After ruling out these two entities, the clinician is left with cerebral salt waste and syndrome of inappropriate antidiuretic hormone, both of which manifest as hyponatremia with natriuresis (urine spot sodium more than 40mEq/L)[6,15]. CSW is a less common etiology of hyponatremia, occurring in 12% of cases. SIADH has been showed as more common, occurring in 75%[8].

Although these two pathological conditions are notorious (CSW and SIADH), it is difficult to distinguish one from the other, and there is a currently tendency to associate both entities in one. Some claim that since the incidence of SAH is low and it can be difficult to distinguish between[1,5,16].

Some investigators suggest that the underlying etiology of hyponatremia seen in patients with aneurysmal subarachnoid hemorrhage is multifactorial, with different mechanisms occurring at different times. Early-phase hyponatremia is consistent with SIADH, late-phase hyponatremia with CSW Another important difference between CSW and SIADH is that cerebral salt waste involves hypovolemia caused by natriuresis, whereas syndrome of inappropriate antidiuretic hormone is a euvolemic or hypervolemic condition[3,17].

Hoffman et al. suggested that the aneurysm location could affect the risk of developing hyponatremia after aSAH. They reported in a cohort study, that the presence of a ruptured anterior communicating artery aneurysm was associated with the development of hyponatremia, but not the etiology of hyponatremia, and patients with ruptured anterior circulation aneurysms would be more likely to develop SIADH given the closer proximity of the aneurysm to the hypothalamic-pituitary-adrenal axis.

Pathophysiology

When an aneurysm ruptures, blood pours into the subarachnoid space leading to a sharp and sudden increase in intracranial pressure, decreasing cerebral perfusion pressure and leading to global ischemia[1,18]. This event explain the mechanism of loss of consciousness that happens in about 50% of the patients. There is a massive sympathetic tone increase that starts to cause systemic complications and a systemic inflammatory syndrome develops. This series of events is part of what is called early brain injury, a process that starts Just after the aneurysmal rupture and is characterized by microcirculatory constriction, microthrombosis, disruption of the blood-brain barrier, vasogenic and cytotoxic edema, endothelia land neuronal death[1].

The possibility that SAH leads to a generalized stress response that involves the hypersecretion of multiple

pituitary hormones, including antidiuretic hormone is an alternative hypothesis[8].

Diagnosis

The initial assessment of SAH patients, and therefore the grading of the clinical condition, is done by means of a scale based on the Glasgow coma scale (GCS). Early and accurate diagnosis, as well as treatment by specialists is therefore essential[2].

Frequently, the patients refer episodes of headache, described as the worst headache ever felt, which is abrupt and peaks in intensity in one hour at most. Around 10-40% of patients have a warning leak or sentinel episode, which is a similar headache that precedes the bleeding by two to eight weeks. Nausea and vomiting may happen in 77% of the cases, loss of consciousness in 53%, *meningismus* in 35%, focal deficits in 10%, and Terson syndrome (vitreous hemorrhage associated with SAH) in 40% of patients. If computed tomography is negative after high suspicion of aSAH, a lumbar puncture to look for blood or xanthochromia in the cerebrospinal fluid. Computed resonance (CT) and magnetic resonance image should be used in order to look for aneurysms. CT angiography has a sensitivity that approaches 100%[1].

Treatment

Timely diagnosis and aggressive treatment of hyponatremia are recommended regardless of etiology[2,3,19]. In the neurocritical patient, the treatment of hyponatremia requires the identification of the degree of severity, the time evolution, the state of the volume and the severity of the clinical condition. In these patients, the appearance of hyponatremia should be considered, depending on the evolutionary moment, as a true medical emergency that will require the establishment of immediate therapeutic measures[5].

Recent recommendations for managing hyponatremia in cerebral aSAH include (1) avoidance of fluid restriction to prevent cerebral ischemia, (2) use of hydrocortisone or fludrocortisone as an early treatment option, (3) correction of hyponatremia with mild hypertonic saline solutions, (4) avoidance of hypovolemia when using vasopressin-receptor antagonists such as conivaptan, and (5) limiting free water intake via intravenous and enteral routes[13].

Early treatment with mineralocorticoids is used to improve functional outcomes or reduce symptomatic vasospasm[2,3,19]. Studies have shown the benefit of corticosteroids in the management sequelae caused by hyponatremia[20].

Water restriction should be avoided in treating hyponatremia due to the risk of developing delayed cerebral ischemia1.

There are no published data on the appropriate treatment of hyponatremia in patients with aSAH. Studies are needed to establish an adequate management protocol for the maintenance of sodium and water homeostasis in patients with SAH[17]. The unresolved issue with hyponatremia is determine the best method to treat hyponatremia in patients with aSAH, as it can be caused by SIADH, CSW, or a combination of both[13,21].

Conclusions

Early recognition and management of hyponatremia in patients with aneurysmal subarachnoid hemorrhage is critical. Late intervention in these patients can result in a poor prognosis, as hyponatremia can trigger serious neurological complications, which can lead to death. Although certain drugs allow for punctual electrolyte correction, the treatment of hyponatremia in these patients remains a challenge because the underlying etiology of hyponatremia is multifactorial, with different mechanisms and occurring at different times. Therefore, additional studies are needed to improve the management of patients with aSAH and optimize therapeutic measures.

Conflict of interest

The authors declare that they have no conflict of interest.

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ORIGINAL

Study on antimicrobial resistance pattern of uro-pathogens at National Referral Hospital, Thimphu Bhutan

Estudio sobre el patrón de resistencia a los antimicrobianos de los uropatógenos en el Hospital Nacional de Referencia, Thimphu Bhutan

Adeep Monger[1], Vishal Chhetri[1], Ragunath Sharma[2], Phurba Wangdi[2], Tashi Choden[2], Tshering Dorji[1]

1. Royal Center for Disease Control, Department of Public Health, Ministry of Health, Thimphu, Bhutan 2. Clinical Microbiology Laboratory, Department of Laboratory Medicine, Jigme Dorji Wangchuck National Referral Hospital, Thimphu, Bhutan

Corresponding author
Mr. Vishal Chhetri
E-mail: vchhetri@health.gov.bt

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Abstract

Introduction: Antimicrobial resistance among uro-pathogens is a global concern. A periodic analysis of the etiologic agents responsible for urinary tract infections and their antibiotic susceptibility patterns is fundamental for a fitted empirical treatment.
Methods: This is a cross-sectional study conducted at Clinical Microbiology unit of Jigme Dorji Wangchuk National Referral Hospital, Thimphu, Bhutan. Urine culture positive samples from January 2017 to December 2020 were included. The routine procedure for urine culture and the threshold cutoff for antimicrobial susceptibility were followed as per the Clinical Laboratory Standard Institute guidelines.
Results: There were a total of 10392 episodes of positive urine culture out of which 80.9 % were from females and 19.3 % were male patients. The mean age was 38.03±19.2 years old and the most affected age groups were 21-30 years old. *Escherichia coli* (79.57%) was the predominant uro-pathogens followed by *Klebsiella spp*. (9.64%). The highest antimicrobial resistance was observed with Amoxicillin (70.5%) and Cotrimoxazole (32.48%), and the least resistance was seen among Nitrofurantoin (10.3%) and Gentamycin (10.6%).
Conclusion: The most prevalent etiologic agents were *Escherichia coli* and *Klebsiella spp*. accounting about two-thirds of the community acquired urinary tract infections. This study suggests Nitrofurantoin and Gentamycin as the choice of agent for empiric treatment of urinary tract infections. In contrary, Amoxycillin should not be used as the first choice for treatment. A valuable data on the different uro-pathogens and its anti-microbial sensitivity patterns has been provided to ultimately benefit the physicians to guide empirical therapy for UTI.

Key words: Antimicrobial resistance, pathogen, urinary tract infection.

Resumen

Introducción: La resistencia a los antimicrobianos entre los uropatógenos es una preocupación mundial. Un análisis periódico de los agentes etiológicos responsables de las infecciones del tracto urinario y sus patrones de susceptibilidad antibiótica es fundamental para un tratamiento empírico adecuado.
Métodos: Este es un estudio transversal realizado en la unidad de microbiología clínica del Hospital Nacional de Referencia Jigme Dorji Wangchuk, Thimphu, Bután. Se incluyeron muestras positivas de urocultivo de enero de 2017 a diciembre de 2020. Se siguió el procedimiento de rutina para el urocultivo y el umbral de susceptibilidad a los antimicrobianos según las pautas del Clinical Laboratory Standard Institute.
Resultados: Hubo un total de 10392 episodios de urocultivo positivo, de los cuales el 80,9% correspondieron a mujeres y el 19,3 % a pacientes masculinos. La edad media fue de 38,03±19,2 años y los grupos de edad más afectados fueron de 21 a 30 años. *Escherichia coli* (79,57%) fue el uropatógeno predominante seguido de *Klebsiella spp*. (9,64%). La mayor resistencia antimicrobiana se observó con amoxicilina (70,5 %) y cotrimoxazol (32,48%), y la menor resistencia se observó entre nitrofurantoína (10,3 %) y gentamicina (10,6%).
Conclusión: Los agentes etiológicos más prevalentes fueron *Escherichia coli* y *Klebsiella spp*. representando alrededor de dos tercios de la comunidad infecciones del tracto urinario adquiridas. Este estudio sugiere que la nitrofurantoína y la gentamicina son los agentes de elección para el tratamiento empírico de las infecciones del tracto urinario. Por el contrario, la amoxicilina no debe utilizarse como tratamiento de primera elección. Se han proporcionado datos valiosos sobre los diferentes uropatógenos y sus patrones de sensibilidad antimicrobiana para beneficiar en última instancia a los médicos para guiar la terapia empírica para la ITU.

Palabras clave: Resistencia a los antimicrobianos, patógeno, infección del tracto urinario.

Introduction

Urinary tract infection (UTI) is one of the major public health problems globally, affecting approximately 150 million people worldwide. The hospitalization rate due to UTI is increasing annually and in United States alone, there were approximately 400000 cases with an estimated cost of 2.8 billion dollars[1]. This is further aggravated with the evolving antimicrobial resistance due to the overuse of empiric broad-spectrum antimicrobials for treatment of uncomplicated UTI[2]. For instance, many studies have reported the alarming antibiotic resistance rates of ampicillin, amoxicillin, nalidixic acid, ciprofloxacin, cotrimoxazole and norfloxacin among the *Escherichia coli* isolates[3,4]. In Bhutan, one of the most prescribed antibiotics for empirical therapy for UTIs is amoxycillin which was reported to be resistant up to 71.4%[5].

Urine culture is the standard method of choice for diagnosis of UTI and its laboratory surveillance data of etiologic agents and their susceptibility profiles is pertinent for empiric treatment[6]. However, in the resource limited settings, urine culture is not routinely performed, thus the data on most common uro-pathogens and its susceptibility patterns are often considered for empirical treatments. In addition, the guidelines state that the empirical therapy should be based on the available information on the etiologic agents and its antibiotic susceptibility testing data[7].

Currently, there is a scarcity of data in the country; hence this study aims to determine the prevalence of uro-pathogens and their susceptibility patterns at Jigme Dorji Wangchuck National Referral Hospital from 2017 to 2020. This information will aid in guiding the physicians for empirical treatment of uncomplicated UTI in the country.

Materials and method

Study Design

A hospital based retrospective cross-sectional study was conducted. The study was carried out in the microbiology unit of Jigme Dorji Wangchuck National Referral hospital, which caters to patients from the Western region of the country.

Study population and study duration

The study included all positive urine culture from 1st Jan 2017 to 31st December 2020. It involved only the review of the sample processing registers for that period. The routine procedure for sample collection and processing of urine samples were followed as per the existing protocols of the laboratory. Bacterial isolates were identified by routine procedures in the laboratory, antibiotic susceptibility testing and the threshold cutoffs were performed as per the CLSI guidelines[8,9]. The antibiotic disks concentration were; amoxicillin 10 mcg, cefotaxime 30 mcg, ceftriaxone 30 mcg, gentamicin 10 mcg, nitrofurantoin 300 mcg, cefazolin 30 mcg, ceftriaxone 30 mcg, nalidixic acid 30 mcg, norfloxacin 10 mcg, co-trimoxazole 25 mcg, gentamicin 10 mcg, nitrofurantoin 300 mcg, cefoxitin 30 mcg, vancomycin 30 mcg, penicillin G 10 units and erythromycin 15 mcg.

Data collection

Patient information; age, sex, laboratory results, including bacterial colony-forming unit counts, organisms cultured and antimicrobial susceptibility results were retrieved. No patient details, such as name were involved and confidentially were maintained.

Data analysis

Data were entered into Epi-Data version 3.1 (Epi-Data Association, Odense, Denmark) and was exported into Epi info version 7 (Centre for Disease Control and Prevention, US) for analysis. A p-value of <0.05 was considered significant.

Results and discussion

A total of 10392 uro-pathogens were isolated and identified over the four-year period 2017-2020. The most commonly isolated pathogens were *Escherichia coli* (79.5%; 95% CI=77.68-79.26%) followed by *Klebseilla spp*. (9.64%: 95% CI=9.17-10.30%) and *Staphylococcus saprophyticus* (3.17%, 95% CI=2.81-3.84%) (**Table I**). *Escherichia coli* were the pre-dominant uro-pathogen isolated over the four-year period. The prevalence of Gram positive uro-pathogens were 7.38% (n=767), and the most predominant species among these were *Staph. saprophyticus* (3.17%) and *Enterococcus spp*. (3.16%).

Among the total episodes of bacteremia involved in the study; 80.9% (n=8415) were female and 19.3% (n=2015) were male. The prevalence of bacteremia in female were statistically significant than the male group (*p* value = 0.0027). The mean age was 38.5 ± 19.8 years old. The most affected age groups were 21-30 years old followed by 31-40 years old. The figure I represents the age distribution of the participants.

The overall antimicrobial resistance for amoxycillin was 70.5 % followed by cotrimoxazole 32.48 % and the least were seen in nitrofurantoin 10.3% and gentamycin 10.6%. Among the two most common Gram negative uro-pathogens, the highest resistance was reported to amoxycillin 62.9 % followed by cortimaxazole 46.55 % (**Table II**). The least resistance was observed for gentamycin (12.69 %) followed by norfloxacin (22.81 %). *Escherichia coli* being the most pre-dominant organism had the highest resistance of 65.2 % to amoxycillin followed by cortimoxazole (40.9 %). The least resistance was seen in nitrofurantoin (6.8 %) followed by gentamycin (7.4%). The resistance rate of amoxycillin for *Escherichia*

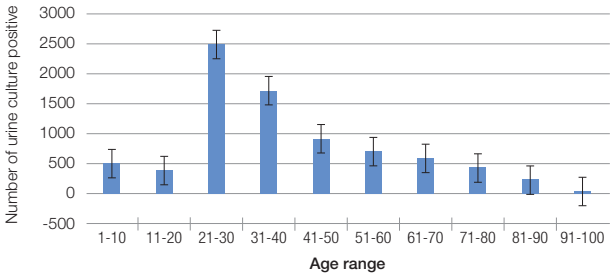
coli has been in a steep rise from 49.1% in 2017 to 76.3 % in 2020. The study also found that 34 % of the *Escherichia coli* isolated were resistant to the third generation cefalosporin antibiotics.

Among the top-two-Gram positive uro-pathogens, the highest resistance was observed in penicillin (61.08%) followed by tetracycline (26.7%). Least resistance was observed in nitrofurantoin (3.5%) followed by cotrimaxazole (21.7%) as presented in **table III**.

This study was conducted in an attempt to have an updated surveillance data of the etiological agents, its anti-microbial susceptibility patterns with respect to time and the local geographical area. This would provide valuable information for the physicians to guide empirical treatments in a resource limited country such as Bhutan.

We found that *Escherichia coli* was the most common uro-pathogen (79.5%) to cause uncomplicated UTI in patients visiting Jigme Dorji Wangchuck National Referral Hospital over the past four years (2017-2020).

Figure 1: Age distribution of patients presented with positive urine culture.



