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# Contents

## Original research

## Review article



## Case report

rfm
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# Perception of the role of oral and maxillofacial surgeons among Peruvian health professionals and students

*Percepción del rol del cirujano bucal y maxilofacial en profesionales y estudiantes del área de la salud en Perú*

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## Abstract

**Introduction:** Practicing oral and maxillofacial surgery in Peru is challenging due to the lack of knowledge of health professionals on the role of oral and maxillofacial surgeons.
**Objective:** To assess the perception of the role of oral and maxillofacial surgeons among Peruvian physicians, dentists, and medical and dentistry students.
**Materials and methods:** Cross-sectional, observational, descriptive study conducted in 2018. The sample consisted of 200 physicians, dentists, and medical and dentistry students from the city of Arequipa, Peru, who were distributed in 4 groups of 50 members each. The questionnaire covered 20 clinical situations and was divided into 5 specific conditions: facial trauma, pathology, reconstructive surgery, oral surgery, and cosmetic and functional surgery. Respondents were asked to indicate the specialist they would refer their patients to for treating each condition (plastic surgeon, otolaryngologist, oral and maxillofacial surgeon and head and neck surgeon).
**Results:** 90% percent of physicians and medical students had a negative perception of the role of oral and maxillofacial surgeons. In contrast, dentists and dentistry students had a positive perception (64% and 58%, respectively).
**Conclusions:** Most physicians and medical students have a negative perception of the role of oral and maxillofacial surgeons. Consequently, medical schools should give priority to the development of programs and courses that address the importance of the role and work of other health professionals, which will allow better multidisciplinary work, and therefore, the provision of more comprehensive healthcare services.
**Keywords:** Oral Surgery; Students, Medical; Dentists; Perception (MeSH).

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## Resumen

**Introducción.** La práctica profesional de la cirugía bucal y maxilofacial en Perú se ve enfrentada a múltiples dificultades debido a la falta de conocimiento de los profesionales de la salud sobre el rol del cirujano bucal y maxilofacial.
**Objetivo.** Evaluar la percepción del rol del cirujano bucal y maxilofacial en médicos, odontólogos y estudiantes de medicina y odontología del Perú.
**Materiales y métodos.** Estudio observacional, descriptivo y transversal realizado en 2018. Muestra: 200 médicos, odontólogos, estudiantes de medicina y de odontología de la ciudad de Arequipa, Perú, distribuidos de manera equitativa en 4 grupos de 50 miembros. El cuestionario cubrió 20 situaciones clínicas y se dividió en 5 categorías específicas: trauma facial, patología, cirugía reconstructiva, cirugía bucal y cirugía estética y funcional. Se solicitó a los encuestados indicar el especialista al que remitirían los pacientes para tratar cada afección (cirujano plástico, otorrinolaringólogo, cirujano bucal y maxilofacial, o cirujano de cabeza y cuello).
**Resultados.** El 90% de los médicos y estudiantes de medicina tuvieron una percepción negativa del rol del cirujano bucal y maxilofacial. Por el contrario, los odontólogos y estudiantes de odontología tuvieron una percepción positiva: 64% y 58%, respectivamente.
**Conclusiones.** La mayoría de médicos y estudiantes de medicina tienen una percepción negativa del rol del cirujano bucal y maxilofacial, por lo que es necesario que las escuelas de medicina den prioridad al desarrollo de programas y cursos en los que se aborde la importancia del rol y el trabajo de los demás profesionales de la salud, lo que permitirá un mejor trabajo multidisciplinario y, en consecuencia, una atención en salud más integral.
**Palabras clave:** Cirugía bucal; Estudiantes de medicina; Odontólogos; Percepción (DeCS).

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## Introduction

In Peru, oral and maxillofacial surgery is a dental specialty recognized by the Dental Surgeon's Work Law.[1] Oral and maxillofacial surgeons (OMFCS) are responsible for the diagnosis and medical or surgical treatment of mouth diseases, jaw injuries and disorders, facial bone fractures, odontogenic infections, dentofacial deformities, as well as the performance of maxillofacial cosmetic surgery procedures.[2,3]

Although this specialty has a key role in the health area, the scope and role of OMFCS is still unclear among health professionals, significantly affecting the timely and appropriate treatment of patients with oral and maxillofacial pathologies. No studies have been conducted in Peru, but, in Brazil, Rocha *et al.*[4] conducted a study to determine the perception of oral and maxillofacial surgery among health professionals and compared the results with another study conducted ten years later.[5] Based on the findings, they concluded that the practice and relevance of this specialty increased in the country during that period. In the UK, Sheikh *et al.*[6] performed a descriptive study to determine the perception of dental and medical students and professionals regarding the scope of oral and maxillofacial surgery and found that most respondents correctly associated the specialty with its scope. In Australia, Lababidi *et al.*[7] determined the number of referrals of patients to oral and maxillofacial surgeons among general practitioners and concluded that most respondents had adequate knowledge of the role of OMFCS.

The objective of this study was to evaluate the perception of the role of OMFCS among medical and dental students and professionals in order to establish measures that improve the status of this specialty in Peru.

## Materials and methods

A cross-sectional, observational, descriptive study was conducted in 2018. The population consisted of physicians and dentists working in public hospitals and final-year dental and medical students from two private universities in Arequipa, Peru.

The sample size was determined by non-probabilistic sampling, as the population of dentists working in these institutions is small; 50 subjects met the inclusion criteria. The other groups had the same size as the dentists' group, reaching a sample of 200: 50 doctors, 50 dentists, 50 medical students and 50 dental students.

The inclusion criteria were being a general or specialist physician or dentist working only in public hospitals and being a final-year medical or dental student at a private university in Arequipa. The exclusion criterion was not being willing to take part in the study.

Surveys were conducted through a self-administered questionnaire made in person at the hospitals and universities. The questionnaire was adapted based on Rocha *et al.*[4] according to the clinical conditions that are treated by OMFCS in Peru. In order to determine its validity, a judgment of five experts was carried out and the Aiken's V coefficient was calculated, obtaining a value V=0.967. To estimate internal consistency reliability, the Kuder-Richardson formula was used, obtaining a value of 0.921.

The instrument used consisted of closed questions inquiring about 20 clinical situations, divided into 5 categories:

*Facial trauma*: jaw fractures, fractures of the upper jaw, orbitozygomatic fractures, dentoalveolar fracture, panfacial fracture.
*Pathology*: biopsy to confirm diagnosis of oral cancer, cystic and tumorous lesions of the salivary glands, jaw tumors and cysts, moderate and severe odontogenic infections.
*Reconstructive surgery*: cleft palate, cleft lip, alveolar bone graft, temporomandibular joint disorders.
*Oral surgery*: dental implants, third impacted molar.
*Aesthetic and functional surgery*: problems with facial appearance due to alterations in dental occlusion, prognathism and maxillary and mandibular retrognathia.

Respondents had to indicate which specialist they would refer the patient to for treating each condition: plastic surgeon, otolaryngologist, OMFCS, or head and neck surgeon.

The variable perception of the role of OMFCS was measured in the following way: if the respondent referred the patient to the OMFCS in the hypothetical clinical situations evaluated, it was considered a positive perception, and if they referred the patient to other specialists, it was considered a negative perception.

A score of 0 was assigned if they chose another professional and a score of 1 if they chose the OMFCS. Based on that, and considering the number of questions per condition, the following scores were established: facial trauma: 0-3 negative perception, 4-5 positive perception; pathology: 0-2 negative perception, 3-4 positive perception; reconstructive surgery: 0-2 negative perception, 4-5 positive perception; oral surgery: 0-1 negative perception, 2 positive perception; cosmetic and functional surgery: 0-3 negative perception, 4-5 positive perception; overall perception: 0-11 negative perception, 12-20 positive perception.

Data management and statistical analysis were performed using SPSS version 23.00. Data was entered directly into SPSS and all entries were validated. Frequency tables were used to present the data, while the test $\chi^2$ was used to compare responses among health professionals. A $p<0.05$ value was considered statistically significant.

The study was conducted in accordance with the ethical principles for research involving human subjects of the Declaration of Helsinki.[8] This study was endorsed by the participating hospitals and universities, and approved by the Ethics Committee of the Universidad Científica del Sur through Minutes No. 033-2018-POS99 of October 12, 2018. Informed consent was obtained from all participants, who voluntarily agreed to take part in the study.

## Results

The demographics of the respondents were analyzed. The predominant age range among medical and dental professionals was 26-40 years with a percentage of 68% and 64%, respectively; the age range among medical and dental students was 20-25 years with a percentage of 78% and 62%, respectively (Table 1). With regard to the distribution by sex, there were more men in the groups of physicians (70%) and dentists (52%), and an equal distribution (50%) in the group of medical students; there were more women (74%) in the dental students group.

**Table 1.** Sample distribution by age.

| Study group | Age range | | | | | | Total | |
|---|---|---|---|---|---|---|---|---|
| | 20-25 years | | 26-40 years | | ≥41 years | | | |
| | n | % | n | % | n | % | n | % |
| Physicians | 0 | 0.0 | 34 | 68.0 | 16 | 32.0 | 50 | 100.0 |
| Dentists | 5 | 10.0 | 32 | 64.0 | 13 | 26.0 | 50 | 100.0 |
| Medical students | 39 | 78.0 | 11 | 22.0 | 0 | 0.0 | 50 | 100.0 |
| Dental students | 31 | 62.0 | 19 | 38.0 | 0 | 0.0 | 50 | 100.0 |
| Total | 75 | 37.5 | 96 | 48.0 | 29 | 14.5 | 200 | 100.0 |

Source: Own elaboration.

Regarding the results of the five categories, differences were found between the percentages of negative perception of the four groups (p<0.001) for facial trauma. Physicians, dentists, and medical students had a negative perception (74%, 56% and 86%, respectively), while dental students had a lower negative perception (46%) (Table 2).

**Table 2.** Perception of the role of oral and maxillofacial surgeons among medical and dental professionals and students.

| | | Physicians | | Dentists | | Medical students | | Dental students | | p |
|---|---|---|---|---|---|---|---|---|---|---|
| Conditions | | n | % | n | % | n | % | n | % | |
| Facial trauma | Negative perception | 37 | 74.0 | 28 | 56.0 | 43 | 86.0 | 23 | 46.0 | <0.001* |
| | Positive perception | 13 | 26.0 | 22 | 44.0 | 7 | 14.0 | 27 | 54.0 | |
| Pathology | Negative perception | 44 | 88.0 | 22 | 44.0 | 39 | 78.0 | 26 | 52.0 | |
| | Positive perception | 6 | 12.0 | 28 | 56.0 | 11 | 22.0 | 24 | 48.0 | <0.001* |
| Reconstructive surgery | Negative perception | 49 | 98.0 | 34 | 68.0 | 46 | 92.0 | 35 | 70.0 | |
| | Positive perception | 1 | 2.0 | 16 | 32.0 | 4 | 8.0 | 15 | 30.0 | <0.001* |
| Oral surgery | Negative perception | 4 | 8.0 | 0 | 0 | 5 | 10.0 | 6 | 12.0 | |
| | Positive perception | 46 | 92.0 | 50 | 100.0 | 45 | 90.0 | 44 | 88.0 | 0.756 |
| Aesthetic and functional surgery | Negative perception | 25 | 50.0 | 7 | 14.0 | 31 | 62.0 | 8 | 16.0 | |
| | Positive perception | 25 | 50.0 | 43 | 86.0 | 19 | 38.0 | 42 | 84.0 | <0.001* |
| Overall | Negative perception | 45 | 90.0 | 18 | 36.0 | 45 | 90.0 | 21 | 42.0 | |
| | Positive perception | 5 | 10.0 | 32 | 64.0 | 5 | 10.0 | 29 | 58.0 | <0.001* |

* $\chi^2$Source: Own elaboration.