Studies at Iran, South Africa, India and Thailand have also reported *Escherichia coli* to be the most common uro-pathogen isolated which is in concordance with the current study[10-13]. These *Escherichia coli* strains are referred to as the uro-pathogenic Escherichia coli (UPEC) that possesses a variety of virulence factors including adhesions, toxins, iron acquisition factors, polysaccharide capsules and other invasions making it the most suitable candidate for invading the host cells causing UTIs[14].

Table I: Frequency of uro-pathogens isolated from 2017-2020.

Organism	2017		2018		2019		2020	
	N	%	n	%	N	%	n	%
Escherichia coli	2170	78.09	2567	78.91	1179	82.22	2313	79.05
Klebseilla spp	260	9.36	315	9.68	117	8.16	333	11.38
Enterococcus spp	73	2.63	151	4.64	41	2.86	74	2.53
Staph saprophyticus	134	4.82	89	2.74	43	3.00	62	2.12
Candida spp	16	0.58	29	0.89	11	0.77	33	1.13
Proteus spp	15	0.54	44	1.35	4	0.28	40	1.37
Pseudomonas spp	59	2.12	35	1.08	27	1.88	62	2.12
Acinetobacter spp	32	1.15	15	0.46	5	0.35	2	0.07
Enterobacter spp	17	0.61	5	0.15	5	0.35	4	0.14
Streptococcus spp	3	0.11	3	0.09	2	0.14	3	0.10
	2779		3253		1434		2926	

Table II: Percentage of resistance pattern of two most common Gram negative uro-pathogens.

Antibiotics	*Escherichia coli*					*Klebseilla spp*				
	2017	2018	2019	2020	Mean	2017	2018	2019	2020	Mean
Amoxycillin	49.1	67.2	68.2	76.3	65.2	71.0	40.5	98.3	93.7	75.9
Cefazolin	27.9	43.4	40.6	44.2	39.0	53.3	57.2	50.0	53.5	53.5
Cefalexin	26.4	43.7	40.5	-	36.9	33.7	23.2	44.8	13.2	28.7
Ceftraxione	24.7	37.8	34.9	38.7	34.0	46.7	55.3	49.1	46.8	49.5
Gentamycin	2.55	8.55	9.18	9.40	7.4	7.8	19.4	21.6	6.9	13.9
Nitrofurantion	4.97	10.9	6.82	4.46	6.8	29.8	13	27.6	6.0	19.1
Norfloxacin	19.8	38.9	38.7	31.8	32.3	19.2	13.8	35.3	10.2	19.6
Cotrimaxazole	35.7	47.4	42.90	37.4	40.9	48.2	51.8	42.2	40.2	45.6

Table III: Percentage of resistance patterns of two most common Gram positive uro-pathogens.

Antibiotics	*Staphylococcus spp*					*Enterococcus spp*				
	2017	2018	2019	2020	Mean	2017	2018	2019	2020	Mean
Ampicillin	-	-	-	-	-	28.7	30.5	43.9	50	38.3
Nitrofurantion	2.06	1.86	4.08	0	2.0	7.86	4.08	8.69	0	5.2
Norfloxacin	2.02	8.41	4.16	7.4	5.5	37.2	60.6	38.6	38.2	43.7
Penicillin	70.2	58.09	70	89.2	71.9	51.2	37.5	50	62.5	50.3
Tertacycline	6.34	9.27	3.7	-	6.4	-	47	-	-	47.0
Cotrimaxazole	9.45	14.01	10.6	3.48	9.4	28.5	57.1	16.6	-	34.1
Cloxacillin	75.3	42.7	27.5	18.5	41.0	-	-	-	-	-

Female are more susceptible than male due to the anatomic shortness of urethra and its proximity to the anus making it easy for the bacteria to ascend into the urinary tract[15]. Likewise, we reported a higher rate of bacteremia among the females as compared to the male subjects (80.9 vs 19.3 %). Similar studies in Thailand and India reported majority of the isolates from female patients[16].

The most affected age groups in our study were 21-30 years old. Similar results were observed by D Prakash (2021) and Zwane (2013)[11,12]. This is attributed to the sexual activeness during this age. The immense sexual intercourse could lead to abrasion in the vaginal tract leading to entry of pathogens causing UTI[17].

The laboratory-based surveillance data captures pertinent aspects on the effectiveness of the empirical treatment and is dependent on the prevalence of resistance among the most common causative pathogen[4]. Studies across other regions showed that *Escherichia coli* was the most frequent uro-pathogens isolated with resistance to amoxicillin; 88.3% in Saudi Arabia, 81.2 % in Iran, and cotrimoxazole by 50% and 79.2 %[16,18]. In the present study we found that amoxycillin resistance rate of 65.2% followed by cotrimoxazole 40.9% among the *Escherichia coli* isolates. Self-medication, availability over the counter and over prescribing of oral amoxycillin is a common practice in Bhutan which may have led to the increasing resistance[19].

The least resistance was seen among nitrofurantoin (10.3%) and gentamycin (10.6%), hence these antibiotics could be used for empirical treatment of UTI effectively. However, a periodic analysis and surveillance data is pertinent. This is because a report from elsewhere, found 78.71% nitrofurantoin resistance[12].

The resistance rate of amoxycillin among the *Escherichia coli* isolates was 49.1% in 2017 and 76.3% in 2020, with an increasing trend each year. This result implies that antibiotic resistance can change overtime and a proper antibiotic program can reverse an outbreak of resistant pathogen. For instance, prevalence of vancomycin-resistant Enterococcus (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA) and other Gram-negative Bacilli were all reduced when such plan was implemented at Methodist Hospital at Indiana[20]. Therefore, we suggest advocacy and sensitization works against irrational use of antibiotics as well as periodic community-based surveillance of antimicrobial resistance.

There are limitations in this study, it included only the Western part of the country and may not represent resistance patterns in other parts of the country. Furthermore, the knowledge on the antibiotic resistance among the uro-pathogens should be documented which will help in development of necessary interventions.

Conclusion

This study provides valuable and updated etiological agents and the antimicrobial susceptibility profiles of uro-pathogens that could be used to guide empirical UTI treatments in Thimphu. This study shows a large number of isolates resistance to amoxycillin and cotrimoxazole and hence it is advisable to provide advocacy and other enhanced sensitization works against irrational use of antibiotics. In addition, there is a need for periodic community-based surveillance of antimicrobial resistance patterns.

Ethical clearance

Permission for waiver of ethical clearance was sought from Research Ethics Board of Health, Ministry of Health, Thimphu, Bhutan via letter no. Reference No. REBH/Approval/2019/091.

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Competeing intrest

Declared none.

Authors contribution

AM and VC carried out the study design, proposal write-up, data analysis and drafting of manuscript. TD, RS and PW was involved with data collection and drafting of manuscript. TC did the data analysis and drafting of manuscript. All the authors read the final version of manuscript and accepted.

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ORIGINAL

Coneixements de salut bucodental dels pediatres d'atenció primària de les Illes Balears

Oral health knowledge of primary care paediatricians in the Balearic Islands

Irene Coll Campayo[1], Jose M. Quintana[2]

1. Centre de Salut de Valldargent, Palma. Escola Universitària Adema.
2. Coordinador Salut Dental. Serveis Centrals, Palma

Corresponding author
José M. Quintana Abraham
E-mail: jose.quintana@ibsalut.es

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Resum

Objectiu: Avaluar els coneixements dels pediatres d'atenció primària de salut (APS) de les Balears en matèria de salut bucodental i determinar les seves necessitats d'aprenentatge.
Material i mètodes: Es tracta d'un estudi observacional descriptiu. Es va enviar un qüestionari anònim al correu electrònic institucional de tots els pediatres de l'APS (113). Les variables d'estudi es van classificar en sis blocs.
Resultats: La taxa de resposta va ser del 34,5% .Edat mitjana 50,2 (± 1,25) anys. El 44% recomanen la visita al dentista des del primer any de vida i un 33% recomana la primera visita al dentista als sis anys, amb l'aparició del Programa d'atenció Dental Infantil (PADI). El 21% va derivar els pacients al dentista per diferents patologies.
Conclusió: Els pediatres coneixen les recomanacions de les guies de salut bucodental. Hem detectat diversos àmbits on calen accions per millorar el seu coneixement.

Palabras clave: Cura dental, higiene oral, caries dental, dieta, pediatres.

Abstract

Objective:To evaluate the knowledge of the Balearic primary health care (PHC) paediatricians regarding oral health and to determine their learning needs.
Material and methods: This was a descriptive observational study. An anonymous questionnaire was sent to the institutional email of all PHC paediatricians (113). The study variables were classified in six blocks.
Results: The response rate was 34,5% The mean age was 50.2 (± 1.25) years. The 44% recommend visiting the dentist from the first year of life and 33% recommend the first visit to the dentist at the age of six, with the onset of Child Dental Care program (PADI). 21% referred the patients to the dentists due to different pathologies.
Conclusion: Paediatricians are aware oral health guidelines recommendations. We detected several domains where actions are needed to enhance their knowledge

Key words: Dental care, oral hygiene, dental caries, diet, paediatricians.

Introducció

La càries dental és una de les malalties cròniques més freqüents que afecten als infants. És un problema de salut pública important a la primera infància, amb impactes negatius al llarg de la vida[1-5].

A nivell mundial, el 60-90% dels infants estan afectats, amb taxes de càries dental molt superiors a l'asma infantil[5,6].

La càries dental és una malaltia progressiva i es pot revertir si es controla de manera precoç, però si no es tracta, es torna més complexa amb el pas del temps[7].

A la darrera enquesta de Salut Oral d´Espanya el percentatge de menors de 5-6 anys amb almenys una dent primària amb caries o obturada era del 35.5%. Als 12 i 15 anys, el percentatge de joves amb història de càries a la dentició definitiva era del 28.6% i 35.5% respectivament.

La Societat Espanyola d'Odontopediatria (SEOP) defensa que la primera visita al dentista es realitzi al primer any de vida, fins i tot durant el darrer trimestre de l'embaràs[8].

L'Organització Mundial de la Salut (OMS) identifica la salut bucodental com a important per a la pràctica interprofessional del sector de la salut primària[9].

El pediatre té un paper fonamental, ja que és qui té el primer contacte amb els infants i els seus pares. Per tant és qui pot detectar lesions en estadis més precoces per derivar-los al seu odontòleg de referència. La seva actitud i nivell de coneixements són factors essencials que afecten a la prevenció i al tractament de les caries de primera infància[10].

Desenvolupar accions per enfortir el paper dels pediatres en la salut bucodental dels nens requereix una comprensió dels seus coneixements i pràctiques actuals[11].

Per tot l'anterior es planteja l'objectiu d'avaluar els coneixements dels pediatres d'atenció primària.

Material i Mètodes

L'estudi realitzat va tenir un disseny descriptiu transversal. Es va sol·licitar un llistat de tots els professionals de pediatria en actiu del Servei de Salut de les Illes Balears. Es va enviar un correu electrònic als 113 pediatres per sol·licitar la seva participació de manera voluntària, la mecanització del qüestionari la portà a terme l´ administrativa que les rebia.

El qüestionari constava de 23 preguntes, de selecció múltiple, 1 resposta correcta. Les preguntes comunes s'agruparen en 6 blocs:

1. Visita al dentista (bloc 1; ítems 1-2)
2. Higiene oral (bloc 2; ítems 3-6)
3. Caries dental (bloc 3; ítems 7-12)
4. Dieta (bloc 4; ítems 13-14)
5. Valoració dels propis coneixements del pediatre/ PADI (bloc5; ítems 15-20)
6. Formació (bloc 6; ítems 21-23)

Les dades demogràfiques foren, gènere, edat, via d'especialització i la illa on exercien. Per assegurar la qualitat de l'estudi, les dades han estat gestionades per la investigadora principal.

Resultats

Participaren del estudi 39 pediatres que representen el 35,1 % del total de Balears: 31 dones (79,5%) i 8 homes amb una edat mitjana de 54,6 ±3,2 els homes i 49,1± 1,6 les dones. La especialització dels participants fou en 26 via MIR (67%), en 8 casos (21%) altres (medicina de família) i en 5 (13%) via MESTO.

En la distribució per illes, la majoria fou de Mallorca, amb un 72%, un 21% de Menorca i un 8% d'Eivissa.

A la **taula I** es mostren les freqüències i els percentatges absoluts de cada ítem dels bloc 1 a 5 del qüestionari.

El 62 % (n= 24) manifesta no haver rebut docència en matèria de salut bucodental durant la seva formació acadèmica o especialitzada.

Al **gràfic 1** es mostra com un 95% dels pediatres (n=37) els hi agradaria rebre formació en salut buco-dental, i a un 5% (n=2) pot ser. També apareix la distribució del tipus de format que prefereixen.

Discussió

A proposta del coordinador del Servei Dental -PADI es va portar a terme una avaluació interna dins el Servei de Salut. El PADI s' encarrega de la prevenció i tractament conservador de la dentició entre el 6 i els 15 anys.

La Direcció Assistencial del Servei de Salut i la Coordinació Autonòmica de Pediatria el varen considerar d'interès (març 2021).

Varen contestar un terç dels pediatres malgrat que és va enviar un segon correu corporatiu per recordar-ho. Cal tenir en compte que els resultats poden estar influïts pel fet que hagin contestat els més motivats.

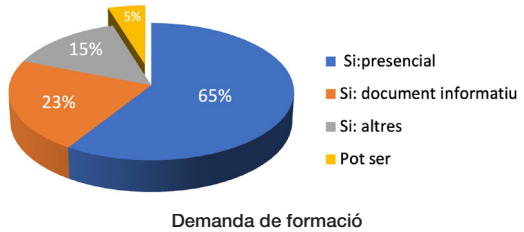
La majoria dels pediatres que han respost demostren tenir coneixements de les preguntes dels distints blocs.

Taula I: Resultats del qüestionari distribuït als pediatres (ítems 1 a 20).

BLOC 1. VISITA AL DENTISTA		
1. A quina edat creu que els infants han de tenir la seva primera visita al professional d'odontologia?	A l'any Al sis anys, amb l'inici del PADI Quan presenten qualque patologia No sap, no contesta	17 (44%) 13 (33%) 8 (21%) 1 (3%)
2. Quan un infant vé a la consulta per un mal de queixal, la vostra actuació és:	Donar analgèsics Donar analgèsics+antibiótic Derivar al dentista sense medicació Altres (especificar)	16 (41%) 10 (26%) 3 (8%) 10 (26%)
BLOC 2. HIGIENE ORAL		
3. A partir de quina edat hi ha que raspallar les dents?	Des de que té dents a la boca Quan ell pugui raspallar-se sol A partir dels sis anys No sap, no contesta	35 (90%) 4 (10%) 0 0
4. Quina concentració de flúor recomanu per a les pastes de dents?	350/450 ppmF 1450 ppmF La que sigui més esconòmica No sap, no contesta	12(32%) 18 (47%) 0 8 (21%)
5. Coneix la "Técnica LEL" d'aixecar el llavi?	No Sí Em sona però no sé exactament en què consisteix No sap, no contesta	30 (77%) 3 (8%) 2 (5%) 4 (10%)
6. La causa més freqüent de sagnat de genives a un nin (de 6 a 12 anys) és:	Recanvi dentari Gingivitis per falta d´higiene Caries Altres	7 (18%) 31 (79%) 0 1 (3%)
BLOC 3. CÀRIES		
7. Considera que la caries és:	Una malatia infecciosa i transmissible Una disbiosis causada pel consum de sucre Una malaltia genètica que s'hereda No sap/no contesta	15 (35%) 19(49%) 1 (3%) 4 (10%)
8. Pèrdua prematura de les dents per caries: té efectes negatius sobre les dents?	Vertader Fals Depèn No sap/no contesta	20 (51%) 2 (5%) 13 (33%) 4 (10%)
9. La caries en dentició temporal ha de rebre tractament odontològic?	Vertader Fals Depèn No sap/no contesta	15 (38%) 1 (3%) 22 (56%) 1 (3%)
10. La lactancia materna perllongada i a demanda (més d'un any): pot afavorir l'aparició de caries?	Vertader Fals Depèn No sap/no contesta	13 (33%) 16 (41%) 7 (18%) 3 (18%)
11. Quina lesió reconeix en aquesta imatge? 	Alteració de l'esmalt: hipoplasia, HMI Placa dental (mala higiene oral) Lesió de caries No sap/no contesta	27 (69%) 9 (23%) 2 (5%) 1 (3%)
12. Quina lesió reconeix en aquesta imatge? 	Alteració de l'esmal: hipoplasia, HMI Placa dental (mala higiene oral) Lesió de caries No sap/no contesta	5 (13%) 1 (3%) 31 (79%) 2 (5%)
BLOC 4. DIETA		
13. La dieta rica en sucres facilita l'aparició de:	Maloclusions dentals Caries Tot tipus de lesions orals No sap/no contesta	0 32 (82%) 7 (18%) 0
14. Quan recomau un canvi de dieta per la raó que sigui: teniu present la salut bucodental?	Sí No A vegades No sap/no contesta	24 (82%) 4(10%) 10 (26%) 1 (3%)

BLOC 5. VALORACIÓ DELS PROPIS CONEIXEMENTS DEL PEDIATRE/PADI		
15. Quina diria que és la primera dent que apareix a la boca (mitjana)?	Les 2 incissives centrals inferios Les 2 incissives centrals superiors Les 4 primeres molars superiors i inferiors No sap/no contesta	34 (87%) 4 (10%) 1 (3%) 0
16. En relació amb la caries: considera que té coneixements per diagnosticar-la?	Sí No Només a les dents definitives No sap/no contesta	21 (54%) 16 (41%) 1 (3%) 1 (3%)
17. En relació amb la gingivitis: considera que té coneixements per diagnosticar-la?	Sí No Només a les dents definitives No sap/no contesta	19 (49%) 12 (31%) 1 (3%) 7 (18%)
18. En relació a les patologies, anterior citades: considera que hauria de poder diagnosticar-les?	Sí, ajudaria en la millora més precoç de la patologia No, prefereixo derivar al dentista Només a les dents definitives No sap, no contesta	37 (94%) 1 (3%) 0 1 (3%)
19. Coneix quina cobertura té el PADI?	Sí No Certes coses sí, però no totes No sap/no contesta	26 (67%) 0 13 (33%) 0
20. Recomana als pares l'ús del PADI per als seus pacients?	Sí, sempre No Quan m'ho demanen els pares No sap/no contesta	38 (97%) 1 (3%) 0 0
BLOC 6. FORMACIÓ		
21. Ha rebut formació en salut bucodental durant la seva formació?	Sí, durant estudis de medicina Sí, com a formació continuada No No sap/no contesta	6(15%) 8(21%) 24 (62%) 1 (3%)
22. Li agradaria rebre qualque tipus de formació en materia de salut bucodental?	Sí No Potser No sap/No contesta	37 (95%) 0 2 (5%) 0
23. Quin tipus de formació prefeririu?	Presencial, seminari, curs Document informatiu Altres	24 (62%) 9 (23%) 6 (15%)

Gràfic 1: Percentatge de pediatres que volen rebre formació en salut bucodental i la seva distribució.



Per altra banda, es mostren deficiències en relació a alguns punts tan importants com el diagnòstic de la lesió que apareix a la imatge de la pregunta 11. Es tracta de una lesió de caries de primera infància (CPI): 69% dels pediatres han contestat que es tracta d'una alteració de l'esmalt i només un 5% que es tracta d'una lesió de caries. Aquesta lesió, pot ser detectada amb la tècnica LEL (aixecar el llavi) del nadó un cop al mes, per cercar signes inicials de CPI. Un 3% diu conèixer aquesta tècnica davant un 77% que afirma desconèixer-la. La CPI representa el patró de caries més agressiu, destructiu i amb les pitjors seqüeles en dentició temporal i el pic més elevat és entre els 13 i 24 mesos.

Aquest resultat contrasta amb un altra que confirma que tot i que els coneixements sobre el tractament de la caries eren escassos, el seu nivell de coneixements sobre higiene oral, caries i hàbits nutricionals era adequat[10].

Diversos estudis mostren que els pediatres tenen una manca de coneixements dels conceptes bàsics d'odontologia, més concretament d'odontologia pediàtrica, segurament conseqüència de la poca formació rebuda durant la seva formació universitària[12,13].

El 44%, recomanen visitar el dentista des del primer any de vida tal i com aconsellen actualment les societats d'odontopediatria però un 33% la recomanen a l´edat de sis anys, amb l´inici del PADI, i un 21% quan presenten patologia.

Les darreres investigacions així com les societats científiques d'odontopediatria indiquen que només les

pastes dentals amb concentracions iguals o majors a 1000 ppmF (parts per milió de fluor), han provat ser eficaces en la reducció de caries. Un 32% (n=12) continuen aconsellant pastes de 350/450 ppmF, insuficient per combatre la caries i un 21% (n=8) desconeix la concentració que ha d'aconsellar.

La gran majoria dels pediatres acceptarien més formació en matèria de salut bucodental, sobretot presencial, per tal de millorar l'atenció dels seus pacients.

La salut bucodental està entre els objectius docents de la rotació per Atenció Primària; per tant pot ser desitjable aprofitar les consultes de PADI a les unitats de salut bucodental dels centres de salut hi hagi dentistes que puguin actuar com a formadors en aquesta etapa.

Conclusió

El nivell de coneixements fou acceptable en diversos ítems, però en altres com la detecció precoç de CPI, la recomanació de la concentració adient de fluor a la pasta, o la edat d'inici de la higiene dental es aconsellable actualitzar els coneixements.

Agraïments
A la Dra. Eugènia Carandell, directora assistencial del Servei de Salut de Balears i a la Dra. Margalida Cañellas, coordinadora de pediatria, al Dr. Joan Llobera i a la Unitat d'Investigació de la Gerència d'Atenció Primària. A tots els pediatres que ens han regalat els seu temps per poder elaborar aquest article.

Conflicte d'interessos
Els autors declaren no tenir cap conflicte d'interessos.

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ORIGINAL

The mechanism of electromagnetic and electrical energies production by the heart; the theory of the heart controls the body's balance, not the brain

El mecanismo de producción de energías electromagnéticas y eléctricas por el corazón; la teoría de que el corazón controla el equilibrio del cuerpo, no el cerebro

Ali Mohammadimoshganbar[1], Gholamreza Mostafavi[2], Amin Hoorandghadim[3]

1. Independent Researcher from Ludwigshafen am Rhein, Germany 2. Independent Researcher 3. Independent Researcher from Tokyo, Japan.

Corresponding author
Ali Mohammadimoshganbar
E-mail: Dr_ali_mohammadi32@yahoo.com

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Abstract

Background: In this article, we have tried to express the general principles of our theory. Our theory rejects the traditional understanding of the brain while establishing a correct view of the role of the brain. We will also describe where information and memory are stored in the body.
Methods: All ideas about the Mechanism of Electromagnetic and Electrical Energies Production By the Heart; The Theory of the Heart Controls the Body's Balance, Not the Brain in different studies were extracted from diverse databases and analyzed and inserted into this survey.
Results: According to our research, the medical science and medical physiology community have a limited understanding of the actual functioning of the heart and brain. In fact, to this day, the functions of the heart have been attributed to the brain. Considering the many details about the heart that have been discovered in recent years, the most important of which is the existence of a large and complex neural network of the heart we examine the role of the heart and find that the heart is responsible for creating and maintaining body balance, therefore keeping the body balance by the heart is to keep the function of all the body's organs in harmony to maintain life. The large neurons system in the heart and aorta that extend to arteries and small arteries indicate that the heart can not only be an organ for pumping blood. According to our research, the control function of the Heart over the body is done by generating Electromagnetic Energy and converting it into Electrical Energy in the Heart. We have discovered the mechanism by which the Heart produces Electromagnetic and Electrical energies, which are the basis of our theory, and will be described in this article. We found the brain's essential function and its relationship to the body's organs based on scientific facts discovered such as neurogenesis and medical events that remain unanswered to this day. Questions such as; Why were brain waves emitted 30 seconds after cardiac arrest? Why does a transplanted kidney work appropriately in a brain-dead patient? will be answered.
Conclusion: We will explain why the brain cannot be the control unit of the body, the center of analysis and thought. We will also explain why we cannot accept that the brain hippocampus is the center of memory because of the phenomenon of neurogenesis and other scientific findings.
Key words: Balancing heart, Cooling brain, Heart function, Brain function, Memories centers, Electromagnetic energy of the heart, Electrical energy of the heart, Body harmony, Short and long term memories..

Resumen

Antecedentes: En este artículo hemos intentado expresar los principios generales de nuestra teoría. Nuestra teoría rechaza la concepción tradicional del cerebro, a la vez que establece una visión correcta del papel del cerebro. También describiremos dónde se almacenan la información y la memoria en el cuerpo.
Métodos: Todas las ideas sobre el Mecanismo de Producción de Energías Electromagnéticas y Eléctricas por el Corazón; La Teoría del Corazón Controla el Equilibrio del Cuerpo, no el Cerebro en diferentes estudios fueron extraídas de diversas bases de datos y analizadas e insertadas en esta encuesta.
Resultados: Según nuestra investigación, la ciencia médica y la comunidad de fisiología médica tienen un conocimiento limitado del funcionamiento real del corazón y el cerebro. De hecho, hasta la fecha, las funciones del corazón se han atribuido al cerebro. Teniendo en cuenta los numerosos detalles sobre el corazón que se han descubierto en los últimos años, el más importante de los cuales es la existencia de una gran y compleja red neuronal del corazón, examinamos la función del corazón y descubrimos que el corazón es el responsable de crear y mantener el equilibrio corporal, por lo que mantener el equilibrio corporal por parte del corazón es mantener la función de todos los órganos del cuerpo en armonía para mantener la vida. El gran sistema de neuronas en el corazón y la aorta que se extienden a las arterias y a las pequeñas arterias indican que el corazón no puede ser sólo un órgano para bombear sangre. Según nuestras investigaciones, la función de control del Corazón sobre el cuerpo se realiza generando Energía Electromagnética y convirtiéndola en energía eléctrica en el Corazón. Hemos descubierto el mecanismo por el cual el Corazón produce energías electromagnéticas y eléctricas, que son la base de nuestra teoría, y que será descrita en este artículo. Encontramos la función esencial del cerebro y su relación con los órganos del cuerpo, basándonos en hechos científicos descubiertos como la neurogénesis y eventos médicos que siguen sin respuesta hasta el día de hoy. Preguntas como: ¿Por qué se emiten ondas cerebrales 30 segundos después de un paro cardíaco? ¿Por qué un riñón trasplantado funciona adecuadamente en un paciente con muerte cerebral? serán respondidas.
Conclusión: Explicaremos por qué el cerebro no puede ser la unidad de control del cuerpo, el centro de análisis y pensamiento. También explicaremos por qué no podemos aceptar que el hipocampo del cerebro sea el centro de la memoria debido al fenómeno de la neurogénesis y otros hallazgos científicos.
Palabras clave: Equilibrio del corazón, Enfriamiento del cerebro, Función del corazón, Función del cerebro, Centros de memoria, Energía electromagnética del corazón, Energía eléctrica del corazón, Armonía del cuerpo, Memorias a corto y largo plazo.

Introduction

Due to scientific research and unanswered questions from medical science, we became skeptical about heart and brain functions. By discovering many details about the heart, such as the presence of the heart's neural network system[1], we believe the heart is not merely an organ for pumping blood. If we consider the general consensus that the heart is only an organ for blood pumping and the brain as the center of body control, analysis, and thought, we will have many unanswered questions such as[2]:

1. Why is there a neural network in the heart?
2. Why does the heart produce electromagnetic energy and electrical energy? What are their functions?
3. Function of the aortic neural network that extends to the smallest arteries?
4. No memory loss with the death of specialized cells (neurogenesis) of the memory center (hippocampus)?
5. Why do we have the phenomenon of neurogenesis?
6. How can there be a successful kidney transplant function in a brain-dead patient?
7. Why were brain waves emitted up to 30 seconds after cardiac arrest in a patient with epilepsy?

In our research, all of the above questions as well as many other unsolved questions be answered.

How electromagnetic energy and electrical energy are produced in the heart, the mechanism of initiating the neural message:

According to many pieces of research, the heart has electromagnetic and electric fields[3]. The heart's electromagnetic field is 5000 times larger than that of the brain, and the heart's electric field is 60 times larger than that of the brain4. How are these energies produced in the heart and what are their functions?

To explain how the heart produces electro-magnetic and electrical energies, we must use some well-known laws of physics, such as Coulomb's Laws, Lorentz, Faraday, Lenz's Law, The Law of Friction, and Einstein's Theory of Special Relativity.

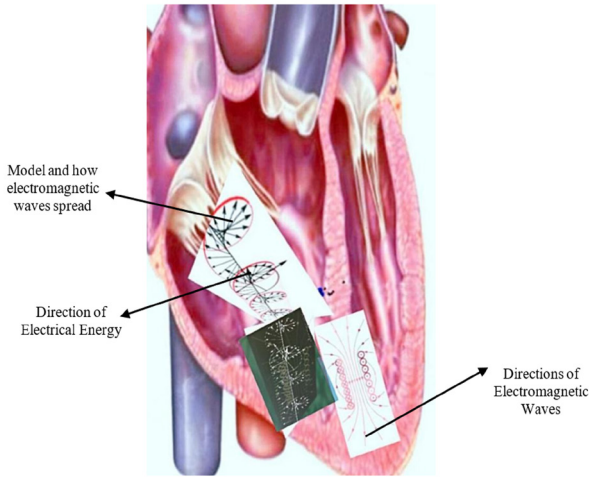
As we know, there are metal ions in the blood, especially iron ions, which have a positive electric charge. Sodium ions are also located on the outer surface of the Myocardium.

After much research and analysis of the laws of physics and human physiology, we have concluded that the heart can produce electromagnetic energy for the following reasons:

1. The shape and type of Endocardial lining is made of plain flat squamous tissue, which increases the level of contact and more friction with the blood.
2. How blood enters and leaves the ventricles (the shape of blood movement in three dimensions).

Due to the structure and function of the heart, blood hits the inner wall of the endocardium very quickly, and due to the way blood moves in the ventricles(tornado-like movement and circular), there is much friction between the surface of the endocardium and the blood. As a result of this friction, energy is generated in the opposite direction of the blood flow. This energy stimulates and moves the positive ions in the blood faster, which according to Coulomb's Laws, the positive ions in the blood cause sodium ions to be expelled from the outer surface of the Myocardium cells into the Myocardial cells. Depolarization occurs due to the expulsion of sodium ions into the Myocardial cells, and blood comes out of the ventricles. When blood is pumped from the ventricles because there is no more blood in the ventricles, there is no propulsive force against the sodium ions, and the sodium ions propagate back to the outer surface of the Myocardial cells according to the concentration gradient (Repolarization). In the heart's atriums, Depolarization and Repolarization occurred by the same mechanism.

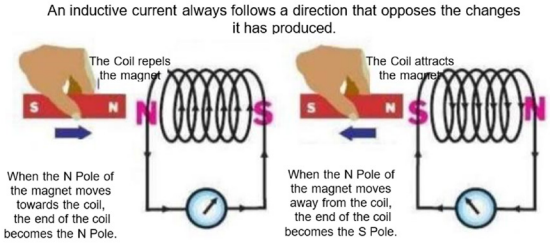
Figure 1: Due to the above shape and the action of continuous contraction and expansion of the heart, the heart produces continuous electromagnetic energy. Electric energy is produced by the continuous production of electromagnetic energy over time.



According to Lorentz's law, an electromagnetic field is created during Depolarization by the drift of electric charges. It means the electro-magnetic energy is produced by the drift of sodium ions into the Myocardium cells.