In the pathology category, significant differences were observed between the percentages of negative perception of the four groups (p<0.001). Physicians, medical students, and dental students had a negative perception (88%, 78% and 52%, respectively); only dentists had a positive perception (56%) (Table 2).

In the reconstructive surgery category, significant differences were found between the four groups (p<0.001). In general, participants would not refer a patient requiring facial reconstructive surgery to OMFCS; therefore, all four groups had a negative perception: physicians by a greater percentage (98%), followed by medical students (92%), dental students (70%) and dentists (68%) (Table 2).

Oral surgery was the only category where no significant differences were observed between the percentages of the four groups (p=0.756). Physicians, dentists, medical students, and dental students had a positive perception of 92%, 100%, 90% and 88% respectively.

In the aesthetic and functional surgery category, significant differences were found between the percentages of the four groups (p<0.001). Negative perception was higher among medical students (62%), followed by doctors (50%), dental students (16%), and dentists (14%) (Table 2).

Finally, the overall perception, which included the five categories, showed significant differences among professionals and students (p<0.001). Physicians had an overall negative perception of 90%, while dentists had an overall positive perception of 64%. Finally, medical students had an overall negative perception of 90%, while dental students had a positive perception of 58% (Table 2).

## Discussion

Currently, in many countries, most health professionals, as well as medical and dental students, acknowledge the relevance of the oral and maxillofacial surgery specialty and its field of action.[3-6,9] In Peru, although the role of OMFCS in the area of health is known, there is still a lack of understanding of their importance among professionals and students, a situation that is confirmed for the first time with the results of this study. This research was carried out in the city of Arequipa and, therefore, the results may not be generalized to other places in the country with different contexts; however, this is the first step to produce the necessary evidence to generate changes in the country. A possible limitation of the study

was the initial lack of interest of some participants, but this was solved once the importance of the objectives was explained to them.

The results of the present study show that most physicians, dentists, and medical students would not refer patients with facial trauma to the OMFCS. This differs from the studies conducted by Labadibi *et al.*[7] and Ifeacho *et al.*[10], in which almost all physicians, dentists and medical students did refer patients with this type of condition to the OMFCS. This may be explained by the fact that this specialty has been officially recognized for more than 40 years in Australia[7] and the United States[10], countries where the studies were conducted.

According to the findings of the present study, a higher percentage of dental students would refer a patient with facial trauma to the OMFCS, a result that coincides with that reported in the studies by Rocha *et al.*[4] and Rocha *et al.*[5], in which dental students had a positive perception of the specialty. It is concerning that in the present study most dentists referred these patients to other specialists, which may be a consequence of the scarce information about the scope of the specialty in dental training in Peru. Therefore, the role of the OMFCS is not clear for these students.

Physicians, medical students and dental students considered that OMFCS are not the most competent specialists to treat oral injuries, concerning results that contrast with studies conducted in Australia[7] and Kuwait.[11] Based on these findings, it can be concluded that the participants do not trust the OMFCS for the management of oral lesions since only the dentists had a positive perception in this category, although the percentage was not conclusive.

For the treatment of conditions requiring reconstructive surgery, it was found that participants in all four groups did not refer the patients to the OMFCS. These results are partially consistent with those reported in the studies of Rocha *et al.*,[4] Rocha *et al.*[5] and Ameerally *et al.*,[12] where physicians and medical students predominantly referred the patients to the plastic surgeon, while most dentists and dental students referred them to the OMFCS. Currently, it is clear that patients requiring reconstructive surgery need to be treated by professionals from different specialties with formal training and experience in all phases of care.[2,13]

In the oral surgery category, most respondents preferred to refer patients to the OMFCS. This coincides with the study carried out in 1996 by Hunter *et al.*[14] and shows that, unlike the others, this area of work of the OMFCS is well recognized among the population of Arequipa.

With regard to aesthetic and functional surgeries, physicians referred patients to the OMFCS and other specialists in the same proportion. Dentists and dental students had a positive perception, while medical students had a negative perception since most preferred to refer the patients to other specialists, perhaps because of the conception that all cosmetic procedures should be performed by a plastic surgeon.

On overall perception, doctors and medical students had a negative perception, while dentists and dental students had a positive perception. These results are worrying when compared to most existing studies, in which the role of oral and maxillofacial surgeons is well recognized by health professionals.[4-7,15]

In Peru, most physicians and medical students do not know the role of OMFCS and are not clear about what conditions these specialists treat, which can lead to the incorrect referral of patients to other specialists. Furthermore, it is alarming that dentists and dental students do not understand clearly the role of OMFCS, taking into account that, although in Peru this specialty is recent, it has existed for approximately 20 years.[16] This does not explain finding a reality that is not very encouraging.

For patients to receive the best comprehensive treatment of conditions in the oral cavity and maxillofacial region, health care providers must have a good understanding of what OMFCS do and teamwork between specialties should be encouraged. The establishment of national guidelines to improve referral criteria should also be promoted. Oral and maxillofacial surgeons have the responsibility to inform their community about the scope of their specialty given the results found in this study.

## Conclusions

Physicians and medical students have a negative perception of the role of OMFCS, so it can be concluded that they do not know the scope of this specialty and, therefore, are unaware of its importance for the team of health professionals. On the other hand, dentists and dental students have a better perception; however, it is not the expected one considering that oral and maxillofacial surgery is a dental specialty.

Undergraduate education, both in dental and medical schools, should be comprehensive and emphasize the field of action of each specialist to avoid future misconceptions that could be detrimental to the timely treatment of patients.

Proper understanding of the scope of this specialty will improve the criteria for referral of patients in the country. It is therefore necessary that medical schools give priority to the development of programs and courses that address the importance of the role and work of other health professionals. This will enable better multidisciplinary work and, consequently, more comprehensive health care.

## Conflicts of interest

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# Detection of anti-tissue transglutaminase IgA antibodies (tTG IgA) in children with type 1 diabetes mellitus

*Detección de anticuerpos IgA antitransglutaminasa tisular (IgA-TGT) en niños con diabetes mellitus tipo 1*

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## Abstract

**Introduction:** Children with type 1 diabetes mellitus (DM1) are more likely to develop celiac disease (CD), which is an underdiagnosed condition due to its variable clinical presentation. Therefore, children with DM1 require periodic monitoring to achieve an early diagnosis of CD.
**Objectives:** To identify positivity for the detection of anti-tissue transglutaminase IgA antibodies (tTG-IgA) in children with DM1, as well as to describe gastrointestinal (GI) symptoms, anthropometric status indicators and gluten intake levels.
**Materials and methods:** Descriptive cross-sectional study. The population was composed of children with DM1 who attended the outpatient service of two pediatric endocrinology centers in Bogotá, Colombia. The Biocard-Celiac® test was used to detect the presence of tTG-IgA. In addition, participants were asked about their GI symptoms and underwent an anthropometric nutritional assessment. Gluten intake was assessed by recording dietary intake for 72 hours. A statistical data analysis was performed using the SPSS software version 22.0.
**Results:** The final sample included 45 children with an average age of 10.6±4.1 years, of which 53% were males. None of the participants had a positive result in the tTG-IgA test. The most frequent GI symptoms were flatulence (48.9%) and abdominal pain (28.9%). Only 3 children (6.7%) were below the height-for-age standard. The average gluten intake was 5.29±3.02 g/day.
**Conclusions:** Although children with DM1 are at increased risk of developing CD, none of the participants tested positive for tTG-IgA.
**Keywords:** Diabetes Mellitus, Type 1; Glutens; Anthropometry; Signs and Symptoms, Digestive (MeSH).

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## Resumen

**Introducción.** Los niños con diabetes mellitus tipo 1 (DM1) tienen mayor probabilidad de desarrollar enfermedad celiaca (EC), la cual es una condición subdiagnosticada debido a que su presentación clínica varía; por lo tanto, es necesario monitorear periódicamente a esta población con el objetivo de diagnosticar a tiempo la EC.
**Objetivos**. Identificar la positividad para la detección de anticuerpos IgA antitransglutaminasa tisular (IgA-TGT) en población pediátrica con DM1, así como describir los síntomas gastrointestinales (SGI), los indicadores antropométricos y los niveles de ingesta de gluten.
**Materiales y métodos.** Estudio descriptivo de corte transversal. La población estuvo compuesta por niños con DM1 que asistieron al servicio de consulta externa en dos centros de endocrinología pediátrica en Bogotá D.C., Colombia. Para detectar la presencia de IgA-TGT se aplicó el test Biocard-dTM Celiac®. Además, se indagó sobre los SGI y se realizó valoración nutricional antropométrica de los participantes. Para evaluar la ingesta de gluten se llevó a cabo un registro dietético de 72 horas. El análisis estadístico de los datos se realizó con el programa SPSS versión 22.0.
**Resultados.** La muestra final estuvo compuesta por 45 niños con una edad promedio de 10.6±4.1 años, de los cuales 53% eran varones. Ninguno de los pacientes presentó positividad cualitativa en el test aplicado para detección de IgA-TGT. Los SGI más frecuentes fueron flatulencias (48.9%) y dolor abdominal (28.9%). Solo en 3 niños (6.7%) se observó talla baja con respecto a su edad. La ingesta promedio de gluten fue 5.29±3.02 g/día.
**Conclusiones**. Pese a que los niños con DM1 tienen mayor riesgo de desarrollar EC, ninguno de los participantes presentó positividad para IgA-TGT.
**Palabras clave:** Diabetes mellitus tipo 1; Enfermedad celiaca; Dieta sin gluten; Antropometría; Signos y síntomas digestivos (DeCS).

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## Introduction

Celiac disease (CD) has a prevalence of 1% in the general population and between 3% and 12% in patients with type 1 diabetes mellitus (DM1).[1] This difference has been associated with some genetic and environmental particularities of these patients, such as increased genetic predisposition linked to HLA-DQ2 or HLA-DQ8 markers, activation of some KIR (killer immunoglobulin-like receptor) genes, and specific features of the intestinal microbiota.[2]

CD is characterized by severe small intestinal mucosa atrophy, which leads to impaired digestion and malabsorption of nutrients and, consequently, produces gastrointestinal disorders and alterations in anthropometric parameters.[3] CD is often under-diagnosed due to the scarce knowledge among health professionals of this condition and because of the variability of its clinical presentation, which includes signs and symptoms such as anemia, constipation, diarrhea, abdominal pain and distention, stunt growth, among others.

Detecting tissue antitransglutaminase IgA antibodies (IgA-TGT), which is mainly done quantitatively, may suggest CD. In other words, measuring IgA-TGT can be used as a screening method to determine the risk of having this disease, as well as to confirm its diagnosis with the support of other serological and duodenal biopsy tests.

The objectives of the present study were to identify the positivity for the detection of IgA-TGT in children with DM1 treated in two pediatric endocrinology centers from Bogotá, Colombia, and to describe the gastrointestinal (GI) symptoms, anthropometric nutritional status and gluten intake of the participants.