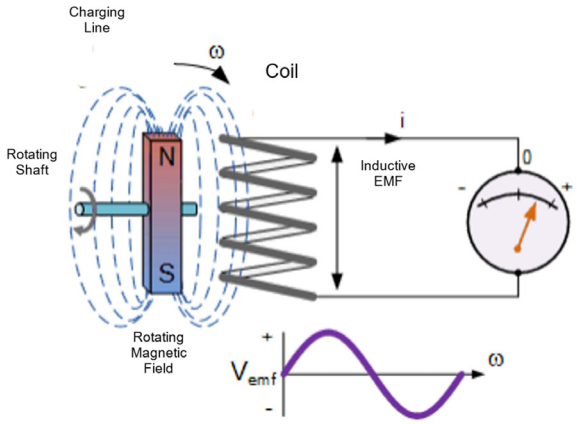
Also, according to Faraday's and Lenz Laws, an electric field is created by changing the magnetic field with time, which is called electromagnetic induction. According to Faraday's and Lenz Laws, if the magnet is stationary in relation to the ring, no electric current is generated; that is, as long as our heart is working, the heart can produce electromagnetic energy, and when the heart stops working, the production of electromagnetic current stops (**Figure 2**).

Figure 2: This shape examines the Law of the Lens, in that it induces an electric current by moving the magnet closer and farther away from the coil.



Also, according to Einstein's Theory of Special Relativity, a moving magnetic field becomes a non-zero electric field and vice versa (**Figure 3**).

Figure 3: An electromagnetic field is created by the rotational motion of the magnet. If the rotation of the magnet is done next to the coil, it will induce electrical energy in the coil.



In other words, the heart is constantly working, constant friction, and the heart generates continuous electromagnetic energy, and because it is working, the electromagnetic energy converts to magnetic waves (heart sound, heart heat, Etc.) and electrical energy.

The electrical energy generated in the heart stimulates the nerve cells of the heart to create a neural message that is electrical.

Heart

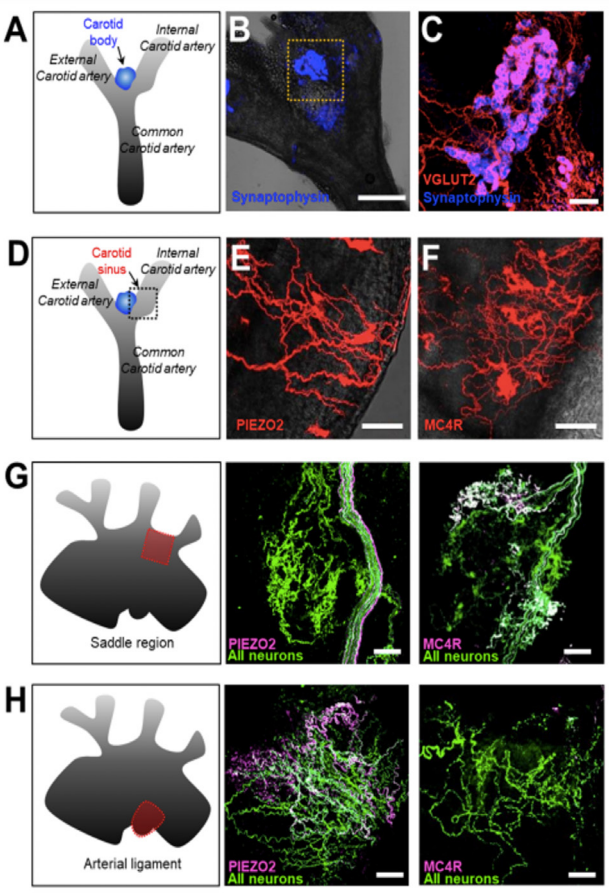
According to recent research, the heart has a complex and sizable nervous system[1], refer to Figure: Posterior View of the 3D Reconstructed Male Rat Heart, the whole-heart view showing the context, extent, and distribution of the intrinsic cardiac neurons (ICN), located on superior and posterior surfaces of the atria. A higher-resolution view of the atria and blood vessels that are shown[1].

The aorta also has many nerve cells (**Figure 4**)[2]. As it is generally understood, blood comes out of the heart's left ventricle through the aorta and is sent to the organs. These nerve cells in the aorta are also extended to the organs. Some studies have shown the presence of axons in arteries and even small arteries[5-9].

Given that :

1. Electromagnetic energy is produced in the heart.
2. The conversion of electromagnetic energy into electrical energy stimulates the nerve cells in the heart wall.
3. The neural network of the heart is extended to the organs through the arteries.

Figure 4: Neuron subtypes that innervate the carotid sinus and aortic arch. (A, D) Cartoon depictions of the carotid sinus. Carotid glomus cells can be visualized (blue) by immunostaining for synaptophysin (B-C). Vagal afferents were visualized by immunochemistry for tdTomato (red) following injection of AAV-flex-tdTomato into NJP ganglia of Vglut2-ires-Cre mice (C), Piezo2-ires-Cre mice (E), and Mc4r-2a-Cre mice (F), scale bars: 400 µm for B; 20 µm for C; 100 µm for E-F. Boxed region in B depicts regions of analysis for panels C, while boxed region in D depicts region of analysis for E-F. Representative images used for quantitative analysis of flower spray terminals in the aortic saddle region (G) and end-net endings in the arterial ligament (H). Vagal afferents were visualized by immunochemistry following injection of Cre-independent AAV-Gfp (green, ALL NEURONS) and AAV-flex-tdTomato (magenta) into NJP ganglia of Piezo2-ires-Cre (PIEZO2) or Mc4r-2a-Cre (MC4R) mice, scale bar 30 µm[2].



We express one part of our theory: electrical energy Produced in the heart stimulates the nervous system and the neurons of the heart and maintains the body's balance by sending messages to the organs. The nervous messages transmit to the organs through neurons in the walls of the arteries.

The purpose of maintaining the balance of the body is to perform the functions of the body's organs in a harmonious manner.

Nowadays, genetic rearrangements in the neurons' DNA and their elongation are accepted[10-13]. So what is the reason for this rearrangement?

According to another part of our theory: The DNA rearrangement of neurons is done during the learning and gaining skill phase in the heart's nervous system while the neurons reach the organs. It occurs follows:
While voluntarily working during the learning process, the heart's electrical energy stimulates the transpositions (jumping gene) of the DNA of the heart's nervous system neurons, causing the genetic rearrangement of the relevant neurons and creating a message along the relevant neurons pathway. We must also point out that precisely the same DNA rearrangement takes place in the neuronal DNA of the target organ, such as the neurons that reach the hands, feet, and other organs. The function of the transposons and DNA rearrangements of the heart's and organs' neurons causes the formation of our long-term memory.

As mentioned, our long-term memory is created by the function of transposons and the rearrangement of neurons' DNA in two versions, the heart and the organs.

How does the short-term memory form? During learning, memorization, and all that is recorded in our short-term memory, new synapses form in the medulla oblongata[14] between the neurons of the organs associated with that activity. These synapses form as the learning process and the repetition of any particular topics progress for faster and more fluent communication between the organs performing that particular activity.

Research has shown that with more repetition and more practice in a particular subject, we will have more efficient synapses, and if we do not do that particular activity, we will gradually lose the relevant synapses (Synaptic Plasticity)[15,16]. These synaptic relationships between neurons coming from the organs in the medulla oblongata form our short-term memory[17]. there is now compelling evidence that changes in synaptic strength occur as a result of certain forms of learning[18].

It should be noted that synapses are formed between the neurons of the organs involved in that particular activity and the brain for optimal energy depletion. Brain neurons that form synapses with neurons of different organs must become more efficient to receive and transmit electrical charges (neural messages) to a specific energy discharge site . This increase in efficiency in transmitting a larger volume of electrical charge is caused by the function of the transposons in the rearranging of the DNA of the brain neurons.

In the following sections of this article, we will explain brain function.

The way we perform involuntary and vital actions (such as eating, every child knows how to eat, breathing, swallowing, urinating, defecating, etc.) has come to us inherently, and there is information about them in the DNA of neurons.

Concerning involuntary actions, the heart's function is to monitor the existence and keep the body's balance. When the body's balance is disrupted, the heart will send messages to the relevant organs to create and maintain the body's balance.

We explain the process of learning and creating short-term and long-term memory with an example in the framework of our theory:

As mentioned, in the case of voluntary and learnable issues (such as how to play musical instruments), by practicing and learning, new synapses are formed in the medulla oblongata (between the organs involved in performing that particular activity, such as the hands, ears, and eyes.) A short-term memory is formed.

Also, new synapses form between the organs involved in that particular function with the brain for faster and optimal energy release.

By practicing and acquiring skills, DNA rearrangement in the neurons of the heart and organs will form by the function of the transposons(jumper gene) that make up our long-term memory.

When the long-term memory is formed, the neurons of the organs take control of the organs' function in that particular activity.

Can the brain be the center of the body's thinking and control?

Considering the following contents, we will now present another part of our theory.

1. Successful pig kidney transplant to a brain-dead patient[19]:

In September 2021, a pig kidney transplant was performed on a brain-dead patient at the Lang-one Center in New York under the supervision of Dr. Robert Montgomery. The pig kidney was transplanted out of the patient's body into a femoral vein. The brain-dead patient also showed signs of kidney failure. The transplanted kidney had an acceptable function in urine production and creatinine excretion during the evaluation period.

Modern medical science claims that the brain is the center of control over the function of the body's organs

and the center of maintaining and keeping the balance of the body.

Our question is: Given the current medical science, how can we justify the proper functioning of a transplanted kidney in a brain-dead patient?

We believe in our theory that the brain is not the unit that controls the body. We will explain the function of the brain in the following.

2.a. The ability to regenerate dead brain cells in zebrafish as well as the phenomenon of neurogenesis:

According to a study conducted at the University of Utah, Dr. Adam Douglass described the study results as follows. (His remarks are available at healthcare.utah.edu). The zebrafish was able to replace lost neurons[20] (in other words, it had rebuilt its brain), an event in the hypothalamus and elsewhere in the brain.

2.b. The phenomenon of neurogenesis in the brain has also been proven[21,22]. It has even been hypothesized that the lack of proper neurogenesis in the hippocampus is a significant cause of depression[23]. Antidepressants also increase neurogenesis in the brain[24].

We ask concerning points 2.a and 2.b: Why did not the fish with destroyed brain cells die? It not only survived, but it also produced new brain cells without any problems. Why should we have neurogenesis in the brain? Why should specialized brain cells die and be replaced with new ones?

The answers to these questions are very logical with our theory.

Before presenting our answer and theory on this, we will raise another issue.

Modern medical science considers that the brain hippocampus is the center of memory and learning. Numerous studies show that neurogenesis is a stable function in the brain, including the hippocampus.

Our question is: Given that the hippocampus of the brain is the center of memory, learning, and the process of neurogenesis (death and birth of neurons) in the hippocampus is continuous, why do we not lose our memory? Why do we not forget what we have learned or mastered in our lifetime? Even other research about mice shows that strengthening a moral habit is directly related to increased neurogenesis in the hippocampus[25]. That is, with hippocampus neurogenesis, the mice did not lose their memory, but their most prominent moral habit was strengthened.

We raise our questions again in this section:

Why do we have neurogenesis?

Why did the fish not die after the destruction of the brain (the thinking and controlling unit of the body)?

Why do we have neurogenesis in the memory center? With neurogenesis in the memory center, why is our memory not impaired?

Our answers to these questions express another part of our theory:

We believe that the brain does not function as a thought, analysis, and memory unit. The brain is a part of our body that releases excess energy that comes from the organs to the brain. As mentioned earlier, the heart controls the organs by sending messages. Some of the electrical energy (nerve message) that reach the organs from the heart is sent to the brain after it causes the organs to function. The brain releases the energy received from the organs in the form of radiation and thermal energy. Research has shown that the temperature of the brain is higher than the center of the body, even during exercise[26]. Since brain neurons are constantly exposed to radiation and energy, they die over time. For this reason, with the phenomenon of neurogenesis, the brain replaces new neurons with destroyed neurons. Neurogenesis is a vital requirement for brain function.

In the section on the heart, we presented our theory of the long-term and short-term memory. The presence of neurogenesis in the hippocampus does not impair our memory because the hippocampus is not the center of our information and memory storage.

According to our theory, the regeneration of damaged organs in Zebrafish is understandable. The Zebrafish can rebuild its organs and even its brain after destruction. Where does the command to rebuild the damaged organ come from if not from the brain? Which organ controls the rebuilding process? The zebrafish was alive after the destruction of the brain, therefore

1. Which part of the fish's body was responsible for maintaining the body balance and keeping the body alive? It certainly was not the Zebrafish's brain.
2. Which part of the Zebrafish's body controlled the process of brain regeneration?

Based on our theory (The Balancing Heart Theory), we believe that the heart not only directs, but also controls the process of organ regeneration. The extension of the heart's neuron fibers to the organs and brain makes the heart able to send commands as well as control the regeneration process. (the heart's neurons are extended to the organs through the walls of the arteries).

The Zebrafish has been able to regenerate the brain.

We believe that the Zebrafish cannot regenerate the heart, because by destroying the heart there is no organ that can command regeneration and control the body's balance. The death of the heart is the death of the body.

The brain's function is also significant. If the brain cannot release energy correctly, the organs cannot function properly, or we cannot perform certain activities properly, or we suffer from problems such as depression and Alzheimer's. This is why drugs that stimulate neurogenesis in the hippocampus of the brain are used to treat depression.

We have expressed our theory in this article and research. We have achieved our results and theory by combining studies done by other researchers and through our experiments.

Results

According to modern medical science, the brain is the center of thought, analysis, and body control. The brain performs these tasks by sending neural messages that are electrical in nature. Scientists attributed these tasks to the brain because:

1. The brain has many nerve cells (neurons) that specialize in transporting electrical charges (nerve messages).
2. Heating or releasing radiation from certain parts of the brain during the operation of a specific body's organ.

Why do we consider the brain as the body analysis unit?
Is the brain's release of energy or radiation a sign of the performance of analysis?
What is the control mechanism that the brain uses over the organs? What is the initiation mechanism of neural electrical messages in the brain?
Why does neurogenesis (the death of specialized neurons and the birth of new neurons) in the brain not cause problems with brain function?
Why do we not forget and lose memories with the death of hippocampal neurons and the birth of new neurons?
Why are our memories not destroyed by neurogenesis of the brain hippocampus?
Why does a transplanted kidney work appropriately in a brain-dead patient?
Is the hippocampus the center of memory?
Is the brain controlling the body?

The conclusion of our theory is no.

The heart has the following characteristics that can help clarify the its role as a unit that controls and maintains the body's balance:
1. The heart is the source of electromagnetic energy and electrical energy. The amount of the electromagnetic field of the heart is 5000 times, while the amount of electric field of the heart is 60 times more than that of the brain[4].
2. The heart has a complex network of neurons[1]. Nerve cells specialize in sending electrical neural messages.
3. There is an extensive neural network in the aorta[2]. Moreover, these neurons are extended to the organs along the arteries and even along the small arteries' wall[5-9]. So it is incorrect to think of the heart's role as only a blood-pumping unit.
4. The proper function of a transplanted kidney in a brain-dead patient[19]: The kidney was placed outside the patient's body and connected only to the femoral vein. (The kidney connected to the artery, the artery originated from the heart, which means the kidney is connected to the heart) Despite this, it still had a good function in producing urine and excreting creatinine.
5. Zebrafish did not die after destroying a part of its brain and rebuilt the damaged part[20].
6. Continuous neurogenesis in the brain and hippocampus has been a proven phenomenon[21,22]. Neurogenesis of the brain hippo-campus (according to modern medical science, the hippocampus is the center of memory) not only does not cause a loss of memories and learning power, but in patients with depression and Alzheimer's, drugs that increase hippocampal neurogenesis improve the patient's condition.

Even a study shown in a population of aggressive mice; enhancement of the mice's most prominent moral trait was directly related to increased hippocampal neurogenesis (hippocampal neurogenesis has not impaired the behavioral memory either)[25].