## Materials and methods

A descriptive cross-sectional study was performed on a convenience sample of children aged 0-18 years with a diagnosis of DM1 and no other diagnosed autoimmune diseases. All patients who attended two outpatient pediatric endocrine centers between January 2011 and June 2016 and between July 2016 and January 2017 were selected.

For the inclusion of participants, the parents of children diagnosed with DM1 were contacted by telephone to invite them to participate in the study. Figure 1 describes the communication and sample collection process.

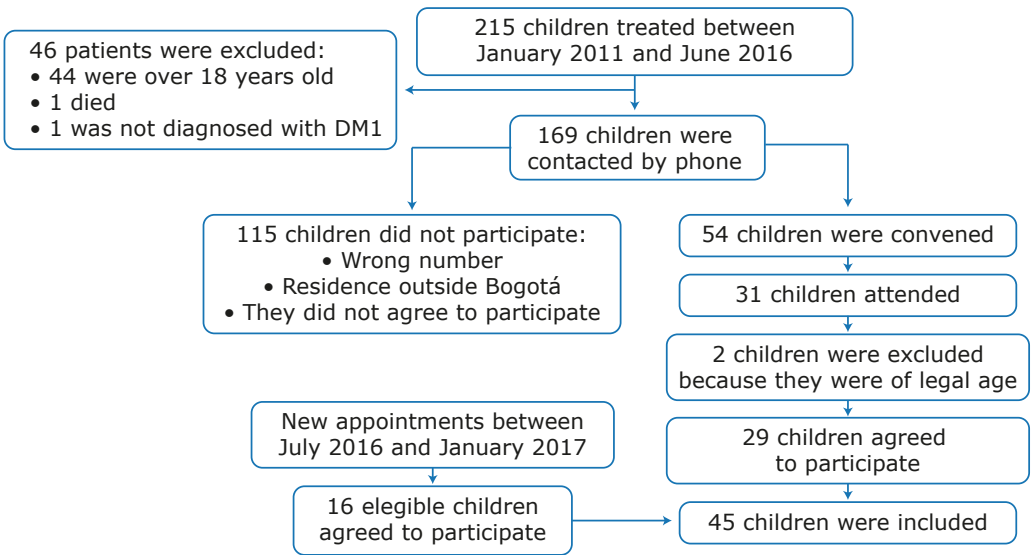


**Figure 1.** Study population.
Source: Own elaboration.

The parents of the children who agreed to take part in the study signed an informed consent, and participants older than 8 years signed an assent. The research followed the ethical principles for medical research on human subjects of the Declaration of Helsinki[4] and took into account the local regulations of the Colombian Ministry of Health established in Resolution 8430 of 1993.[5] Furthermore, the research was approved by the ethics committees of the Universidad El Bosque through Minutes No. 005-2016 of March 8, 2016, and Universidad Nacional de Colombia through Minutes No. 021-277-15 of December 10, 2015.

A survey on GI symptoms suggestive of CD was carried to collect the data following the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines. This instrument assesses the presence of symptoms such as vomiting, nausea, abdominal pain and distension, flatulence, constipation, diarrhea, and irregular bowel habits, among others. It also investigates aspects such as bowel habits, the characteristics of bowel movements according to the Bristol scale[6] and the frequency of bowel movements. The survey was sent by e-mail.

Based on the protocol of the International Society for the Advancement of Kinanthropometry, weight, height, skin folds (triceps, biceps, subscapular and suprailiac) and cephalic, waist and brachial circumferences were measured. The analysis and interpretation of weight-for-height, height-for-age and BMI-for-age indicators was carried out using the Anthro and Anthro Plus programs of the World Health Organization (WHO).[7,8] Fat percentage was determined with the Siri formula, using the Nutritional Application tool of the Spanish Society for Pediatric Gastroenterology, Hepatology, and Nutrition, and was

interpreted according to the percentiles for age.[9] Waist circumference was determined following the same process[10]

The participants received an e-mail with the appointment confirmation, as well as the food anamnesis form so that the child and their guardian could record food intake during the three days prior to the appointment. The information had to include portion size, which was corroborated with the eNasco food modules on the day of the consultation. The dietary analysis was performed using the DIAL program based on the average of intake during those three days.[11] To calculate gluten intake (g/day), the daily grams of protein ingested from wheat, rye, oats and barley were taken as reference and multiplied by the conversion factor 0.8.[12]

Anti-IgA antibodies were measured by lateral flow immunochromatography using the BiocardTM Celiac® test, a laboratory test that allows screening for CD and in which IgA is not measured to determine positivity for tissue transglutaminase.[13]

The information was tabulated in a database in Microsoft Excel 2016 and then exported to SPSS version 22.0 for the corresponding descriptive statistical analysis. Categorical variables, absolute values and percentages were used. Means and standard deviations were reported for continuous quantitative variables (σ), while medians and interquartile ranges were used for interval variables. The Shapiro-Wilk test was applied to assess whether data were compatible with a normal distribution. In case data were not normal, non-parametric tests, such as Pearson's chi-square, were used to compare proportions and the Wilcoxon–Mann–Whitney test was used to compare means and medians; when the distribution was normal, tests such as Fisher's t-Student were used to compare proportions and ANOVA to compare means and medians. A 95% confidence level ($p<0.05$) was considered for all statistical tests.

## Results

Forty-five children diagnosed with DM1 and an average age of 10.7±4.1 years were included and assessed between January 2011 and June 2016 and between July 2016 and January 2017. The average age at which children were diagnosed with DM1 was 6.6 years and the average time from diagnosis to assessment was 3.5 years. 53% of them were boys and the distribution by age group was as follows: preschoolers under 5 years: 13.3%; school children between 6 and 10 years: 31.1%; and adolescents between 11 and 18 years: 55.6%.

Although the test was not conclusive in two patients, none of the participants showed qualitative positivity for IgA-TGT. Only 7 children (15.6%) did not report GI symptoms; in those who did, the most frequent symptom was flatulence (48.9%), followed by abdominal pain (28.9%), nausea (26.7%), abdominal distension (20.0%), constipation (11.1%), diarrhea (8.9%), and vomiting (4.4%). The consistency of the stools in 68.9% of the participants was between types 3 and 4 according to the Bristol scale, with an average frequency of 1.8±1.3 times per day.

Regarding height-for-age, 55.6% of patients were between +1 and -1 σ and 25% between -1 and -2 σ; 3 children had low height-for-age. About body mass index (BMI), 60% of the children were between +1 and -1 σ and 31.1% were overweight (>+2 σ). 48.8% of the participants were in the normal body fat percentile ranges, although 46.3% presented some degree of excess fat. With respect to waist circumference, 59.1% were within the 25$^{th}$-75$^{th}$ percentiles and 15.9% were above the 75$^{th}$ percentile.

Of the 45 participating children, only 38 completed the food intake forms; in them, the average gluten intake was 5.29±3.02g/day, which is equivalent to the daily consumption of a ±69g portion of crackers or a ±97g portion of white bread. Although there was no significant difference between groups, there was a tendency towards increasing gluten intake as age increased.

## Discussion

None of the participants tested positive for IgA-TGT according to the lateral flow immunochromatography test, for which a sensitivity of 96.7% and a specificity of 93.5% have been reported.[14] A previous study conducted in Valle del Cauca (Colombia)[15] found that 10.4% of 115 children with DM1 tested positive for IgA-TGT, while a study conducted in Cuba reported that only 1.2% of 595 children with the same condition tested positive for this antibody.[16]

The ELISA test determines positivity for IgA-TGT when the values of these antibodies are >50 U/mL; sensitivity of 92% and specificity of 100% have been reported for this tool.[17] There are several studies that have reported positivity using this method: Landaeta *et al.*[18] described positivity of 3.4% in 118 Venezuelan children, Brandt *et al.*[19] reported positivity of 21% in 19 children from the state of Pernambuco (Brazil), Araújo *et al.*[20] reported 10.5% positivity in 354 children in the city of Recife (Brazil), Al-Hussaini *et al.*[21] reported 24.5% positivity in 106 Saudi children, Joshi & Madvariya[22] found 15.49% positivity in 71 children in Western India, Bhadada *et al.*[23] reported 11.1% positivity in 189 children from northern India, Al-Sinani *et al.*[24] found 17% positivity in 103 Omani children, and Honar *et al.*[1] reported 14% positivity in Iranian children.

In the present work, this test did not yield any results in two patients, which could be explained by an IgA deficiency or because the IgA antibody titer was low in the sample collected. In these cases, it was considered that their anthropometric nutritional status was adequate and that the only reported GI symptom was flatulence, which are characteristics similar to those of the majority of the population analyzed.

On the other hand, Baker *et al.*[25] found that 42% of evaluated diabetic patients were diagnosed with CD 10 years after the onset of DM1, while Bhadada *et al.*[23] found that the diagnosis was made 5 years later. In the present study, the children were diagnosed with DM1 on average 3.5 years before the time of assessment, so even though the result for IgA-TGT was negative for most participants, they should be tested annually (as a screening procedure) to determine if they are positive in the future.

Regarding GI symptoms, the study by Costa-Gomes *et al.*,[26] published in 2016 and conducted on a sample of 111 Brazilian children diagnosed with DM1, found abdominal pain (30.6%) and abdominal distension (28.8%) as the most common symptoms, which is consistent with the study by Bhadada *et al.*[23] conducted in India. In the present study, the results coincide with what these authors

found and what is reported in most research works: abdominal pain is one of the most frequent GI symptoms.

Concerning gluten intake, Hoppe *et al.*[27], in a study conducted in Danish children, reported the following average intake values: 1.79 g/day, 3.74 g/day, 5.22 g/day, 6.74 g/day and 7.4 g/day for children 6-7 months of age, 8-9 months, 10-11 months, 12-24 months and 25-36 months, respectively. The average gluten intake established in the present study was around 5.29 g/day, therefore, in some patients, it is lower than that reported by Hoppe *et al.*,[27] which may be due to the fact that eating patterns in Denmark are different and the intake of gluten source foods is usually higher due to the unavailability of other cereals. In Colombia, according to the 2010 ENSIN,[28] 92.5% of the population consumes rice or pasta daily and 76.1% eats bread, *arepas* (round patty made of corn flour) or cookies, so it can be said that other cereals such as rice or corn are used; this, in turn, indicates that the intake of sources of gluten in the country is lower.

Joshi & Madvariya,[22] in a study conducted in India with children aged 0-18 years and diagnosed with DM1, found stunting in 18.2% of the sample. In Colombia, according to the ENSIN 2010,[28] 13.2% of children under 5 years and 10% of children between 5 and 17 years have low height. However, in the present study, this variable was lower than the national average, as only 3 children had low height; the gluten intake of these participants was below the average consumption and their BMI was normal. Still, since the height of the children's parents was not known, it was impossible to determine whether the delay was due to a family characteristic.

No child had a deficit in the BMI indicator. On the contrary, 26.7% were between >+1 and ≤+2 σ and 4.4% between >+2 and ≤+3 σ, which is above the figures reported in the ENSIN 2010,[28] where 4.8% of children under 5 and 17.5% of those over 5 were above +2 σ. This is also in line with the data published by da Costa *et al.*,[29] who found in a 2016 study that 30.3% of 195 Brazilian children diagnosed with DM1 had BMI between >+1 and ≤+2 and 9.7% between >+2 and ≤+3. Similarly, Łuczyński *et al.*,[30] in a sample of 500 Polish children with diabetes, found that 30.2% were overweight or obese, similar to what has been reported in the present study.

As for waist circumference, which has been associated with excess weight, of the 25 children over 10 years of age, 14 were above the 75$^{th}$ percentile; 71.4% were females. Other studies[29,31] have associated puberty with increased risk of obesity in children with DM1 due to decreased insulin sensitivity, peripheral glucose metabolism and exogenous hyperinsulinism, which, together with the anabolic effect of insulin, generates lipogenesis. In addition, and in agreement with the findings of this research, Wysocka-Mincewicz *et al.*[32] reported that the female sex is a risk factor for obesity in adolescents with DM1.

To measure the levels of gluten intake, a factor of 0.8 was used and all foods considered to be sources of this protein (pasta, bread, crackers, and oat) were included. However, some foods that may contain it, such as sausages, sauces, additives, among others, could not be included in the calculation of the reported total because their exact content was unknown.

While no children was positive for IgA-TGT, the American Diabetes Association and ESPGHAN recommend monitoring children with DM1 regularly, regardless of the presence or absence of symptoms, considering the characteristics of this population and the increased risk of autoimmune diseases such as CD.

In summary, the present study is an approach to understanding, on the one hand, the risk of presenting CD in children with DM1 and, on the other, the anthropometric nutritional status, the presence of GI symptoms and gluten intake in this population. These results seek to sensitize parents and health professionals directly involved (endocrinologists, gastroenterologists, and nutritionists) about the importance of implementing periodic screening to detect early the risk of having CD. In this context, more studies, preferably cohort studies, need to be conducted in Latin America with diabetic children to establish the frequency of CD in the region and thus make early diagnoses that help improve quality of life and avoid associated complications.

## Conclusions

According to the results obtained, none of the participants tested positive for IgA-TGT, even though all had a higher risk of developing CD because they had DM1.

Likewise, it was identified that the most frequent GI symptom was flatulence, that most children had an adequate anthropometric nutritional status according to the ranges of normality established by the WHO, and that the average gluten intake was 5.29±3.02 g/day.

## Explanatory note

This manuscript derives from the master's thesis entitled "Estudio CED3: Detección cualitativa de anticuerpos IgA contra la transglutaminasa tisular (AtTG), en niños con diabetes tipo 1 en Bogotá" (CED3 study: Qualitative detection of IgA antibodies against tissue transglutaminase (AtTG) in children with type 1 diabetes in Bogotá.)[33]

## Conflicts of interest

None stated by the authors.

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# Huber opposition transfer for improving hypoplastic thumb: results of a case series

*Transferencia de Huber para mejorar la oposición del pulgar hipoplásico: resultados de una serie de casos*

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## Abstract

**Introduction:** Abductor digiti minimi transfer (also known as Huber opposition transfer) allows restoring thumb opposition. This method has several advantages over other opposition transfer techniques, as it replaces the intrinsic muscles of the thumb with another intrinsic muscle of the hypothenar region, thus improving the volume of thenar eminence. It is used preferably in thumb hypoplasia types II and III.
**Objective:** To describe the functional results of a series of patients with thumb hypoplasia who underwent Huber opposition transfer.
**Materials and methods:** Descriptive, observational study conducted in 11 patients with thumb hypoplasia who underwent Huber opposition transfer and with a minimum follow-up of 6 months. Furthermore, some of these patients had undergone pollicization due to their type of hypoplasia.
**Results:** The average age at the time of surgery was 35 months and the average follow-up period was 15.4 months. Average opposition function, according to the modified Kapandji index, improved from 1.63 (range 1-2) to 3.72 (range 2-4).
**Conclusion:** Good functional results were obtained using this technique, achieving overall improvement in opposition function according to the Kapandji index. In 9 patients, the index increased to grade 4 and in 1 it went from grade 1 to grade 3; in 1 case, improvement was not significant (grade 1 to grade 2), since the patient presented with finger stiffness associated with VACTERL. Huber opposition transfer allows achieving good functional opposition results in patients with thumb hypoplasia.
**Keywords:** Thumb; Tendon Transfer; Congenital Abnormalities; Hand (MeSH).

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## Resumen

**Introducción.** La transferencia del abductor *digiti minimi* o transferencia de Huber permite restaurar la oposición del pulgar y presenta varias ventajas sobre otras técnicas de transferencias de oposición, ya que reemplaza musculatura intrínseca del pulgar por otro músculo intrínseco de la región hipotenar, lo que mejora el volumen de la eminencia tenar. Este procedimiento es usado preferiblemente en los tipos II y III de hipoplasia de pulgar.
**Objetivo.** Describir los resultados funcionales de la transferencia de Huber en una serie de pacientes con hipoplasia de pulgar.
**Materiales y métodos.** Estudio observacional descriptivo realizado en 11 pacientes con hipoplasia de pulgar operados mediante la técnica Huber y a quienes se les había realizado un seguimiento mínimo de 6 meses. Además, algunos habían sido sometidos a pulgarización debido al tipo de hipoplasia que presentaban.
**Resultados.** La edad promedio de los participantes al momento de la cirugía fue de 35 meses y el tiempo promedio de seguimiento fue de 15.4 meses. El promedio de la función de oposición, según la escala modificada de Kapandji mejoró de 1.63 (intervalo de 1-2) a 3.72 (intervalo 2-4).
**Conclusión.** Se obtuvieron buenos resultados funcionales al emplear esta técnica, logrando una mejora general de la oposición según la escala de Kapandji: en 9 pacientes aumentó a grado 4 y en otro pasó de 1 a 3; solo en 1 caso la mejora no fue significativa (grado 1 a 2) dado que el paciente presentaba rigidez de los dedos asociada a VACTERL. La transferencia de Huber es una técnica que permite obtener buenos resultados funcionales de oposición para el pulgar hipoplásico.
**Palabras clave:** Pulgar; Transferencia tendinosa; Anomalías congénitas; Mano (DeCS).

Vergara-Amador E, Castellar-Torres Y. [Transferencia de Huber para mejorar la oposición del pulgar hipoplásico: resultados de una serie de casos]. Rev. Fac. Med. 2020;68(3):352-5. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n3.75081.

## Introduction

Thumb hypoplasia is a congenital abnormality that, according to the Blauth classification, can present with the complete absence of the thumb or different degrees of affectation ranging from type I to type V. This classification is useful as it not only describes the degree of hypoplasia but also guides treatment and prognosis.[1]

Thumb hypoplasia has an incidence ranging from 3.4 to 16 cases per 10 000 births and is often bilateral (20-60% of cases) and accompanied by abnormalities in the limbs, spine, and other organs. This condition can occur within the VACTERL association, a group of birth defects that tend to co-occur and mainly affect parts of the body such as vertebrae, anal atresia, heart, trachea, esophagus, kidney, and limbs.[2,3]

The opposing movement of the thumb, which is particularly important for the correct functioning of the hand as it supports pincer grasp movements, is often affected in thumb hypoplasia due to atrophy or absence of the thenar muscles.

Abductor digiti minimi (ADM) transfer is a technique proposed by Eugen Huber in 1921 and used to restore the opposing movement of the thumb in patients with median nerve palsy.[4] In theory, this method has advantages over other types of opposing transfers, since it replaces the intrinsic muscle of the deficient thumb with a muscle from the hypothenar region, which also helps to increase the volume and improve the appearance of the atrophied thenar eminence.[5] This technique is often used in hypoplasia types II and type III.

Consequently, the aim of the present work was to describe the functional results obtained with the ADM transfer, also known as Huber transfer, in patients with thumb hypoplasia.

## Materials and methods

This is a descriptive and retrospective observational study conducted in patients with thumb hypoplasia who underwent Huber opposition transfer to improve the function of their thumbs. Some of these patients had undergone pollicization because of the type of hypoplasia they presented.

The initial sample was composed of 14 patients with the same number of thumbs operated. However, patients that had undergone more surgeries to improve thumb opposition or other congenital malformations of the hand that altered its functionality and who could not be followed for at least 6 months or contacted for reassessment were excluded. The final sample consisted of 11 individuals.

The variables evaluated were age, sex, laterality, classification (according to Blauth), abnormalities of the contralateral thumb, additional surgeries, follow-up time, assessment of thumb opposition, and instability of the metacarpophalangeal (MCP) joint of the thumb.

Opposition of the thumb was evaluated based on a modification of the Kapandji index,[6] a widely used instrument that assesses thumb opposition based on where on their hand the patient is able to touch with the tip of their thumb and that is very practical to implement in children; it should be noted that the original version of the instrument has a score from 1 to 10. In the modified version used for the present work, the values ranged from 0 to 4, and the equivalencies were very similar depending on the location reached by the tip of the thumb: 1 radial side of the middle phalanx of the index finger; 2 radial side of the distal phalanx of the index finger; 3 tip of the index finger; 4 tip of the little finger (only this value changed and is equivalent to Kapandji's score 6).

This is a retrospective study that did not require performing any new procedure on the participants. Participants' anonymity was kept at all times. The patients' data were obtained after their legal guardian signed an informed consent. This work was approved by the Ethics Committee of the Faculty of Medicine of the Universidad Nacional de Colombia through Minutes 010-159-18 of June 15, 2018, and followed the ethical principles for research on human beings established in the Declaration of Helsinki[7] and Resolution 8430 of 1993 of the Ministry of Health of Colombia.[8]

## Procedure

Figures 1, 2, and 3 show the details of the technique. A slightly curved incision was made over the ulnar edge of the hand, going from the base of the little finger to the pisiform bone. ADM was located and released from its insertion; the muscle was lifted, and its origin was left intact in the proximal side. On some occasions, it was possible to visualize the nerve branch of the ulnar nerve that enters deep into the base of the muscle.