Hippocampal neurogenesis means the death of specialized cells in the memory center, however it does not disrupt memories because the hippocampus is not a center for storing information and memory.

Our theory (The Balancing Heart Theory) stat-es:

The heart is responsible for maintaining and controlling the body's balance. The heart produces electromagnetic energy and electrical energy[3,4]. This electrical energy stimulates the neurons of the heart's nervous system (Electrical stimulation is a technique that has been used to promote nerve regeneration)[27]. The heart uses its neural network to send neural electrical messages to all organs through the neurons in the walls of the arteries.

In the case of involuntary work, the organs perform their activity, because they have information on how to perform automatic actions in their neuronal DNA. In case of imbalance or stressful and critical conditions, the heart intervenes and acts to create and maintain balance by sending messages to the relevant organs.

In the state of voluntary work and learning, when we begin to learn a particular subject, the body starts to make synapses between the involved neurons in that

particular subject in the medulla oblongata area so that the neurons of the collaborating organs communicate more smoothly and faster in performing that specific activity. These synapses define our short-term memory. Synapses are also created between the neurons of organs and the brain to drain excess energy more rapidly and efficiently from the brain.

With repetitive learning, synapses become more efficient, and if not repeated, synapses weaken until they eventually disappear.

By repetition of learning, practice, and acquisition of skills, genetic rearrangements happen in the heart's nervous system and the organ's neurons that are related to that particular activity due to the function of the transposons. These genetic rearrangements in the DNA of neurons determine our long-term memory. We have two copies of long-term memory, one in the heart's nervous system and the other in the neurons that reach the organs.

The brain has a higher temperature than the body due to its function[26]. As mentioned, the heart is responsible for controlling the organs and maintaining the body's balance by sending neural messages (which are electrical) to the organs. Excess electrical energy reaching the organs from the heart must be expelled from the organs and the body.

The organs send this excess energy to the brain, and the brain releases the extra energy. The brain releases energy in the form of thermal energy and radiation. During this time, brain neurons degenerate and are replaced by new neurons. The cause of neurogenesis is the death of neurons due to the release of energy from the brain, and the phenomenon of neurogenesis is a vital requirement for the brain to continue working correctly. Lack of neurogenesis prevents the proper release of excess energy of the organs, which impairs the function of an organ in the body whose extra energy in the brain is not adequately discharged or released.

Answer to the unsolved question

We can understand many unknowns in medical science by invoking the Balancing Heart Theory.

Based on our theory, we can explain the process of brain waves releasing up to thirty seconds after cardiac arrest. The COURIER JOURNAL has published the above article on March 11th, 2022. The website address of the above newspaper is: courirjournal.com

Dr. Ajmal Zemmar explained that in an 87-year-old patient with epilepsy and cerebral hemorrhage (The patient's brain did not have a function.) thirty seconds before and after cardiac arrest, the patient's brain emitted certain brain waves similar to waves emitted while dreaming. The patient's brain could not dream or think due to old age and epilepsy, as well as cerebral hemorrhage.

We intend to describe the process based on the theory of the balancing heart.

The only organ that can be a source for the patient's brain waves is the heart. The waves are emitted from the heart and take time to leave the brain in the form of brain waves.

According to the simple laws of physics, when the source of the wave propagator disappears, it still takes time for the last issued waves to disappear.

For example: if someone throws a stone into the water, a wave starts, the stone is submerged in the water, but the wave continues for some seconds until it disappears. Another example is when someone uses a home Wi-Fi network with a mobile phone, when the Wi-Fi device is disconnected, the mobile phone will have access to the Internet for some seconds. In this case, when the heart stopped sending the nerve messages, the last signals sent by the heart took thirty seconds to exit through the brain in the form of brain waves.

Future directions, Suggestions

Our theory puts many paths ahead for scientists and researchers.

1. Suggestion to Dr Bartley Griffith:
While we admire the effort to transplant a pig's heart into a human28, 29, if our theory is followed: the chances of a successful transplant of a recombinant pig heart into a human will be much higher if one can use the DNA of a patient's heart neuronal system to produce a recombinant heart.

Treatment of diseases

2. With the accurate knowledge of the heart's nervous system, the ways to treat severe illnesses such as Parkinson's can be discovered.

3. Concerning the use of electromagnetic wav-es to treat depression

There are certainly differences by accurately measuring the wavelengths of electromagnetic waves release from the heart of a person with depression and comparing them to healthy peo-ple[30].

By placing a patient with depression in a room with electromagnetic waves similar to those of healthy people (this energy and electro-magnetic waves can be generated in a special laboratory), we can treat a person with depression without medicine.

Based on the Theory of The Balancing Heart, we are very interested in collaborating with eager scientists and institutions for great discoveries.

Conflict of interest

Authors do not have any conflict of interest to declare.

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REVIEW

How anti-inflammatory and antioxidant dietary supplements are effective in undermining COVID-19 pathogenesis: the role of vitamin C and D

Cómo los suplementos dietéticos antiinflamatorios y antioxidantes son efectivos para socavar la patogénesis de COVID-19: el papel de la vitamina C y D

Zafer Yönden[1], Alireza Mohammadzadeh Shabestari[2], Arman Ghayourvahdat[3], Hannaneh Azimizonuzi[3], Seyyedeh Touran Hosseini[4], Amin Daemi[1]

1. Department of Medical Biochemistry, Faculty of Medicine, Cukurova University, Adana, Turkey
2. Department of Dental Surgery,Mashhad University of Medical sciences, Mashhad, Iran
3. Inventor Member of International Federation of Inventors' Associations , Switzerland
4. Department of Biotechnology, Institute of Natural and Applied Sciences, Cukurova University, Adana, Turkey

Corresponding author
Amin Daemi
E-mail: phd_bio@yahoo.com

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Abstract

Due to lack of effective treatment for novel pandemic coronavirus disease (COVID-19) caused by severe acute respiratory syndrome corona-virus-2 (SARS-CoV-2), the prevention strategies are the best choices to significantly control increasing number of patients. Numerous studies suggest an association between vitamin D and C and the outcomes of SARS-CoV-2 infection. Therefore, supplementation of vitamins such as D and C has been recommended prevention and treatment of the COVID-19. Vitamin D as an immunomodulator hormone could affect various respiratory infections by maintaining the immune system and blocking hyper-inflammatory responses like cytokine storm through decreasing viral replication and regulating the levels of pro-inflammatory/anti-inflammatory cytokines. There are also some evidences that vitamin D could alter severity of COVID-19. The effectiveness of vitamin C in the prevention and treatment of coronavirus has also been undertaken by several studies. Due to the important role of vitamin C in the immune system, a deficiency of this vitamin may increase the incidence, severity and the risk of death of COVID-19 disease. This could explain by this fact that vitamin C deficiency increases the risk of infections, decreases the immune system response and increases the risk of pneumonia. People with chronic diseases as high-risk COVID-19 patients also showed deficiency of these vitamins which could explain the severity and the high rate of mortality among them. Thus, it seems that sufficient vitamin D and C level in serum may have positive impact on decreasing risk of COVID-19 infection. Considering all aspects, we try to overviewed on the potential role of supplementation of vitamin D and C in COVID-19 disease. We summarized suggested impacts of these vitamins on SARS-CoV-2 and its pathogenesis. We also discussed mechanisms in which these two vitamins involved that could alter the COVID-19 infection.

Key words: COVID-19, SARS-CoV-2, vitamin D, vitamin C, inflammation, treatment, supplementation.

Resumen

Debido a la falta de un tratamiento eficaz para el síndrome respiratorio agudo severo, la nueva enfermedad pandémica por coronavirus (COVID-19) causada por -2 (SARS-CoV-2), las estrategias de prevención son las mejores opciones para controlar de forma significativa el creciente número de pacientes. Numerosos estudios sugieren una asociación entre la vitamina D y C y los resultados de la infección por SARS-CoV-2. Por lo tanto, se ha recomendado la suplementación de vitaminas como la D y la C para la prevención y el tratamiento del COVID-19. La vitamina D, como hormona inmunomoduladora, podría afectar a varias infecciones respiratorias manteniendo el sistema inmunitario y bloqueando las respuestas hiperinflamatorias como la tormenta de citoquinas mediante la disminución de la replicación viral y la regulación de los niveles de citoquinas proinflamatorias/antiinflamatorias. También hay algunas evidencias de que la vitamina D podría alterar la gravedad de la COVID-19. La eficacia de la vitamina C en la prevención y el tratamiento del coronavirus también se ha llevado a cabo en varios estudios. Debido al importante papel de la vitamina C en el sistema inmunitario, una deficiencia de esta vitamina puede aumentar la incidencia, la gravedad y el riesgo de muerte de la enfermedad por COVID-19. Esto podría explicarse por el hecho de que la deficiencia de vitamina C aumenta el riesgo de infecciones, disminuye la respuesta del sistema inmunitario y aumenta el riesgo de neumonía. Las personas con enfermedades crónicas como los pacientes con COVID-19 de alto riesgo también mostraron deficiencia de estas vitaminas, lo que podría explicar la gravedad y la alta tasa de mortalidad entre ellos. Por lo tanto, parece que un nivel suficiente de vitamina D y C en el suero puede tener un impacto positivo en la disminución del riesgo de infección por COVID-19. Teniendo en cuenta todos los aspectos, tratamos de hacer un resumen sobre el papel potencial de la suplementación de vitamina D y C en la enfermedad de COVID-19. Hemos resumido los impactos sugeridos de estas vitaminas en el SARS-CoV-2 y su patogénesis. También discutimos los mecanismos en los que estas dos vitaminas están involucradas y que podrían alterar la infección por COVID-19.

Palabras clave: COVID-19, SARS-CoV-2, vitamina D, vitamina C, inflamación, tratamiento, suplementación.

Introduction

Nutrient is as important issue in maintenance of immune system. Immune dysfunction due nutrient deficiency could increase prevalence of various respiratory infections. Multi essential micro-nutrient such as vitamins supplementation could reduce the incidence and prevalence of respiratory infection[1].

Following the emergence of a novel coronavirus from Wuhan, China, in December 2019, the respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected the whole world and is declared a pandemic by World Health Organization (WHO) on March 26, 2020.1 According to World metrics, this novel virus has been responsible for approximately 461,650,510 infections, of which 6,051,400 patients have died worldwide up to March 16, 2022[2]. After months of medical communities' efforts, one of the hottest topics is still the role of vitamin D in the prevention or treatment of COVID-19. Several functions, such as modulating the adaptive immune system and cell-mediated immunity, as well as an increase of antioxidative-related genes expression, have been proven for vitamin D to prevent and treat of acute respiratory infections. According to available investigations, it seems that such functions lead to cytokine storm suppression and avoid acute respiratory distress syndrome (ARDS), which has been studied on other pandemics and infectious diseases in recent years. To the best of our knowledge, unfortunately, after several months, there is no adequate high-quality data on different treatment regimens, which raise questions about gaps in scientific works such as observational studies without a control group or non-randomized controlled studies with retrospective nature covering a small number of patients[3]. The same issue is debatable for ascorbic acid or vitamin C with antioxidation and anti-inflammatory properties which confirmed in infections and sepsis. SARS-CoV-2 could also cause sepsis and ARDS with severity and critical illnesses. Effect of this vitamin as a cofactor has been also confirmed on cellular immunity and vascular integrity[4].

COVID-19: The immune system response

SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) receptor of type II alveolar cells of lungs and enters into the cells and spread its viral RNA to replicate. Through recognition of viral RNA by pattern recognition receptors (PRRs) in innate immune response[5], a series of downstream signaling activates Nuclear factor kappa B (NF-κB) and type I interferon to the produce pro-inflammatory cytokines and antiviral proteins respectively. SARS-CoV-2 also leads to endocytosis of ACE2 that maintain a proinflammatory cycle to promote accumulation of angiotensin II that resulted in acute lung damage. Furthermore, the studies confirmed association of enhanced inflammation and thrombosis in COVID-19 infection due to endothelial dysfunction and activation of coagulation. The angiotensin-converting enzyme 2 receptor (ACE2r) has been also overexpressed as the entry door for COVID-19 in endothelial cells leading to impaired endothelial homeostasis by IL-6[6,7].

Non-specific proteins (NSPs) of SARS-CoV are the key of inhibition the host innate immune response by inhibition of the expression of INF-β by binding to the host 40S ribosomal subunit and inhibition of translation and increasing translation efficiency of the viral mRNAs relative to human mRNAs[8].

SARS-CoV increases levels of interferon gamma (IFN-γ), IL-1, IL-6, IL-8, IL-12 induced protein 10 (IP-10), and Monocyte chemoattractant protein-1 (MCP-1) and also over activates of the T helper type 1 (Th1) cells-mediated immune response and subsequent increase in natural killer (NK) cells and polymorphonuclear neutrophils (PMN) which could cause lung damage. The severity of disease could increase by higher levels of IL2, IL6, IL7, IL10, Granulocyte colony-stimulating factor (GCSF), IP10, MCP1, Macrophage Inflammatory Protein (MIP)-IA, and Tumor necrosis factor (TNF) that heighten inflammatory responses and parenchymal damage which resulted in ARDS[9].

SARS-CoV-2 engages inflammasome and triggers pyroptosis in human monocytes, and cause infection. Pyroptosis could activate caspase-1, produce IL-1ß, cleavage gasdermin D, and enhance pro-inflammatory cytokine levels in human primary monocytes[10].

Level of IL-6 due to pleiotropic activity and having extensive effects on major biological systems of the body and the pathogenesis of diseases increases in the COVID-19 patients and is associated with the severity of the disease and mortality that make it potential predictor of COVID-19 severity in hospitalized patients. IL-6 promotes expression of the Tissue Factor (TF) gene and TF protein with procoagulant activity that have prothrombotic effects on human endothelial cells. IL-6 also increases expression of ACE2r protein that modulates the effects of COVID-19 on endothelial cells. The studies showed higher level of IL-6 was in COVID-19 patients with severe clinical complications than mild COVID-19 patients[11]. IL-6 also significantly increases levels of Caspase-1 protein as inflammatory mediator[10].

In cytokine storm as a consequence of severe COVID-19 infection, the level of IL-10 is increased earlier than IL-6. This feature is specifically seen in SARS-CoV-2 rather than SARS. Identified elevated levels of IL-6 and IL-10 are introduced as predicted covariates of severity of COVID-19 disease by clinical trials which represented pathological role of IL-10 in COVID-19 severity[12].

Hyperinflammation could be induced by SARS-CoV-2 N protein that promotes NLRP3 inflammasome through

mechanistically interaction, maturates proinflammatory cytokines that lead to aggravate lung injury and increase excessive inflammation[13].

Vitamin D responsibility in immune system response to COVID-19

The importance of the role of vitamin D in immune system is regulation of immune cells including dendritic cells (DCs), macrophages, natural killer cells and B-cells which involve in innate and adaptive immune system to regulate some immune responses with anti-inflammatory effects[14].

1,25-dihydroxyvitamin D (1,25 (OH)2D), the active form of vitamin D, synthesized from its precursor 25-hydroxyvitamin D (25-OHD) via the enzyme 1α-hydroxylase (CYP27B1) in immune cells (antigen-presenting cells: APCs) like macrophages and DCs in response of pathological invasions and also epithelia to activate dendritic cells and macrophages. This could represent importance of vitamin D as a regulator of the immune system response[15]. Vitamin D activates enzyme of 1-α hydroxylase to upregulate synthesis of calcitriol in antigen-presenting cells (APCs) to mediate antimicrobial action and anti-inflammatory effects. Vitamin D in innate immune system enhances increased chemotaxis, phagocytosis, phagolysosomal fusion, and barrier function in innate cells. Vitamin D3 upregulate cAMP in macrophages, monocytes, and epithelial cells and decrease anti-inflammatory cytokines. Moreover, vitamin D decreased cytokine secretion by effect on CD4+ T cells[16].