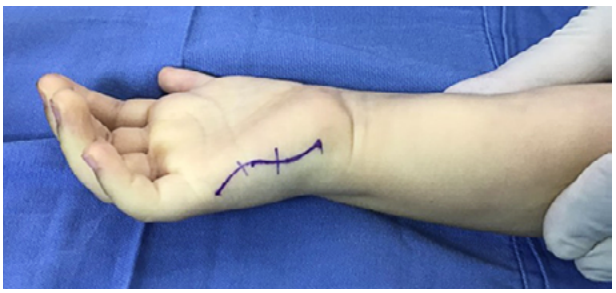

**Figure 1.** Incision on the ulnar edge of the hand.
Source: Document obtained during the study.

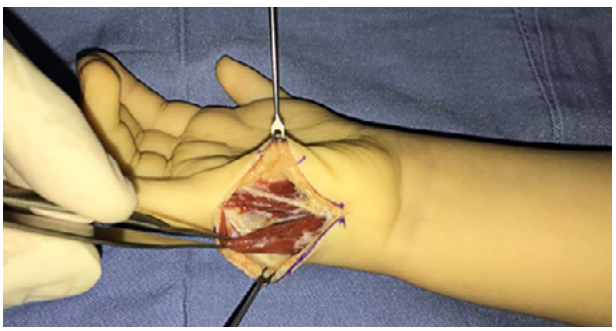

**Figure 2.** Dissection of the abductor digiti minimi muscle
Source: Document obtained during the study.

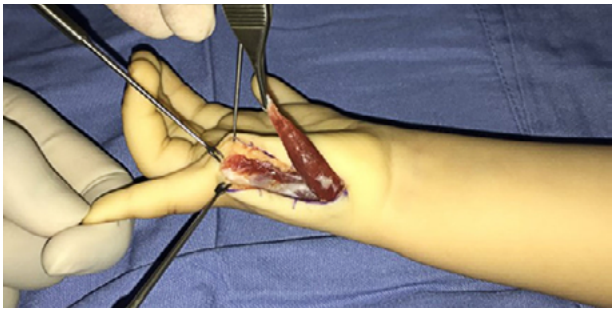

**Figure 3.** Harvest of abductor digiti minimi muscle.
Source: Document obtained during the study.

Figures 4 and 5 show the second incision made in the dorsal and radial side of the MCP joint of the thumb, which was used to create a subcutaneous tunnel, first with scissors and then with Kelly clamps. This tunnel ran from the origin of the ADM in the pisiform bone to the second incision in the MCP joint of the thumb; it had to be wide enough to allow adequate movement of the ADM over the superficial palmar fascia. The muscle was transferred through the tunnel to the second incision, and the insertion of the abductor pollicis brevis on the dorsum of the proximal phalanx of the thumb and the dorsal capsule of the MPC joint was sutured with 4/0 polypropylene. On several occasions, it was necessary to open the first web space and reconstruct the ulnar collateral ligament of the MPC joint because it was unstable.

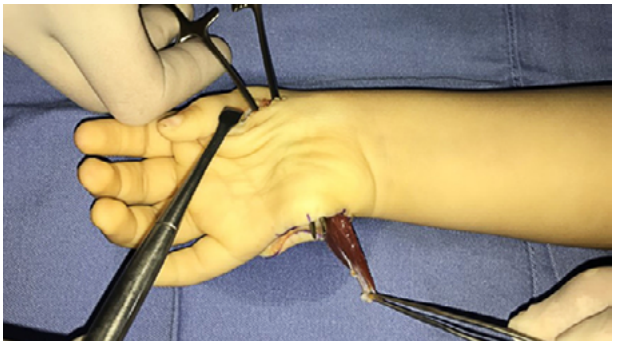

**Figure 4.** Transfer of the abductor digiti minimi muscle through a subcutaneous tunnel to the thumb.
Source: Document obtained during the study.

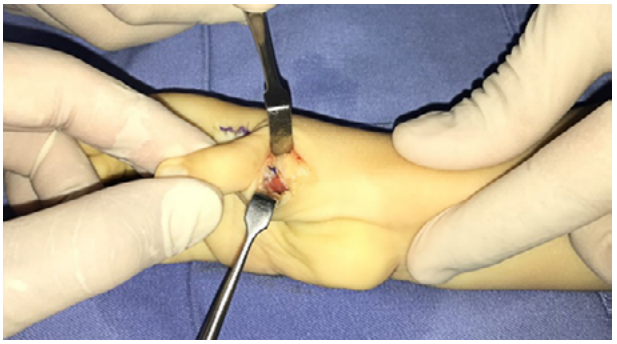

**Figure 5.** Suture of the abductor digiti minimi muscle at the insertion of the abductor pollicis brevis on the dorsum of the proximal phalanx of the thumb and the dorsal capsule of the metacarpophalangeal joint.
Source: Document obtained during the study.

## Results

The average age of the patients analyzed at the time of surgery was 35 months (range 28-60 months), with a median of 30 months, and average follow-up time of 15.4 months (range 6-60 months); 54% of the patients were male. There were 3 cases of hypoplasia type II and 2 cases of hypoplasia type III; the other 6 cases had undergone pollicization. Moreover, 5 patients had undergone reconstruction of the MPC joint of the thumb, of which 2 presented with hypoplasia type IIIA and 3 with hypoplasia type II. Regarding laterality, 6 patients presented difficulty in the right hand and 5 in the left hand.

According to the modified Kapandji index, the average of the opposing function of the thumb before surgery was 1.63 (interval of 1-2), increasing to 3.72 (interval 2-4) after surgery. Figures 6 and 7 show the results for 2 patients.

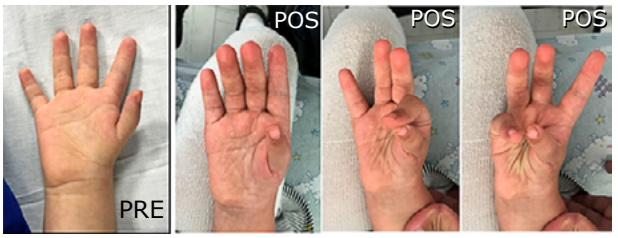


**Figure 6**. Pre-operative assessment (type I) and satisfactory post-operative outcome (type IV).
Source: Document obtained during the study.

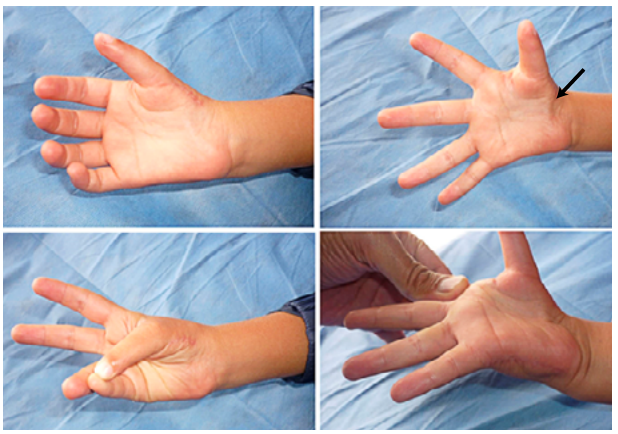

**Figure 7.** Abductor digiti minimi transfer at 18 months with type IV result on modified Kapandji index.
→ Abductor digiti minimi in the thenar region.
Source: Document obtained during the study.

In none of the cases there were any immediate postoperative complications or the need to perform additional surgical procedures.

## Discussion

Thumb hypoplasia is a pathology that alters thumb function and, consequently, of the hand, as it hinders opposition and affects dexterity. Thumb hypoplasia type I, and sometimes type II, does not require any specific management, but hypoplasia type IIIA, and some type II cases, require surgical treatment to reconstruct the finger; some of these procedures are transfers to improve thumb opposition as the technique described by Huber. In type IIIB, IV, and V, pollicization is usually performed.[9,10]

The literature reports some studies that assess the Huber transfer method,[11,12] but they do not have an adequate and objective evaluation of the results obtained in the procedures. Given the inherent difficulty of carrying out studies with young children, especially under the age of 3, assessment with the Kapandji index may not be possible, altering the evaluation. In these cases, making drawings or marking points so that the child can reach them with the thumb is recommended, and the help of the parents is necessary for achieving this.

The rotation of the ADM, which arises from the pisiform bone, can produce compression of the ulnar nerve, since the transferred muscle is located on the Guyon's canal. This finding, reported by Cawrse & Sammut,[13] is known as a rare complication that forces the reversal of muscle transfer. For this reason, and in order to give greater length to the transferred muscle, some authors remove the proximal ADM muscle from the pisiform bone, the flexor retinaculum and the flexor carpi ulnaris.[12-14] In the present series, this complication was not observed and neither was the transfer of the ADM as a myocutaneous flap,[15,16] which is more useful in children with greater atrophy of the tissues in the thenar region.

The participants in the present study had good functional results with the Huber technique after their thumb-opposition function improved: in 9 patients, it increased to type IV and in another it went from I to III; only in 1 case it did not improve significantly (type I to II) because the patient had a stiffness of the fingers associated with a VACTERL. Finally, good stability of the MPC joint was achieved.

The small size of the sample was one of the limitations of the present study due to the type of pathology analyzed.

## Conclusions

The findings prove that the Huber technique is an effective therapeutic option that has the advantage of using an intrinsic hand muscle with a similar function. It also guarantees a better aesthetic appearance by filling the thenar region and allows good functional opposition results for the hypoplastic thumb, which are very similar to those described with other techniques such as the flexor digitorum superficialis lasso tendon transfer.[17]

## Conflicts of interest

None stated by the authors.

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## Acknowledgements

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# Swimming and menstruation: a qualitative study in elite female swimmers

*Nadar con la menstruación: un estudio cualitativo en nadadoras de élite*

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## *Abstract*

**Introduction:** Menstruation in athletes, from a qualitative approach, is an underexplored phenomenon.
**Objective:** To describe the experience of elite swimmers from a sports league in Bogotá D.C. regarding menstruation and their sports practice.
**Materials and methods:** Qualitative descriptive study based on in-depth interviews administered to nine swimmers aged between 18 and 29 years, who were enrolled in the following categories: swimming races, water polo and open water swimming. The interviews were transcribed and processed using NVivoPro®.
**Results:** All participants reported swimming while on their menstrual periods. For them, menstruation is a serious issue that affects their performance and well-being. The most relevant difficulties reported include the need to conceal and restrict it; psychological symptoms such as depression, and physical symptoms such as cramps; the lack of empathy from some coaches; the limited information these athletes receive from health personnel on menstrual physiology and menstrual hygiene management, and the lack of knowledge on alternative menstruation management methods such as the menstrual cup. Positive aspects include the support received by their peers and female coaches, who make them feel understood as women.
**Conclusions:** Menstruation has an impact on the well-being and performance of elite female swimmers. Therefore, the physiological, psychological, and social implications of women involved in professional sports should be addressed to provide better support to these athletes, as this will contribute to improving their quality of life and overall health condition.
**Keywords:** Menstruation; Swimming; Sexual Health; Qualitative Research (MeSH).

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## *Resumen*

**Introducción.** La menstruación en atletas es un fenómeno poco explorado desde una mirada cualitativa.
**Objetivo.** Describir la experiencia de nadadoras de élite de una liga deportiva de Bogotá D.C. en relación con la menstruación y su práctica deportiva.
**Materiales y métodos.** Estudio cualitativo descriptivo basado en entrevistas a profundidad. Participaron 9 nadadoras entre 18 y 29 años de las modalidades natación carreras, waterpolo y natación en aguas abiertas. Las entrevistas se transcribieron y se procesaron con el programa NVivoPro®.
**Resultados.** Todas las participantes reportaron nadar durante su menstruación. Para ellas, la menstruación representa un serio problema que afecta su bienestar en la práctica de este deporte. Las principales dificultades descritas fueron la necesidad de ocultarla y restringirla; los síntomas psicológicos como la depresión y físicos como los cólicos; la poca empatía de algunos entrenadores; la escasa información que reciben por parte del personal de salud sobre la fisiología y manejo de la higiene menstrual, y el desconocimiento de métodos alternativos de manejo como la copa menstrual. Como aspecto positivo se reportó el apoyo de sus pares y entrenadoras, lo que hace que se sientan comprendidas en su condición de mujeres.
**Conclusiones.** La menstruación es una condición que afecta el bienestar y desempeño de las nadadoras de élite, por lo tanto es necesario que sus implicaciones fisiológicas, psicológicas y sociales sean reconocidas en escenarios de alto rendimiento deportivo para brindar un mejor apoyo a estas atletas, lo que contribuirá a mejorar su calidad de vida y salud integral en general.
**Palabras clave:** Menstruación; Natación; Salud sexual; Investigación cualitativa (DeCS).