Production of cathelicidin antimicrobial peptide (CAMP) as antimicrobial peptides and interleukins including IL-4, IL-5, and IL-10 as type 2 anti-inflammatory cytokines is also induced by vitamin D in immune cells that increase immune system efficiency. ILs upregulate the NF-kB inhibitory protein IkBa to block NF-kB p65 activation. In addition, vitamin D could also stimulate conversion of proinflammatory M1 macrophage to the anti-inflammatory M2 phenotype[9].

Vitamin D also altered the mRNA expression of SARS-CoV-2 entry genes such as Tmprss2 and Ctsl genes that change activation of spike protein of SARS-CoV-2 for membrane fusion and viral control by the humoral immune response[17].

The renin-angiotensin system (RAS) is also involved in inflammation. Once RAS is activated by renin, angiotensin II levels increase, eliciting inflammation via NF-κB activation which in turns stimulates proinflammatory cytokines such as TNF, IL-6, and IL-12. ACE2 halts RAS activation. Vitamin D can decrease renin to revert the proinflammatory cycle[18].

Vitamin D could inhibit differentiation, maturation and antigen presentation of DCs which resulted in preventing autoimmunity and promoting self-tolerance by reducing expression of CD1a, CD40, CD80, & CD86, CCL4 & CCL19 and MHC class II, that decreasing activation of T cells. Adverse impact of this vitamin on DCs cells lead to decreased production of IL-12 and IL-23 that switches the immune axis from Th1 to Th2 phenotype. vitamin D also enhances development of regulatory T cells in viral infections. vitamin D could inhibit the inflammatory response to SARS-CoV-2 infection and also maintain the antiviral state of immune system by increasing the expression of IκBα protein and decreasing the expression of phosphorylated STAT-1 along that decline mRNA levels of IRF1, IRF7, IFN-β and CXCL8[19].

Vitamin D could reduce the cytokine storm by decreasing production of Th1 cells and suppressing the progress of inflammatory cascade by altering the proinflammatory cytokine signatures which has been implicated in severe COVID-19 infection. The active metabolite of vitamin D, Calcitriol (1,25(OH)2D3), prevents the production of proinflammatory cytokines, such as IFN-γ, TNF alpha, IL-2, IL-17, IL-21, NF-κB and toll-like receptors on monocytes and lead to upregulation of IL-4, IL-5 and IL-10[20].

Calcitriol also decreased the expression of adhesion molecules, as well as lipopolysaccharide-induced expression of receptor of the advanced glycation end product and IL-6 and upregulates a NF-κN inhibitor, IkB alpha and also upregulates the expression of ACE2. These implications may be uniquely applicable to the disease pathogenesis and severity of COVID-19[21].

Vitamin D significantly reduces effects of IL-6 on expression of TF and ACE2r genes that modulating effects of COVID-19 on endothelial cells via modulation of NF-κB and STAT3 activation[22].

Vitamin C responsibility in immune system response to COVID-19

Immune cells are highly enriched with vitamin C to modulate immunological functions including scavenging of oxidative species, trigger signaling pathways, activation of pro-inflammatory transcription factors and signaling cascade, regulation of inflammatory mediators, and phagocytosis and increasing neutrophil motility to the site of infection that require for the prevention of COVID-19 infection. During COVID-19 infection, dysfunctional immune system produced free radicals. Vitamin C as an emerge antioxidant enhances the immune system against oxidative stress that could cause severe lung injury in COVID-19 infection by neutralizing free radicals and creating balance between oxidants and antioxidants[23].

Vitamin C could influence replication mechanisms and life cycles of viruses by interaction with ACE2 by inhibiting the receptor binding domain (RBD) that disrupts binding SARS-CoV-2 to ACE2 receptor [24]. Vitamin

C can decrease cellular expression of ACE2 receptors in lung small airway epithelial cells (SAEC) and human microvascular endothelial cells (HMEC) at the protein and the RNA levels.

The Antioxidant properties of vitamin C can explain immunomodulating effects of it. Vitamin C could exhibit its impact on cellular and humoral immune response in lower concentrations and lymphoproliferative, chemotactic effects and enhanced natural killer cells activity in higher concentrations[25].

Antiviral effects of vitamin C is represented in its active form (L-dehydroascorbic acid (DHA) by inhibiting replication of viruses via upregulation several important pathways in antiviral responses include eIF2 signaling, autophagy, interferon response, and the JAK/STAT pathway[26].

NF-κB play a crucial role in immune system including regulation of cytokine and chemokines genes, inflammatory mediators, adhesion molecules, and apoptosis inhibitors as primary proinflammatory transcription factor. Vitamin C can inhibit the activation of NF-κB, production of TNF-α and IL-6[27].

Granulocyte-macrophage colony-stimulating factor (GMCSF) is a hemopoietic growth factor and cytokine that enhances survival, activation and differentiation myeloid cell populations such as monocytes, macrophages, neutrophils and eosinophils. This factor has beneficial effects in inflammatory disease. Vitamin C could reduce the GMCSF signaling responses that regulate cytokines redox-signal transduction in immune cells to control inflammatory responses. The other mentioned role for vitamin C is regulating the proliferation and function of T cells, B cells, NK cells to inhibit the progression of cytokine storms for improving immune system. Vitamin C also enhances lung epithelial barrier function, improving ARDS symptoms and respiratory function by control epigenetic and transcriptional factors of protein channels to regulate clearance of alveolar fluid.

Vitamin C could also directly inhibit of protease enzymes such as 3-chymotrypsin protease, which are responsible for SARS-CoV-2 entry production of interferon, and maturation of T-lymphocytes. Vitamin C also acts as a protection of these immune cells against oxidative damage[23].

Evaluation of administration of vitamin or in combination of other substances (such as vitamin D) in some clinical trials revealed benefit effects of that for treatment or prevent severe COVID-19. The effective dosing of vitamin C reported ranging from 250 to 500 mg orally to 10-24 g intravenous (IV) daily. The use of high-dose vitamin C is also reported for management and treatment of hospitalized COVID-19 patients by reduce cytokine storms in ARDS. According to these findings, for management the COVID-19 infections particularly sever one, many hospitals and health centers in China and USA have already started administrating IV vitamin C[4].

Concluding these findings, vitamin C possesses positive impacts on curing of infection and this may play a protective role in the current COVID-19 pandemic through boosting the immune system. Vitamin C could improve signaling cascades and signaling pathways and immune cells functions. These properties could be noteworthy for prevention and treatment of COVID-19 infection and improving immune system against COVID-19 infection.

Vitamin D deficiency

One of the proposed risk factors for numerous viral respiratory diseases is vitamin D deficiency.

Three factors have been identified as causing vitamin D deficiency including
(1) inadequate consumption by unhealthy diet with low D-rich foods such as cereals or Breastfeeding infants (low vitamin D in human milk)
(2) impaired absorption or metabolism of vitamin D because of skin type, pregnancy, smoking, obesity, age, may affect the related genes, diseases such as Crohn's disease and celiac diseases kidney and liver illness or taking medications like steroid drugs,
(3) limitation in sunlight (ultraviolet B (UVB)) exposure due to modern lifestyle, wearing full-cover clothes for jobs, cultural, religious and geographical reasons , air pollution that may cause less access to the UVB rays[28].

Vitamin D deficiency could cause impaired immune responses due to less available precursor of vitamin D (25-OHD) for synthesis of active form of vitamin (1,25 (OH) 2D)[15].

Although several attempts tried to confirm effects of this vitamin deficiency as immunomodulatory factor, on increased risk of COVID-19, higher severity and increased rate of hospitalization of patients, most of them represented conflicting results[29]. Moreover, some studies have ruled out an effective link between vitamin deficiency and these conditions[30,31].

However, rather than study of D3 serum levels, the polymorphisms of vitamin D binding protein (DBP), a specific transport protein which could influence on the plasma vitamin D and DBP concentrations, may possibly influence the results of these such studies and should be considered in study participants and checked out by genotyping[32].

For invasion host's cells, SARS-CoV-2 uses the angiotensin-converting enzyme 2 as the entry receptor and Transmembrane Protease Serine 2 (TMPRSS2) for S protein priming through Renin-Angiotensin-System which could be elevated by vitamin D deficiency which could increase the risk of COVID-19 infection[33].

In addition, the lack of vitamin D is a risk factor for the development of autoimmune and neuropsychiatric disorders[41].

Some studies confirm association of vitamin D deficiency with greater severity and higher mortality with higher rates of hospital admissions with longer hospital stays of COVID-19 patients. The severity of COVID-19 infection is measured by rates of mortality, hospital admission and duration of hospital stay.

Vitamin C deficiency

In spite of most of animals, human is unable to synthesis vitamin C in liver. Thus, it should be obtained regularly as an essential nutrient by people. Contrary to popular belief, studies show that vitamin C deficiency is likely to be common globally particularly in low-income countries[34,35]. In addition to low vitamin C diet, pregnancy, breastfeeding, overactive thyroid, inflammation, diarrhea, surgery, burns and smoking are mentioned as causes of vitamin C deficiency.

As an infection, COVID-19 has been studied for status of vitamin C deficiency among patients. The results showed sever depleted vitamin C status and interestingly elevated markers of oxidative stress among patients[36].

The clinical evidences confirmed reduced plasma levels of vitamin C in critically ill and ICU COVID-19 patients[37].

However, there are challenges on short-term administration of intravenous vitamin C in treating patients with COVID-19. Some results showed that this strategy could not reduce the risk of severity and mortality in patients with COVID-19[38].

Other studies showed that vitamin C therapy didn't reduce major health related outcomes in COVID patients and no significant benefit were observed on severity of illness and mortality[39,40].

Discussion

Prevention and treatment, COVID-19 pandemic has become the first topic for world health. Several strategies and clinical trials are suggested to decline rates of severity and its complications and necessary mortality of COVID-19 infection.

The vitamin D is the well-known supplementation for decreasing risk of SARS-CoV-2 infection due to several roles that mentioned for this supplement. It has shown that vitamin D receptor expressed in innate immune cells including monocytes, macrophages, DCs and could increase the differentiation of monocytes to macrophages. It also stimulates these immune cell proliferation and cytokine production. Vitamin D mainly has inhibitory effects in adaptive immunity on proliferation of B-cells, generation of plasma cell and secretion of immunoglobulin, Th1 cytokines and Th17 differentiation. It also increased apoptosis of B-cells[41].

These roles could explain the results that confirm vitamin D deficiency leads to exacerbated respiratory disease and severity and mortality of COVId-19 infection[42].

Vitamin C as an effective antioxidant factor could eliminate reactive oxygen and reactive nitrogen species. It also increases regeneration of other important antioxidants such as glutathione and vitamin E to their active state. This vitamin also improves innate immune system by promoting collagen synthesis to support the integrity of epithelial barriers. It also stimulates production, function and movement of neutrophils, lymphocytes and phagocytes. The emerge function in activity of NK cells that has important role in COVID-19 infection. It could also enhance differentiation and proliferation of lymphocytes[43].

Both vitamins could disrupt binding of SARS-Cov-2 virus to host cells through ACE2 by altering associated genes and downregulating signaling cascades. Deficiency of them could increase efficiency of cytokine storm that cause higher severity and eventually death in patients[44]. Overview of several studies concluded that supplementation with vitamins C and D improve the inflammatory response and decrease the severity of disease in patients with COVID-19[45].

Concluding remarks

Critical role of vitamin D and vitamin C in regulation and modulation of immune system in viral infections including covid-19 has been observed in studies.

Vitamin D could modulate immune cells and induce immune tolerance and has beneficial effects on immune function in autoimmunity. Following, the studies found that vitamin D deficiency modulates the number of immune cells in COVID-19 patients particularly in the number of NK cells[46]. The association of vitamin D deficiency with COVID-19 severity has been also confirmed[47]. A strong association was also found between lower 25(OH)D levels and increased rate of SARS-CoV-2 positivity and COVID-19 severity[48].

There is a controversial whether vitamin D level deficiency could increase risk of severe COVID-19 or the low vitamin level is a consequence of COVID-19. However, in both conditions, the treatment of vitamin D deficiency is highly recommended by clinical trials to prevent SARS-CoV-2 infection and also to achieve significant decrease in inflammatory marker[49].

In spite of numerous reported observational studies, fewer comprehensive studies have been conducted on vitamin C supplement in COVID-19 infection which increases the challenges and discussions about it. Considering the results, it seems that vitamin C with several immune supportive role showed minimal effect on risk of SARS-CoV-2, but could shorten duration of illness and decrease severity of COVID-19 infection and importantly prevent progression to more severe conditions such as pneumonia, ARDS, sepsis and COVID-19[50].

Conflict of interest

Authors do not have any conflict of interest to declare.

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CASE REPORT

Chromoblastomycosis of the heel with carcinomatous degeneration in a 32 - year - old man

Cromoblastomicosis del talón con degeneración carcinomatosa en un hombre de 32 años

Fanjalalaina Malinirina Ralahy MD[1], Joël Razafimahefa MD[2], Tahiriarivelo Randriamanantena MD[3], Nomena Randrianarisoa MD[4], Rivo Rakotoarivelo PHD[5], Fahafahantsoa Rabenja Rapelanoro PHD[6]

1. Service d'orthopédie CHU Tambohobe Fianarantsoa
2. Department of anatomo-pathology CHU Andrainjato
3. Department of maxillofacial surgery CHU Tambohobe Fianarantsoa
4. Service d'orthopédie CHU Fianarantsoa
5. Faculty of Medicine of Fianarantsoa
6. Faculty of Medicine of Antananarivo

Corresponding author
Fanjalalaina Malinirina Ralahy
E-mail: fafah.ralahy@gmail.com

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Abstract

Introduction: Chromoblastomycosis is a wart dermatosis. Madagascar is one of the worst affected countries in the world. Rare sporadic cases of malignant degeneration of chromoblastomycosis have been reported in the literature. This observation reports a case of degeneration of a case of inveterate chromoblastomycosis of the heel.
Observation: This was a 32-year-old young man who consulted for a chronic heel injury on his left foot that progressed for several years. For 8 months, the budding has rapidly increased in size with the appearance of inguinal lymphadenopathy. The lateral heel x-ray showed osteolysis of the greater tuberosity of the calcaneus. A biopsy made it possible to make the diagnosis of squamous cell carcinoma infiltrating chromoblastomycosis. A trans-femoral amputation was performed associated with an inguinal lymph node dissection. At 24 months of follow-up, the patient was in complete remission.
Conclusion: Carcinomatous degeneration is an insidious course and is a dramatic twist in chromoblastomycosis. Radical early treatment with amputation and lymph node dissection can achieve a good result.

Key words: Chromoblastomycosis, heel, osteolysis, squamous cell carcinoma, surgical amputation.

Resumen

Introducción: La cromoblastomicosis es una dermatosis verrugosa. Madagascar es uno de los países más afectados del mundo. Se han informado en la literatura casos esporádicos raros de degeneración maligna de cromoblastomicosis. Esta observación informa de un caso de degeneración de un caso de cromoblastomicosis inveterada del talón.
Observación: Se trata de un joven de 32 años que consulta por una lesión crónica en el talón del pie izquierdo de varios años de evolución. Desde hace 8 meses, la gemación ha aumentado rápidamente de tamaño con la aparición de adenopatías inguinales. La radiografía lateral de talón mostró osteólisis de la tuberosidad mayor del calcáneo. Una biopsia permitió hacer el diagnóstico de cromoblastomicosis infiltrante de carcinoma de células escamosas. Se realizó una amputación transfemoral asociada a una linfadenectomía inguinal. A los 24 meses de seguimiento, el paciente se encontraba en remisión completa.
Conclusión: La degeneración carcinomatosa es un curso insidioso y es un giro dramático en la cromoblastomicosis. El tratamiento temprano radical con amputación y disección de ganglios linfáticos puede lograr un buen resultado.

Palabras clave: Amputación quirúrgica, carcinoma de células escamosas, cromoblastomicosis, talón, osteólisis.

Introduction

Chromoblastomycosis is a manifestation of a fungal cutaneous infection, commonly caused by *Fonsecaea, Phialophora,* and *Cladophialophora spp. Chromoblastomycosis* is found in tropical and subtropical climate zones, especially in Philippines, Malaysia, Venezuela, India and Brazil. Madagascar represents the most important focus of this fungal disease in the world with one case for every 480 inhabitants[1]. The contamination consists of a direct inoculation of the fungus into wounds from contaminated materials. This is almost seen in adults, walking barefoot in rural forest. Occasional sporadic cases of malignant transformation of chromoblastomycosis have been reported in the litterature. Herein, we report a case of chromoblastomycosis of the heel with carcinomatous degeneration. The purpose is to provide additional knowledge of this insidious evolution.

Case presentation

A 32 - year - old man presents with a budding wound of the right heel. He works in the tropical forest reserve of the centre - east of Madagascar. Other than a regular artisanal alcoholic consumption, his past medical history was unremarkable.

The disease started 10 years earlier after a wood splinter injury of the left heel in the forest. Despite local wound cares, he noticed a slowly progressive raised lesion in the central zone of the initial wound in an apyretic context. He was then referred to the local health center and underwent 3 surgical excisions during the disease course, respectively 2 years, 2 years and 6 months, 4 years after the initial injury, which were all followed by relapse.

Since 8 months, the budding lesion increased rapidly in size and inguinal lymph nodes were enlarged. He also complained of inflammatory disabling pain over the lesion. The pain was increasingly intense, particularly at night, radiating to the leg and the posterior face of ipsilateral knee.

At presentation, the patient was apyretic, had a performance status score of 4 and the body mass index was 17,9kg/m^2. A large cauliflower – like lesion that entirely involved the whole posterior part of the right foot has been noticed and measured about 20 cm in diameter. Superficial skin was inflamed and showed collateral circulations (**Figure 1**). An enlarged firm and fixed inguinal lymph node measuring 3 cm in diameter has been also observed. The rest of the physical examination was unremarkable.

Biological evaluation revealed normal blood count results and HIV test result was negative. Radiographs of the left heel in projection profile demonstrated an osteolytic lesion of the calcaneal tuberosity characterized by centripetally disorganized opacities with a superposed wave aspect in the distal margin (**Figure 2**).

A biopsy has been performed between a normal - appearing tissue and the lesion. Histopathological examination revealed an invasive squamous cell carcinoma arising from chromoblastomycosis (**Figure 3**).

Despite the limited availability of imaging, staging procedures only included chest X-ray and abdominal ultrasound that did not perceive any malignant localisation.

The patient underwent a transfemoral amputation with inguinal lymph node dissection. Histopathological

Figure 1: Ulcero-budding heel wound with central fissures and peripheral inflammation.

Figure 2: Radiographs of the left heel : osteolytic lesion of the calcaneal tuberosity

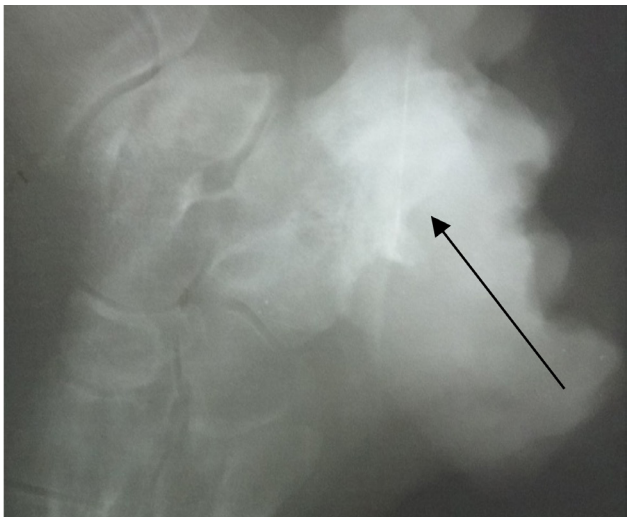
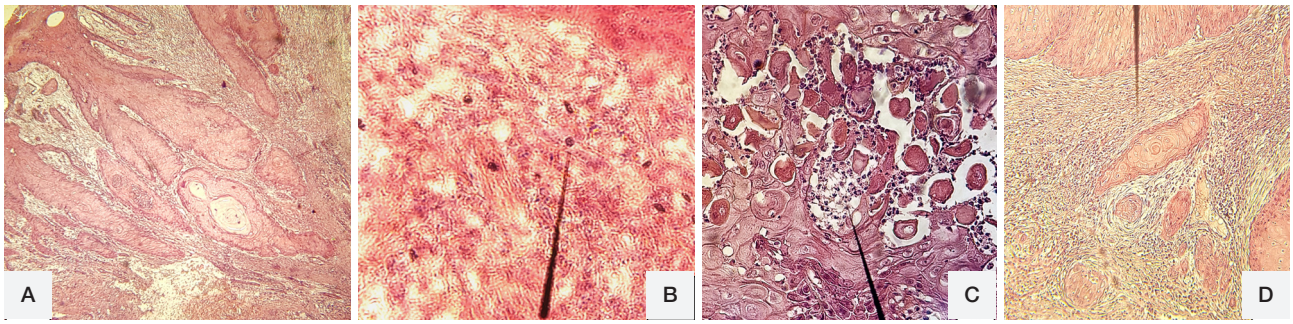


Figure 3: Invasive squamous cell carcinoma arising from chromoblastomycosis.
A, pseudoepitheliomatous hyperplasia. **B**, fumagoïd bodies or sclerotic bodies (arrow). **C**, inflammatory cells exocytosis, intraepidermal abcess (arrow). **D**, Malignant transformation , characterized by atypical cells, infiltrating deeply into the dermis. (Hematoxylin Eosin staining x 400)



examination of the surgical specimen confirmed the diagnosis. A total of 24 lymph nodes were examined, among which 3 were metastatic. Based on a multidisciplinary decision, no adjuvant treatment was conducted. At 24months - follow up, the patient was alive and well with complete remission.

Discussion

The first report of malignant transformation of chromoblastomycosis was described by Caplan in 1968[2] in a patient from Nicaragua. Since then, 10 other cases have been reported especially in tropical rainforest areas like Brazil and Madagascar. In all those cases, the median age of patients was 63 years old [39 - 72][3]. In the present paper, we describe the first case of neoplastic degeneration of chromoblastomycosis in a patient under 35 years of age.

Six species are recognized to cause chromoblastomycosis, which are *Chladophialophora carrionii, Fonsacea compacta, Fonsacea pedrosoi, Phialophora verrucosa, Rhinocladiella aquaspersa* and *Exphiala*[4]. The disease is characterized by the presence of sclerotic bodies or muriform bodies, in infected tissues. In Madagascar, the prevalence rate is among the highest reported in the world and the main causative agents are Fonsacea pedrosoi and *Chladophialophora carrionii*[4]. Those 2 species have been also mostly implicated in malignant transformation of chromoblastomycosis[6]. In our case, the diagnosis has been made histologically on a biopsy specimen that did not allow isolating the causative agent.

The infection usually results from a traumatic injury and a direct inoculation of the fungus. Thus the foot is the most frequently involved site. The primary lesion is represented by a papule that slowly enlarges and forms a friable and easily bleeding vegetating lesion. However, ulcerated patterns may also be observed. The wound could be secondarily infected with bacteria. Lesions that evolved over 10 years with clinical characteristic changes may suggest a malignant degeneration. In our case, the pain exacerbation and the presence of new lesions with ulcerated pattern on the primary lesion have motivated the patient to consult. Carcinomatous degeneration of chromoblastomycosis is included among malignant transformation of chronic wounds of infectious (paracoccidioidomycosis, leishmaniasis, lobomycosis, tropical ulcers and chronic osteomyelitis) or traumatic (burn scars, traumatic wounds) causes. Malignant transformation usually occurs more than 10 years after the primary lesion. It has been reported that chronic inflammation produces cytotoxic molecules (leukotrienes, prostaglandins) and free radicals which may induce nuclear alterations and activate or increase oncogene expressions[7]. Besides, prolonged local Voriconazole therapy is also associated with a high risk of malignant transformation[8]. The most common histologic type is squamous cell carcinoma. Malignant melanoma has been also described in rare cases[6]. Evolution is almost always favorable after surgery, except in the presence of visceral metastasis. Amputation is usually required as extensive local and regional spread is mostly encountered. This has been observed in our cases and transfemoral amputation with inguinal lymph node dissection has been performed. To prevent the possibility of malignant transformation as well as to avoid amputation, the disease should be early – treated. The combination of antifungal drugs with immunoadjuvant compounds such as glucan and imiquimod have been investigated in recent years. The glucan, which is an immunomodulator, is considered as an effective treatment, in injectable formulation and associated with itraconazole[6]. Imiquimod, an immunomodulatory agent that exhibits antitumor and antiviral effects, is also effective in external use, 4 times a week and combined with itraconazole[9]. There are also data to suggest that terbinafine, initially used by Esterre et col[10], is effective in conjunction with amphotericin B, and some other therapeutic approaches such as surgery, phototherapy and CO2 laser. However, the real challenge for countries with a fragile health system like Madagascar is to ensure early diagnosis and access to treatment.

Conclusion

Carcinomatous degeneration is an insidious and dramatic progression of the lesions of Chromoblastomycosis. Early treatment represented by radical amputation associated with lymph node dissection showed good results.

Conflict of interest

Authors do not have any conflict of interest to declare.

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CASE REPORT

Barotrauma during apnea testing for brain death. Barotrauma and apnea testing

Barotrauma durante la prueba de apnea para muerte cerebral. Pruebas de barotrauma y apnea

Mehmet Turan Inal[1], Dilek Memis[1], Ece Burçak Ceritoglu[2], Hilal Karakaş[2], Osman Simsek[3], Fazlı Yanık[4]

1. Trakya University Faculty of Medicine, Department of Anesthesiology and Reanimation, Prof. Dr.
2. Trakya University Faculty of Medicine, Department of Anesthesiology and Reanimation, Assis. Dr.
3. Trakya University Faculty of Medicine, Department of Neurosurgery, Assoc. Prof. Dr.
4. Trakya University Faculty of Medicine, Department of Thorasic Surgery, Assoc. Prof. Dr.

Corresponding author
Prof. Dr. Mehmet Turan Inal
E-mail: mehmetturaninal@yahoo.com

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Abstract

The apnea test is used for the diagnosis of brain death. Various complications have been reported to have developed during the apnea test.

A 44-year-old woman was hospitalized in the intensive care unit due to unconsciousness due to a posterior inferior carotid artery aneurysm. On the forty-ninth day of her hospitalization in the intensive care unit, the patient had no motor response and all brain stem reflexes were negative. Brain death was considered in the patient, but subcutaneous emphysema and bilateral pneumothorax developed within minutes during the apnea test. The patient underwent bilateral tube thoracostomy. The patient could not be diagnosed with brain death and died on the fiftieth day of her hospitalization.

This report emphasizes that multiple complications can be observed during the apnea test and underlying mechanisms and therapeutic approaches are discussed.

Key words: Brain death, apnea test, barotrauma.

Resumen

La prueba de apnea se utiliza para el diagnóstico de muerte cerebral. Se ha informado que se han desarrollado varias complicaciones durante la prueba de apnea.

Una mujer de 44 años fue hospitalizada en la unidad de cuidados intensivos por pérdida del conocimiento debido a un aneurisma de la arteria carótida inferior posterior. Al cuadragésimo noveno día de su hospitalización en la unidad de cuidados intensivos, la paciente no tenía respuesta motora y todos los reflejos del tronco encefálico eran negativos. Se consideró muerte cerebral en el paciente, pero se desarrollaron enfisema subcutáneo y neumotórax bilateral en cuestión de minutos durante la prueba de apnea. El paciente se sometió a una toracostomía con tubo bilateral. La paciente no pudo ser diagnosticada de muerte encefálica y falleció al quincuagésimo día de su hospitalización.

Este informe enfatiza que se pueden observar múltiples complicaciones durante la prueba de apnea y se discuten los mecanismos subyacentes y los enfoques terapéuticos.

Palabras clave: Muerte encefálica, prueba de apnea, barotrauma.

Introduction

Brain death (BD) is the event of irreversible damage to all brain functions, including the brain stem[1]. The guidelines of the American Academy of Neurology are often used for for determining brain death[2]. During the apnea test, the patient is temporarily disconnected from the ventilator and PaCO2 levels are allowed to rise, while careful monitoring of the patient is required. A positive test is defined by the complete absence of respiratory effort under these conditions[2].

Numerous complications were reported during the apnea test used in the diagnosis of brain death[3-8]. The occurrence of subcutaneous emphysema and pneumothorax during apnea testing is relatively rare, and many physicians may not be aware of the possibility of these complications. The mechanism for this situation was as follows: direct trauma to the tracheobronchial tree during catheter insertion for oxygen delivery and another mechanism is excessive air trapping in the lungs due to the high flow rate of oxygen. As a result it can cause increased pressure in the lungs and even pneumothorax. This may result in acute hemodynamic or pulmonary instability and even cardiac arrest, as well as lead to premature termination of the apnea test or decreased perfusion of organs that can be employed to transplantation[3-8].

In this case report, we aimed to present the diagnosis and treatment modalities of a patient who developed subcutaneous emphysema and pneumothorax during the apnea test.

Case report

A 44-year-old female patient who was operated on for bleeding from the PICA aneurysm was admitted to the intensive care unit due to impaired consciousness. Although no pathology was detected on the cranial CT scan of the patient, the patient was intubated orotracheal, and mechanical ventilation treatment was started because infiltrates were found in PA lung X-ray and Glasgow Coma Scale was $E_4M_3V_1$. The patient had a history of hydrocephalus.

Percutaneous tracheotomy was performed on the 11th day of hospitalization. On the 49th day of hospitalization, no brain or brain stem reflexes could be found in the patient. The patient's body temperature was 36.6°C and blood pressure was 110/70. The chest radiograph of the patient who received dopamine at a dose of 5 ug/kg/min was normal. After pre-oxygenation with 100% oxygen from the patient whose cardiovascular functions were stable, the partial oxygen pressure in arterial blood gas was 559 mmHg. The patient, who also met other conditions before the apnea test, was withdrawn from the mechanical ventilator and a 12-french catheter was placed 4-5 cm below the tracheotomy cannula to provide an oxygen flow of 4 L/min. Subcutaneous emphysema was detected in the face and chest area of the patient 1 minute later. Tachycardia of up to 160 beats/minute developed in the patient. In the lung auscultation performed in the patient whose apnea test was terminated, and he was connected to a mechanical ventilator, bilateral respiratory sounds were absent. Bilateral pneumothorax was detected in the PA lung X-ray taken with the patient, and bilateral tube thoracostomy was performed. Although subcutaneous emphysema and pneumothorax did not progress, the patient was considered dead one day after the apnea test could not be performed again, since hemodynamic stability could not be achieved.

Discussion

In this case report, subcutaneous emphysema and pneumothorax developing during the apnea test were reported.

Different cases of pneumothorax development during apnea testing have been reported in the literature[3-8]. The pneumothorax cases were evaluated in a systemic review published by Gorton et al.[3]. It was pointed out that the development of pneumothorax was rapid-mostly in minutes-in most of the patients. In the same review, it was reported that in a significant part of the cases, absence of breath sounds, development of hypoxia, and detection of subcutaneous emphysema were symptoms of pneumothorax. In our patient, similar to the review, subcutaneous emphysema developed within minutes after oxygen administration at the beginning of the apnea test. There were no bilateral breath sounds on lung auscultation. The development of subcutaneous emphysema during oxygen insufflation at the beginning of the apnea test made us think that the patient might develop pneumothorax. The definitive diagnosis of the patient was made with thorax CT.