Caballero-Guzmán A, Lafaurie-Villamil MM. [Nadar con la menstruación: un estudio cualitativo en nadadoras de élite]. Rev. Fac. Med. 2020;68(3):356-62. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n3.76135.

## Introduction

Menstruation is a biological process with cultural and social meaning, often negative,[1,2] that plays an important role in the construction of the female identity and body image.[3] The effects of menstruation on physical and mental health, and on sexuality, as well as the perceived limitations it imposes on spare time, are part of the situations to which women are exposed during this stage.[4] In spite of its relevance, menstruation is a subject that is little considered in scientific spheres, perhaps due to factors such as the silence that women keep about everything it implies or the little education they have about it.[5]

Women have competed in the Olympic Games since 1900,[6] and from then on, their participation has increased, so much so that for the 2016 Rio Olympics, they represented 45% of the competitors.[7] However, it should be noted that women's sport performance differs from that of men for biological, psychosocial, and cultural reasons related to the sports environment.[8-10]

In Colombia, Konovalova & Rivera-Echeverry[11] report that more than 91% of female athletes compete and train while they are on their period. On the other hand, Maturín-López & Landázuri-Munares[12] describe that 24.8% of the analyzed athletes perceived they had a worse physical performance, while 13% felt that their performance was better. The latter finding could be related to the fact that the athletes perceive an increase in flexibility, as stated by Prado-Seoame.[13] During the premenstrual and menstrual phases, the levels of estrogens and progestins decrease, producing psychological changes such as depression and irritability, and physical discomforts such as breast tension and abdominal pain, which negatively affect sports performance.[14-16]

Regarding the regularity of the menstrual cycle, no alterations have been found in elite swimmers.[17,18] However, Coste *et al.*[19] found that in this population there is a relationship between highly demanding training sessions and increased energy expenditure, on the one hand, and the increase in cases of hyperandrogenism (polycystic ovarian syndrome), on the other.

Using oral contraceptives is common among sports women so that their periods do not coincide with competitions since they consider that during those days, they must deal with pain and the discomfort its treatment implies;[20] besides, if bleeding is controlled, anxiety diminishes.[21-23]

Menstruation, from the experience of female athletes, has been little studied. Some of the few investigations on this subject were carried out by Moreno-Black & Vallianatos,[24] who found that the participants in their study felt uneasy about the possibility of having their clothes stained with blood and that their sanitary pads would "notice." In turn, Suee-Held[25] showed that female athletes are concerned about the perception that their male counterparts have on menstruation and that they fear using tampons during competitions because leaks could occur, and the string can be exposed.

Menstruation affects swimmers in a particular way, so their experience needs to be analyzed in a specific way. In this sense, the objective of this research was to describe the experience of a group of elite female swimmers belonging to a sports league in Bogotá D.C., Colombia, with respect to menstruation and its impact on sports practice.

## Materials and methods

This is a qualitative study with a descriptive phenomenological approach, in which the experience of female swimmers concerning menstruation and sports practice was analyzed.[26,27]

In-depth interviews were conducted[28,29] to ask questions about the menstrual education received, experience of menarche, menstrual hygiene methods (MHM) used, experiences with menstruation in the sports environment, pain management, and possible solutions to difficulties. The interview script was reviewed by an expert and subjected to a pilot test with a senior female swimmer and a junior female swimmer.

The criteria for inclusion were women swimmers in the senior category (between 18 and 29 years old) who belonged to a sports league in Bogotá D.C. and carried out more than three training sessions per week. Given the characteristics of the study and the subject matter to be explored, the sample was defined using the snowball strategy, a non-probabilistic sampling technique in which existing study subjects provide referrals to recruit future subjects,[30] that is, qualified persons are asked to identify individuals or groups with special knowledge of the phenomenon;[26,31] this is a very useful strategy to access groups that are difficult to reach or when participants do not want to expose themselves publicly.

Three coaches were contacted through the Bogotá Swimming League to select the participants, referring the first three; they, in turn, helped to contact other swimmers. Data collection was stopped when the content saturation criteria were reached; consequently, nine swimmers were included in the final sample, three for each modality: swimming races, water polo, and open water swimming. Swimmers from three different modalities were included to control bias.

The interviews lasted two hours, were carried out in non-sporting places according to the participants' time and availability, and were carried out by the principal researcher, who had no previous contact with the interviewees. The interviews were recorded and transcribed verbatim. The obtained narrations were entered in text into the NVivo Pro® program to facilitate the work and ensure transparency between the coding work and the information analysis.

The thematic analysis was done following the Giorgi's method for phenomenological studies, which seeks to describe the experiences of the interviewees.[32] Each emerging theme was contrasted with relevant literature and illustrated with quotes from participants.

As per Mora,[29] criteria of credibility were applied, on the one hand, by supporting the analysis of the narrative material obtained and comparing the findings with those reported by other authors. Furthermore, criteria of confirmability were applied by practicing the reflexibility inherent to the agreement between researchers with different professional backgrounds and by receiving feedback from the participants on the results.

The narratives were ordered within the units of meaning identified from the objectives of the study and categorized according to the main axes of meaning; likewise, the descriptions were compared and contrasted to later recognize units with common meanings.[30] Each participant was given a pseudonym to preserve their identity when quoting them.

This research followed the ethical principles for medical research in humans stipulated in the Declaration of Helsinki 2013[33] and was considered of minimal risk according to the Resolution 8430 of 1993 of the Ministry of Health of Colombia.[34] The interviewees read and signed the informed consent. The Research Ethics Committee of the University El Bosque approved this work through Minutes No. 005-2017 of March 23, 2017. The confidentiality and anonymity of the data and the protection of the privacy and identity of the participants were guaranteed.[35]

## Results

The results were arranged into six main themes: characterization of the participants, experience of menarche, MHM, accidents and leaks, physical discomfort of menstruation, and solutions given by the participants. They are described below.

### Characterization of the participants

Table 1 shows the characteristics of the participants of the study: pseudonym assigned, age, educational attainment, modality practiced, and age at which they started practicing the sport.

**Table 1.** Characterization of the participants.

| Pseudonym | Age | Education attainment | Sports modality | Age of initiation of sports practice |
|---|---|---|---|---|
| Ana | 19 years | Fourth semester of higher education | Swimming races | 10 years |
| Valeria | 21 years | Fifth semester of higher education | Swimming races | 5 years |
| Violeta | 18 years | First semester of higher education | Swimming races | 9 years |
| Sofía | 23 years | Seventh semester of higher education | Water polo | 13 years |
| Natalia | 22 years | Sixth semester of higher education | Water polo | 13 years |
| Camila | 21 years | Ninth semester of higher education | Water polo | 11 years |
| Juliana | 27 years | University graduate | Open water swimming | 9 years |
| Lorena | 22 years | Fourth semester of higher education | Open water swimming | 9 years |
| Antonia | 18 years | Fifth semester of higher education | Open water swimming | 9 years |

Source: Own elaboration.

The age range of the participating swimmers was between 18 and 27 years old, with a median of 21 years; on average, the interviewees had practiced swimming for more than 9 years, and their starting age in this sport was between 5 and 13 years, with a median of 9 years. Only one interviewee had graduated from the university; the others were university students.

### Experience of menarche

Table 2 presents the general aspects of menstruation in the participants: age of menarche, presence of dysmenorrhea, presence of menstrual irregularities and MHM.

**Table 2.** General aspects of menstruation in the participants.

| Case | Age of menarche | Dysmenorrhea | Irregularities | MHM |
|---|---|---|---|---|
| Ana | 12 years | Yes | None | Tampon |
| Valeria | 11 years | Yes | None | None |
| Violeta | 14 years | Yes | None | None |
| Sofía | 13 years | No | None | Tampon |
| Natalia | 12 years | Yes | Oligomenorrhea | Tampon |
| Camila | 12 years | Yes | Amenorrhea | None |
| Juliana | 12 years | Yes | Amenorrhea | Tampon |
| Lorena | 12 years | Yes | Amenorrhea | Tampon |
| Antonia | 9 years | Yes | None | Tampon |

MHM: menstrual hygiene methods.
Source: Own elaboration.

The interviewees had their menarche between 9 and 14 years of age, with an average age of 11.8 years, and all began their sporting life before this event. Although the athletes had received information about the menstrual period in their homes and schools, they experienced fear and surprise when they had their first menstruation: "You never know what's going on, so it freaks you out, I realized I was bleeding" (Violeta). Likewise, there was evidence of grief because they left their childhood state and had to face the changes inherent to the reproductive life: "I went to the bathroom, I got sad [...] we have to deal with (sic) the rest of our lives" (Natalia).

### Menstrual hygiene methods

When the participants were asked about the MHM they used to train or compete, it was found that those who practiced swimming races did not use any, while the water polo and open water swimmers used tampons. None of the athletes had used the menstrual cup and only one knew of its existence.

One of the reasons for not using any MHM was that they were told so, as stated by one of the interviewees: "My coach said that swimming stops the flow. I don't have it while I am swimming" (Antonia). Moreover, the fear of using tampons was evident: "Tampons scare me because of the things that have been said about them, many myths. I do not use them" (Violeta). Similarly, among the girls that used this method, it was found that Natalia, a water polo player, stated that it is unsafe after a while: "I spent a lot of time during tournaments in the pool, I was three, four, five hours in the water and when I came out of the pool I had a stream of blood on

my leg; it was terrible". The other five tampon users reported feeling greater security during their period while practicing sports with this method: "Now I swim with tampons. I love them" (Ana).

Menstrual flow is considered an unpleasant substance that defies physical and social limits and puts the emotional stability and identity of swimmers at risk, which is why MHM are required to ensure safety and protection.

### Accidents and leaks

Menstruation is a private matter for swimmers, and it is a topic that is not discussed within the social or sports sphere. The fear of having "accidents" or leaks was present in the narratives of eight interviewees, who stated that the menstrual period interferes with their peace of mind and sports performance. The clinical signs and symptoms of menstruation must remain hidden, making it a process that challenges the distinction between public and private matters. The interviewees think that a menstruating woman should be discreet to avoid being exposed to shame, which is greater in the presence of men. Furthermore, they emphasize that it is more difficult for them to take care of themselves when they are in a bathing suit because this situation leaves them more exposed: "When it's time to compete, it must go unnoticed because it would be really embarrassing that people realized that I'm menstruating" (Violeta).

### Physical discomfort during menstruation

All the interviewees consider menstruation as a problem in the sports environment: there is a menstruation-discomfort-aversion concept in which this process is seen as an impediment to swim: "I think that menstruation is what bothers us the most because it is a bad thing. I am prepared for the competition and then I have my period. It is a blow for me as an athlete" (Natalia).

The need to overcome the physical discomfort derived from the menstrual period is part of the female experience, especially in competitive sports, as it has more significant repercussions since athletes must maintain intense physical activity despite feeling pain, fatigue, and nuisance. One of the interviewed swimmers referred to this issue and said that it is a situation that affects performance: "In sports it is the most complex issue. We prepare and then the period comes. We feel tired, slower, heavier, with a lot of discomfort" (Natalia).

Cramps are the main physical discomfort experienced during menstruation; it was reported by eight of the interviewees, being a constant problem: "Lots of cramps, always" (Juliana). To treat this symptom, six interviewees reported using antispasmodic medications, the best option to reduce pain and be able to continue with the competition: "Swallowing pills, I have to take a lot" (Juliana).

Menstruation affects the physical and mental state of female athletes, reducing their sports performance. In this regard, the participants reported that there is a significant lack of understanding of this situation, for example, on the part of the coaches, who are not empathic: "Swimming with cramps, waist pain, leg pain. The coach says, 'Do it, it will go away if you swim. That's a big lie. It gets worse. All the coaches plot it" (Lorena).

In order to modify the menstrual cycle so that it does not coincide with sports competitions, two swimmers reported using oral contraceptives following medical indications: "They made us take birth control pills to extend the cycle" (Juliana).

When analyzing the presence of menstrual cycle alterations, four interviewees said they had irregular cycles at some point in their life and three reported having periods of amenorrhea that were not related to sports activity. These swimmers, even though they know the anorexia-amenorrhea-osteoporosis triad, said that they did not have their periods because of changes of location and the climate: "I did not have it for nine months and I had no risk of pregnancy. According to the doctors, it happened because the climate changed" (Juliana).

On the other hand, four participants perceived menstruation as positive for sports performance, specifically in terms of increased speed: "With menstruation, performance improves. Sometimes, when I menstruate during a competition, I sometimes do better than when I'm not" (Violeta).

### Solutions proposed by the participants

The interviewees stated that it is necessary to change how menstruation is perceived from the beginning of sports life. Since the main perceived problems are lack of knowledge and discomfort, they proposed that health professionals carry out educational processes that fit their experiences and concerns: "Medical training, learn about other methods to avoid accidents. Girls have to be trained from a young age, make recommendations [...] I learned from a senior" (Violeta). They also said that trainings should address alternative methods: "I recently heard that there was a method different from the usual ones, which is menstrual cups. It seems good to me because it will change my life, it will give me more security" (Natalia). Finally, they asked for the development of an institutional guideline for coaches with information on women's issues: "Guidelines for male coaches" (Lorena).

Similarly, the interviews showed their desire to make the sports environment better for female athletes and having more women coaches hired for this job: "Women should be given the opportunity. They will understand the menstrual cycle and that would allow us to have a better sports and personal life" (Camila). The desire of having female health personnel available was also evident: "A female sports doctor, that would be the best. Because with a man you do not feel confident enough to talk about these issues. It is easier with a woman" (Juliana).

## Discussion

This study describes the perceptions of a group of elite female swimmers regarding how they experience menstruation while training or competing. For this group of athletes, as for Beauvoir,[36] menstruation is a biological process that limits women's freedom and its clinical signs and symptoms have implications at the physical and emotional level; it also reflects social and cultural prejudices. As described by Ortega *et al.*,[37] the shame reported by the interviewees, together with the need to hide their periods from coaches and male counterparts, is

related to the ancestral rejection of menstruation, which, according to Nussbaum,[38] is tied to a misogynist culture that considers the feminine as shameful and the woman's body and its fluids as repugnant and close to animality.

Menstruation is a subject with little visibility in sports medicine. This may be because, according to Costello *et al.,*[39] only 39% of studies in sports medicine have been conducted on female athletes and many of them probably do not address this physiological process. Likewise, menstruation in the analyzed population is endowed with negative social and cultural meanings, which is consistent with what was stated by Brantelid *et al.*[40] and Lamborn.[41] In addition, the results suggest that issues related to the menstrual experience are ignored, thus hindering the approach to women's health in a comprehensive manner, as stated by Valls-Llobet.[42]

Menarche in the participants occurred at an age similar to the Colombian average (between 11.3 and 12.7 years);[11,43] before this event, the swimmers experienced the same feelings of uncertainty described by González & Montero.[44] This could be explained by the fact that, despite advances in sex education, young women still perceive the arrival of the first menstruation as a strange and unexpected situation, and it is generally associated with the end of childhood and the beginning of fertile life.[45]

Menstruation as an impediment, according to Rodríguez-White,[46] is a concept reinforced by the menstruation-discomfort-aversion triad that entails the idea of denying any impact that menstruation may have and reinforces negative attitudes in the imaginary. Similarly, according to Puyana-Villamizar,[45] this situation, is related to suffering, dirtiness, and concealment.

Menstruation can alter sporting performance, not only because women feel the need to hide it, but because it causes physical and psychological symptoms and the discomfort derived from handling them.[24,25,47] For Young,[48] menstrual blood is a fluid that challenges physical and social boundaries, and when women menstruate they risk losing their emotional stability (normality), so swimmers demand MHM to ensure their safety and protection. Regarding these methods, it was found that using tampons made the interviewed swimmers feel more secure, although they were cautious when they had to stay underwater for a long time because there is a great risk of blood leaking out when coming out of the water.[49]

The knowledge of MHM is limited to the traditional ones: only one participant knew about the menstrual cup and although she had not used it, she had the perception that it was safer. Several authors have presented studies on this particular issue and on the fears and benefits of using different methods.[50-56]

Young women trust those who live and understand female processes (other female swimmers, coaches, and health staff). This situation, reported by Fernandez-Olguin,[57] allows us to understand why blood leaks in front of men are embarrassing for female athletes.

The physical experience is related to pain, tiredness, and discomfort. In this respect, Konovalova & Rivera-Echeverry[58] found that Colombian sportswomen suffer from abdominal pain, mastalgia, lumbago and general malaise during their periods. In the present study, six interviewees said that menstruation limits their performance, while three claimed to have better results in terms of speed; this coincides with what was reported by Prado-Seoane.[13]

Menstrual irregularities such as oligomenorrhea and amenorrhea, although present, were not of concern to participants as they were attributed to environmental factors. Other studies, such as Mountjoy *et al.,*[59] Humphrey,[60] Weiss-Kelly & Hecht[61] and Ranson *et al.,*[62] do not directly correlate high performance sports to menstrual irregularities, but associate them with other factors involved such as increased energy expenditure and caloric restriction, which cause hormonal changes.

The little attention paid to the menstrual period in the sports environment and the scarce empathy that some coaches have for the participants regarding their clinical signs and symptoms make it necessary to have a better understanding of this phenomenon. This, added to the scarce information that swimmers receive,[58] makes the female experience more difficult and produces psychological and social insecurities, so it can be said that menstruation education helps female athletes.[63]

The group of swimmers interviewed suggested the implementation of comprehensive sex education policies tailored to their experiences and concerns. As stated by Chrisler *et al.*[3] and Britton,[64] this process requires including issues such as the concept of secrecy, social isolation, safe handling of MHM, and the benefits and negative effects of menstruation. Other recommendations for the formulation of these policies include pain management, access to modern MHM, reducing the stigma of menstruation, and educating colleagues, coaches, and family members to provide support, as proposed by Bobel.[4]

## Conclusions

While significant progress has been made regarding women's equality in sports, it is important to build more spaces for equity. Menstruation is a physiological process organized and interpreted in a social and cultural way that has a specific impact on the sports environment and on the quality of life of female athletes. Specifically, the problems faced by female swimmers are related to physical aspects (menstrual cramps and back pain), psychological aspects (depression and irritability) and social aspects (concern about keeping menstruation hidden). Therefore, these issues must be addressed by health professionals, coaches, and family members to provide comprehensive care to women from the beginning of their sporting career.

There is a gap in knowledge about menstrual physiology, MHM and their alternatives, and treatment of cramps and other associated symptoms that impact sports performance. Participants perceive that in the sports environment more importance is given to their performance than to their overall well-being, which is why more guidance and support is needed.

Based on the testimonies of the interviewed female swimmers, it could be said that it is necessary to improve the perception of menstruation in the sports environment, recognizing its biological, psychological and social implications, and thus help athletes in general to lead a fuller and more satisfactory life.

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## Conflicts of interests

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# Physiological changes associated with respiratory muscle training in patients on mechanical ventilation

*Cambios fisiológicos relacionados con entrenamiento muscular respiratorio en pacientes con ventilación mecánica*

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## Abstract

**Introduction:** Respiratory muscle training is a technique that aims to increase the strength of the respiratory muscles. However, few studies have addressed physiological changes related to this intervention in patients on mechanical ventilation.
**Objective:** To determine the physiological changes associated with respiratory muscle training in patients on mechanical ventilation.
**Materials and methods:** A secondary data analysis was performed. The population was made up of the 62 patients in the experimental group of the main study, who received respiratory muscle training. Heart rate, respiratory rate, blood pressure, oxygen saturation, and tidal volume values were obtained. The difference between the means of each of the variables was analyzed through the paired t-test, while physiological changes between training sessions were analyzed using the Kruskal-Wallis test. Differences with a $p<0.05$ value were considered statistically significant.
**Results:** Statistically significant differences were found between physiological variables before and after respiratory muscle training ($p<0.05$), except for tidal volume and mean blood pressure ($p>0.05$). In contrast, when the effect was evaluated according to the number of training sessions received by the patients, no significant differences were observed in any of the variables ($p>0.05$).
**Conclusions:** Respiratory muscle training is a viable and tolerable therapeutic intervention in this population.
**Keywords:** Training; Safety; Intensive Care; Physical Therapy Specialty; Respiratory Muscles (MeSH).

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## Resumen

**Introducción.** El entrenamiento muscular respiratorio es una técnica fisioterapéutica usada para incrementar la fuerza de la musculatura respiratoria, sin embargo pocos estudios han abordado los cambios fisiológicos relacionados con esta intervención en pacientes con ventilación mecánica.
**Objetivo.** Determinar los cambios fisiológicos relacionados con el entrenamiento muscular respiratorio en pacientes con ventilación mecánica.
**Materiales y métodos.** Se realizó un análisis de datos secundarios. La población estuvo conformada por los 62 pacientes del grupo experimental del estudio principal, quienes recibieron entrenamiento muscular respiratorio. Los valores de frecuencia cardiaca, frecuencia respiratoria, presión arterial, saturación de oxígeno y volumen corriente fueron registrados. La diferencia entre el promedio de cada una de las variables fue analizada mediante la prueba de t pareada, mientras que para el análisis de los cambios fisiológicos entre sesiones de entrenamiento se empleó la prueba de Kruskal-Wallis. Las diferencias con un valor $p<0.05$ se consideraron como estadísticamente significativas.
**Resultados.** Se observaron diferencias estadísticamente significativas entre las variables fisiológicas antes y después del entrenamiento muscular respiratorio ($p<0.05$), a excepción de volumen corriente y la presión arterial media ($p>0.05$). Por el contrario, cuando se evaluó el efecto según el número de sesiones de entrenamiento recibidas por los pacientes, no se observaron diferencias significativas en ninguna de las variables ($p>0.05$).
**Conclusiones.** El entrenamiento muscular respiratorio es una intervención terapéutica viable y tolerable en esta población.
**Palabras clave:** Entrenamiento; Seguridad; Cuidado intensivo; Terapia física; Músculos respiratorios (DeCS).

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## Introduction

Mechanical ventilation (MV) is a life-support treatment often used in intensive care units (ICUs) as part of the standard management of acute respiratory failure.[1] 33% percent of patients admitted to the ICU require MV;[1] of these, 5% fail their first attempt to wean[2] and require prolonged MV, which has been associated with complications such as changes in respiratory mechanics, airway injuries, acute lung injury, and pneumonia.[3,4] Since functionality in patients with prolonged MV is affected when they leave the ICU, and consequently their quality of life worsens, it is necessary to implement strategies to accelerate weaning and thus reduce sequelae of this treatment.