The mechanism of development of subcutaneous emphysema and pneumothorax during the apnea test has not been clearly defined. The first possible mechanism is direct trauma to the tracheobronchial tree during catheter insertion for oxygen delivery; This mechanism may be valid in our patient as the symptoms develop immediately. Another mechanism is excessive air trapping in the lungs due to the high flow rate[3-5]. High flow rates (high 6 L/min) can cause tracheobronchial trauma. Air entrapment may occur if the oxygen cannula occludes most of the diameter of the tracheotomy or endotracheal tube. The high flow rate is believed to cause the development of subcutaneous emphysema and pneumothorax[3-5]. Gorton et al.,[3], in their review, recommended using a small oxygen insufflation catheter that would not obstruct

the lumen of the endotracheal tube, using tape to fix the oxygen insufflation catheter, and not advancing the insufflation catheter deeper than 35 cm. Goranovic et al.[4] reported that during the apnea test, the diameter ratio of the endotracheal tube/insufflation catheter <1.75 and the O_2 flow >10 L/minute may be related to high insufflation pressures. In their case report, the patient had high pressure at the end of the insufflation catheter and direct contact of the insufflation catheter with the trachea, which could have caused a small perforation of the tracheal membrane. This perforation was manifested by noise, shoulder, and upper thorax movements, subcutaneous emphysema, and apical pneumothorax. In the study of Henry et al.[6] on manikins, it was reported that the use of an insufflation catheter with a diameter less than 70% of the inner diameter of the endotracheal tube and 6 L / min of airflow may reduce the risk of procedural complications. In another study, the authors recommended using a cannula that is significantly smaller than the inside diameter of the endotracheal tube to avoid air trapping during the apneic oxygenation procedure[7]. In our patient, we advanced the oxygen insufflation cannula[4-5] cm into the tracheotomy cannula and our oxygen flow rate was 4 l/minute. We used a 12 french aspiration tube to deliver oxygen to our patient, and the patient had a 7.5 tracheotomy cannula. In most of the publications, the patient was given an apnea test in the first few days of admission to intensive care, but in our case, we administered an apnea test to the patient on the forty-ninth day, we think that weakening and thinning of the trachea may increase the risk of developing subcutaneous emphysema and pneumothorax.

Gorton et al[5]. reported in their study that the apnea test was repeated in only half of the cases that developed pneumothorax during the apnea test. The same authors reported that in some cases that developed pneumothorax in their case series, the heart and lung were excluded from the donation list. This situation will result in the inability to use the organs even if the patients are diagnosed with brain death. In our case, the apnea test could not be performed again due to hemodynamic instability and the patient died the next day.

When brain death guidelines are reviewed, the frequently used American Academy of Neurology guidelines recommend 6 L/min oxygen administration with an oxygen cannula placed at the level of the carina through the endotracheal tube, but there is no recommendation on the size of the oxygen cannula[2]. In the ANZIC guideline, another resource used in the diagnosis of brain death, attention is drawn to pneumothorax that may develop during the apnea test[8].

As a result, if hemodynamic deterioration develops during the apnea test, pneumothorax should be considered and prompt treatment should be provided. We believe that all physicians performing apnea tests should consider the possibility of this complication.

Conflict of interest

Authors do not have any conflict of interest to declare.

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CASE REPORT

Hypothyroidism presented with dysarthria and generalized weakness: a case report and review of literature

Hipotiroidismo presentado con disartria y debilidad generalizada: informe de un caso y revisión de la literatura

Irene (Tai-Lin) Lee[1], Ivanshi Gondalia[2], Nicholas Harford[2], Michael Naso[2]

1. Center for Global Health, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA.
2. Griffin Hospital, Derby, CT, USA.

Irene (Tai-Lin) Lee
E-mail: heyttymonica@gmail.com

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Abstract

Generalized muscle weakness is a common complaint in the emergency department. The presence of concomitant dysarthria often triggers the suspicion of an acute stroke. However, none of these symptoms are specific to stroke and up to 30% of dysarthric patients ended up having another disease. Endocrine disturbance is a well-known mimicker of stroke and should always be considered in patients presenting with generalized weakness. It was estimated that over 70% of patients with hypothyroidism had complaints suggestive of muscle dysfunction. Although bulbar muscle involvement is rare, a few case reports have described undiagnosed hypothyroidism presented with dysarthria and generalized weakness. Here we described a 64-year-old female admitted for acute weakness in bilateral upper and lower extremities causing difficult ambulation and slurred speech. On physical examinations, the muscle power was 3/5 in all four limbs, and dysarthria was appreciated. She was initially treated for an acute stroke until she was found to have a significantly elevated serum creatinine kinase (CK) level and serum thyroid-stimulating hormone (TSH). Her CK was 977 U/L, TSH 289, free T4 <0.07, and T3 0.3. She also had dyslipidemia. Repeat history and medication reconciliation revealed poor compliance to Synthroid treatment for Hashimoto thyroiditis. Her muscle power and speech drastically improved after intravenous levothyroxine of 100mcg daily. Hypothyroid myopathy typically affects the type II fast-twitching muscle, leading to retarded muscle contractions. CK is elevated in about 60-90% of the patients and does not correlate to the severity of muscle involvement. Although mostly progressive, cases with an acute presentation of generalized weakness have been reported due to superimposed metabolic or electrolyte imbalance. In addition, dysarthria can be attributed to bulbar myopathy and/or glucosaminoglycan deposition. A review of literature identified two cases of hypothyroidism presented with dysarthria. The other two patients were diagnosed only after the routine thyroid function test came back positive. It appears that hypothyroidism is an underrated cause of dysarthria and that associated symptoms are frequently missed in the initial history due to low physician suspicion. Therefore, the initial assessment for these patients should include relevant history, physical examination, and a TSH level. Treatment is thyroid hormone replacement therapy. Prompt recovery of muscle weakness and dysarthria is expected, typically within 2 months.

Key words: Hypothyroidism, dysarthria, weakness.

Resumen

La debilidad muscular generalizada es una queja frecuente en los servicios de urgencias. La presencia de disartria concomitante suele hacer sospechar un ictus agudo. Sin embargo, ninguno de estos síntomas es específico del ictus y hasta el 30% de los pacientes con disartria acaban teniendo otra enfermedad. Las alteraciones endocrinas son un mimetismo bien conocido del ictus y siempre deben tenerse en cuenta en los pacientes que presentan debilidad generalizada. Se calcula que más del 70% de los pacientes con hipotiroidismo presentan quejas que sugieren una disfunción muscular. Aunque la afectación de los músculos bulbares es rara, algunos informes de casos han descrito hipotiroidismo no diagnosticado que se presenta con disartria y debilidad generalizada. Aquí describimos a una mujer de 64 años que ingresó por una debilidad aguda en las extremidades superiores e inferiores bilaterales que le dificultaba la deambulación y la dificultad para hablar. En la exploración física, la potencia muscular era de 3/5 en las cuatro extremidades y se apreciaba disartria. Inicialmente fue tratada por un accidente cerebrovascular agudo, hasta que se descubrió que tenía un nivel de creatinina quinasa (CK) sérica y de hormona estimulante de la tiroides (TSH) significativamente elevados. Su CK era de 977 U/L, TSH 289, T4 libre <0,07 y T3 0,3. También tenía dislipidemia. La repetición de la historia y la conciliación de la medicación revelaron un mal cumplimiento del tratamiento con Synthroid para la tiroiditis de Hashimoto. Su fuerza muscular y su habla mejoraron drásticamente tras la administración de levotiroxina intravenosa de 100mcg diarios. La miopatía hipotiroidea suele afectar al músculo de contracción rápida tipo II, lo que provoca un retraso en las contracciones musculares. La CK está elevada en aproximadamente el 60-90% de los pacientes y no se correlaciona con la gravedad de la afectación muscular. Aunque la mayoría de las veces es progresiva, se han descrito casos con una presentación aguda de debilidad generalizada debido a un desequilibrio metabólico o electrolítico superpuesto. Además, la disartria puede atribuirse a la miopatía bulbar y/o al depósito de glucosaminoglicano. Una revisión de la literatura identificó dos casos de hipotiroidismo presentados con disartria. Los otros dos pacientes fueron diagnosticados sólo después de que la prueba rutinaria de la función tiroidea resultara positiva. Parece que el hipotiroidismo es una causa infravalorada de disartria y que los síntomas asociados se pasan por alto con frecuencia en la historia inicial debido a la baja sospecha del médico. Por lo tanto, la evaluación inicial de estos pacientes debe incluir la historia pertinente, la exploración física y un nivel de TSH. El tratamiento es la terapia de sustitución de la hormona tiroidea. Se espera una pronta recuperación de la debilidad muscular y la disartria, normalmente en dos meses.

Palabras clave: Hipotiroidismo, disartria, debilidad.

Introduction

Generalized muscle weakness is a common complaint in the emergency department (ED) with inexhaustible differential diagnoses. Patient history and careful neurological examinations are crucial as some etiologies may be life-threatening[1]. Dysphagia and dysarthria indicate possible brain-stem stroke, but any causes affecting the bulbar muscles can appear similarly. The non-specific nature of weakness was demonstrated in a prospective observational study involving 79 consecutive patients presenting with generalized weakness. The final diagnosis encompassed 14 distinct international classification of disease-10 codes and endocrine, nutritional, and metabolic diseases were the second most frequent cause (14%)[2]. However, the list of endocrine, nutritional, and metabolic disturbance is equally heterogeneous, including hypothyroidism, hypoglycemia, adrenal insufficiency, and periodic paralysis due to electrolyte imbalance[1]. Hypothyroidism results from deficiencies in the thyroid hormones, thyroxine (T4) and triiodothyronine (T3). It is estimated that 3-10% of the world population has clinical or subclinical hypothyroidism[3]. Patients may complain about fatigue, cold intolerance, constipation, irregular menses, and weight gain, reflecting a generalized slowing of metabolic processes[4]. On physical examinations, dry skin, coarse hair, generalized non-pitting edema, macroglossia, and bradycardia may be appreciated[3,4].Diagnosis is made through laboratory data showing a high serum thyroid-stimulating hormone (TSH) concentration and low serum free T4 level. In addition, hyponatremia, dyslipidemia, and hyperuricemia are not uncommon[3]. Hypothyroid myopathy occurs in 30-80% of hypothyroid patients as weakness, spasm, pain, or stiffness in the muscles[5]. Serum creatine kinase is often elevated[6]. Atrophy of the fast-twitching muscles and hypertrophy of the slow-twitching muscles due to glucosaminoglycan deposition in muscle fibers may be observed on physical examinations[7]. Although rare, hypothyroidism presenting with generalized muscle weakness and dysarthria is possible. Here we presented a patient with undertreated hypothyroidism who endorsed progressive generalized weakness and slurred speech. The stroke workup was negative and the initial history disclosed symptoms pertinent to hypothyroidism. Intravenous levothyroxine was commenced and her muscle strength improved drastically. The clinical presentations, differential diagnosis, pathogenesis, and management of hypothyroid myopathy were summarized in the discussion.

Case report

A 64-year-old female presented to our ED due to acute weakness in bilateral upper and lower extremities causing difficult ambulation and slurred speech. Her past medical history was remarkable for Hashimoto thyroiditis, dyslipidemia, asthma, osteopenia, and primary hyperparathyroidism. On examination, the temperature was 97.7°F, the blood pressure 205/102 mmHg, the heart rate 51 beats per minute, and the oxygen saturation 99% while the patient was breathing ambient air. A review of systems was notable for progressive weakness, lethargy, and psychomotor retardation for one month. She was prescribed Synthroid 125 mcg daily but had had varying TSH readings from <0.015 to 9.77 due to poor compliance. Her last dose of Synthroid was one week prior to admission. On evaluation, the patient was alert and oriented. She had mild periorbital swelling and a thyroid goiter. Her muscle bulk was compatible with her age and there was no non-pitting edema or induration in the legs. Strength in both arms and legs was assessed as 3/5. She had no focal neurological deficits and deep tendon reflexes were normal. Computed tomography and magnetic resonance imaging of the brain revealed no acute ischemic or hemorrhagic change. Electrocardiography showed regular sinus rhythm with no acute ST changes. Routine thyroid function tests reported a TSH of 289, free T4 <0.07, and T3 0.3. The lipid panel revealed a cholesterol level of 420, low-density lipoprotein 287, high-density lipoprotein 81, and triglyceride 312. The complete metabolic panel was normal except for an elevated creatine kinase (CK) at 977 U/L. Under high suspicion for hypothyroid myopathy, intravenous levothyroxine 100 mcg daily was commenced. Her muscle power improved to 3/5 in both upper and lower extremities on the second day of hospitalization and fully recovered after three days of levothyroxine treatment. Her thyroid function normalized and her subjective symptoms improved. She was discharged on Tirosint 125 mcg daily.

Discussion

Myopathy in hypothyroid patients is not fully understood. T4 deficiency reduces mitochondrial electron transport chain efficiency, which causes selective atrophy of the fast-twitching (type IIb) muscle and the clinical presentation of retarded muscle contractions[7]. At the same time, compensatory hypertrophy and glycosaminoglycan deposition results in prolonged oxidative damage and eventually rhabdomyolysis[7]. Although a TSH plus free T4 level suffices for the diagnosis of hypothyroid myopathy, their value does not always correlate with the severity of muscle weakness[7]. CK is a non-specific marker widely used to diagnose muscle injury. Causes of an elevated CK include inflammatory myopathies, dystrophinopathies, rhabdomyolysis, and certain medications[9]. CK is elevated in about 60-90% of hypothyroid patients even years before clinically overt muscle diseases[6]. In contrast, CK usually remains normal in other endocrine myopathies such as hyperthyroidism, hyperparathyroidism, and

Cushing's syndrome[9]. Electromyography can be helpful but is neither sensitive nor specific[7]. Typical findings include short-duration, polyphasic, and low-amplitude motor unit action potentials[10]. Hoffmann syndrome is a subtype of hypothyroid myopathy characterized by proximal muscle weakness and pseudohypertrophy of the calf muscles[10]. Muscle biopsy is not usually needed but will show type II fiber atrophy, type I fiber hypertrophy, mitochondrial inclusions, glycogen accumulation, disorganized myofibrils, focal necrosis, and minimal inflammatory infiltrates[7].

Besides muscle damage, hypothyroidism rarely presents with periodic paralysis due to disturbance in potassium ion metabolism. T4 normally increases the number and efficiency of the hydrogen-potassium ATP pump on the distal convoluted tubules[11]. Therefore, hypothyroidism predisposes patients to hypokalemia when there is a concomitant cause of renal potassium wasting. However, periodic paralysis is more commonly seen in patients with hyperthyroidism due to intracellular potassium shift and 14 cases associated with hypothyroidism had been reported[11].

Another interesting finding in our case was dysarthria. Stroke remains the most important differential diagnosis for acute dysarthria but up to 30% of these patients ended up having another disease[12,13]. A review of literature identified only two cases of bulbar muscle involvement in hypothyroid patients. The first case was a 43-year-old man presented to the ED with dizziness, blurred vision, and slurred speech for one day, suspected to have a brain-stem infarction. The patient had sleep apnea but no history of thyroid disorder[14]. The second case was a 39-year-old female complaining about dysarthria for 6 months. She had sleep apnea but her past medical history was otherwise unremarkable[15]. Both cases were diagnosed after the routine thyroid function tests came back positive and the second history revealed long-standing hypothyroid symptoms that were initially neither reported nor asked for. Dysarthria attributed to hypothyroidism may be caused by myopathy in the articulating muscles, edematous swelling of laryngeal and hypopharyngeal structures, and macroglossia from glucosaminoglycan deposition[14,15]. We were able to identify hypothyroid myopathy at the initial evaluation given the patient's positive medical history. However, dysarthria could also be the presenting symptom in patients with no known thyroid disease, as in the two previous cases. Physicians should maintain a high vigilance when other features such as fatigue, cold intolerance, weight gain, sleep apnea, and dry skin are noted.

Prompt recovery of muscle weakness and dysarthria is expected, typically within 2 months, after adequate hormone replacement therapy.

Conclusion

Hypothyroidism should be considered in patients presenting with generalized muscle weakness with or without dysarthria, an elevated CK level, and a negative stroke work-up. A focused history and thyroid function tests usually confirm the diagnosis. Rapid recovery with thyroid hormone replacement is expected.

Competing interests

The authors have no competing interests to declare that are relevant to the content of this article.

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