Respiratory muscle training (RMT) is a physical therapy strategy used to increase respiratory muscle strength and improve exercise tolerance to facilitate weaning from MV.[5,6] This intervention has been implemented in patients with chronic obstructive pulmonary disease and heart failure, achieving effective results.[7] In patients on MV, evidence is growing and its implementation is suggested in populations with well-defined criteria, taking into account specific vital signs and ventilator parameters.[8]

The reported benefits of RMT in ICU patients are increased maximal inspiratory pressure,[5,9-11] increased tidal volume[10] and improved exercise tolerance and performance of daily activities.[11] Multiple controlled clinical trials have evaluated tolerance to RMT and the presence of adverse events in patients on MV,[5,9-11] reporting that it is a tolerable and safe strategy in this population; however, little research has assessed physiological changes related to RMT in these patients. Some of these research works are the study conducted by Santos-Pascotini *et al.*,[12] who evaluated RMT-related changes in tidal volume, respiratory rate and heart rate in 14 tracheostomy patients with difficult MV weaning, and determined that this strategy did not produce significant changes in the variables evaluated; in turn, Bissett *et al.,*[8] studied the physiological response to RMS in a cohort of 10 tracheostomy patients and reported that it was a safe therapeutic intervention in this population.

Considering that, to date, there are no reports in the literature of studies conducted in Colombia on the subject and that it is important to highlight the relevance of surveillance and monitoring of vital signs and tidal volume during RMT,[13] the objective of this study was to determine the physiological changes related to RMS in patients on WV ≥48 hours in a quaternary care clinic in Cali, Colombia, during the period 2014-2015.

## Materials and methods

A secondary data analysis was performed in the framework of the study "Efficacy of respiratory muscle training in weaning from mechanical ventilation in patients with mechanical ventilation for 48 hours or more: a randomized controlled clinical trial".[14]

The population consisted of 62 patients who were part of the experimental group of the main study and met the following inclusion criteria: 1) mechanical ventilation for ≥48 hours, 2) aged ≥18 years, 3) first time requiring mechanical ventilation, 4) intubation at the quaternary care clinic where the study was conducted or other health care facilities and referred no later than 12 hours after intubation, and 5) $PaO_2$>60 mmHg, $FiO_2$≤0.5, PEEP<8 cmH20, RASS agitation and sedation scale between -1 and 01[5], and mean blood pressure >60 mmHg without vasopressors or with minimal requirement of vasopressors (dobutamine or dopamine <5 mcg/kg/min/, or epinephrine <1 mcg/kg/min). Patients who met any of the following conditions were excluded: neuromuscular disease, central nervous system injury, spinal cord injury above T5, severe scoliosis, severe kyphoscoliosis, pectus excavatum, pectus carinatum, pre-hospital ventilator support at home, tracheostomy, infection by multi-resistant bacteria, or pregnancy.[14]

The ethical principles established in Resolution 8430 of 1993[16] and the Declaration of Helsinki[17] were followed. The Ethics Committee of the Universidad del Valle approved this study by means of Minutes No. 003-016 of March 31, 2016.

The experimental group in the main study was included in an RMT program twice a day, every day, using the Respironics® Threshold IMT Respiratory Muscle Trainer (Respironics Inc., USA). Following the recommendations made by Caine & McConnell[18] *and* Sprague & Hopkins,[19] the initial RMT load was adjusted to 50% of the maximal inspiratory pressure and, in each session, 3 series of 6-10 repetitions were performed, depending on patient's tolerance, with a rest interval of 2 minutes between series.[18-20]

At the end of each series, dyspnea was evaluated using the modified Borg scale.[21] RMT and the records of the evaluated variables were applied by four physiotherapists who are part of the ICU team of the clinic; they were assigned for the development of the project and had experience in the care of critically ill patients. The physiotherapists were trained according to the indications of the research team, which were based on previous research.[9,22]

The training session was interrupted when the patient presented one of the following signs: 1) breathing rate >35 breaths per minute or >50% at the beginning of the session, 2) heart rate >140 beats per minute or >20% at the beginning of the session, and 3) paradoxical breathing, agitation, hemoptysis, sweating, or arrhythmia.[20]

Patients received the RMT sessions until they were extubated or until they presented any of the following conditions: 1) verbal or written request from the patient or his/her guardian to be excluded from the protocol; 2) septic shock,[23] which was considered if the patient presented systolic blood pressure <90 mmHg, mean blood pressure <65 mmHg and hyperlactation (lactic acid >4 mmol/L), or 3) tracheostomy.

At the beginning of the study, the following data were obtained for each patient: age, sex, height, type of health insurance, diagnostic classification, place of orotracheal intubation, score in the APACHE II classification system, reason for admission to ICU, mechanical ventilation modalities, and medications received during ICU stay.

The main variables assessed (heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, mean blood pressure, oxygen saturation and tidal volume) were recorded at rest and immediately after the end of each training series. Vital signs and tidal volume measurements were performed using a Nihon Kohden monitor and a Maquet mechanical ventilator (Servo-i 300), respectively.

### Data analysis

The information collected in the main study was entered into a database previously designed in Epi Info™ 7 and subsequently exported to Stata 12 for analysis. The creation of the database and the typing was carried out by the researchers of the study, and an external evaluator compared the typed data with the records contained in the collection forms to evaluate the quality of the data.

To assess the normality of the data, the Shapiro-Wilk test was used. To assess changes in physiologic variables, the difference between the average of each variable before the start of the first RMT series and after the end of each RMT session was analyzed using the paired t-test. To analyze physiological changes according to the number of RMT sessions, the population was divided into three categories: patients who received one RMT session, patients who received two RMT sessions and patients who received more than two RMT sessions. Non-parametric variance was analyzed using the Kruskal-Wallis test for each of the variables. A value $p<0.05$ was statistically significant.

## Results

Table 1 presents the clinical and socio-demographic characteristics of the participants.

**Table 1.** Clinical and socio-demographic characteristics.

| Variables | | n (%) |
|---|---|---|
| Age (years) | | 61(40-70) * |
| Sex | Male | 33(53.23) |
| | Female | 29(46.77) |
| Height (cm) | | 162.00(9.38) † |
| Race | White | 23(37.10) |
| | Mestizo | 23(37.09) |
| | Black | 10(16.12) |
| | Indigenous | 6(9.68) |
| OTI | OTI at the clinic | 49(79.03) |
| | OTI at other care facility | 13(20.97) |
| APACHE II | | 26.54(11.47) † |
| Reason for admission | Medical | 45(72.59) |
| | Surgery | 17(27.41) |
| Diagnostic classification | Respiratory | 29(46.78) |
| | Gastrointestinal | 19(30.64) |
| | Cardiovascular | 13(20.97) |
| | Kidney | 1(1.61) |
| MV mode | Assist | 42(30-72) * |
| | Control | 6(0-27) * |
| | Spontaneous | 0(0-3) * |
| Medication | Midazolam | 143.5(55-232) |
| | Fentanyl | 9575(3450-18150) |
| | Dexmedetomidine | 0(0-9150) |
| | Propofol n (%) | 2(3.23) |
| | Norcuron® n (%) | 1(1.61) |

OTI: orotracheal intubation; VM: mechanical ventilation.
* median and interquartile range.
† mean and standard deviation.
Source: Own elaboration.

The median age of the patients in the study was 61 years. 45 (72.59%) were admitted to the ICU for medical reasons, and the respiratory system was the most affected system in 29 (46.78%).

Patients received between 1 and 14 RMT sessions, distributed as follows: 26 (42%), one session; 31 (50%), 2 sessions; and 5 (8%), 3 to 14 sessions, for a total of 159 sessions. Table 2 presents the changes in the participants' physiological parameters before and after RMT.

Thus, it was observed that after RMT, the means of all physiological variables had a statistically significant increase ($p<0.05$), except for tidal volume and blood

pressure. However, when the effect of RMT was evaluated according to the number of sessions received by the patients, no statistically significant differences were observed in any of the variables (Table 3).

**Table 2.** Changes in physiological variables before and after respiratory muscle training.

| Vital sign | Pre-training | | Post-training | | p-value |
|---|---|---|---|---|---|
| | Median | SD | Median | SD | |
| Heart rate (BPM) | 81.16 | 19.57 | 82.95 | 20.22 | 0.020 |
| Breathing rate (BRPM) n=154 | 18.34 | 5.17 | 19.42 | 5.94 | 0.000 |
| Mean arterial pressure (mmHg) n=158 | 86.75 | 12.63 | 88.29 | 13.46 | 0.050 |
| Systolic blood pressure (mmHg) | 125.56 | 1.44 | 129.94 | 1.56 | 0.000 |
| Diastolic blood pressure (mmHg) | 67.36 | 14.29 | 68.99 | 13.80 | 0.030 |
| % of oxygen saturation | 98.1 | 2.29 | 98.71 | 1.94 | 0.000 |
| Tidal volume (ml) | 447.04 | 105.59 | 456.36 | 97.21 | 0.200 |

SD: standard deviation; BPM: beats per minute; BRPM: breaths per minute.
Source: Own elaboration.

**Table 3.** Changes in physiological variables before and after training according to the number of sessions received.

| Number of sessions | Pre-training | | Post-training | | p-value |
|---|---|---|---|---|---|
| | Median | Range Intercuartilíco | Median | Range Intercuartilíco | |
| Heart rate (BPM) | | | | | |
| 1 | 80 | 70-95 | 80 | 73-96 | 0.9 |
| 2 | 77 | 69-90 | 80 | 71-91 | |
| 3-4 | 76 | 66-92 | 79 | 72-92 | |
| Respiratory rate (BRPM) | | | | | |
| 1 | 16 | 14-20 | 17 | 14.5-21.5 | 0.7 |
| 2 | 16 | 15-22 | 18 | 15-24 | |
| 3-14 | 18 | 15-22 | 20 | 16-23 | |
| Mean blood pressure (mmHg) | | | | | |
| 1 | 86 | 78-92 | 86 | 79-96 | 0.61 |
| 2 | 89 | 77-100 | 91 | 80-103 | |
| 3-14 | 85 | 77-92 | 83.5 | 78.5-97 | |
| Systolic blood pressure (mmHg) | | | | | |
| 1 | 125 | 112-134 | 123 | 118-141 | 0.91 |
| 2 | 126 | 118-143 | 130 | 120-151 | |
| 3 a 14 | 121 | 111-132 | 127 | 116,5-139,5 | |
| Diastolic blood pressure (mmHg) | | | | | |
| 1 | 67 | 59-77 | 68 | 61-78 | 0.63 |
| 2 | 69 | 69-77 | 71 | 61-81 | |
| 3-14 | 64 | 58-75 | 66.5 | 59.5-76.5 | |
| % of oxygen saturation | | | | | |
| 1 | 99 | 97-100 | 100 | 99-100 | 0.19 |
| 2 | 99 | 97-100 | 99 | 98-100 | |
| 3-14 | 99 | 97-100 | 100 | 98-100 | |
| Tidal volume (mL) | | | | | |
| 1 | 440 | 397-518 | 455.5 | 403-505 | 0.52 |
| 2 | 464 | 400-513 | 440 | 401-516 | |
| 3-14 | 420 | 385-485 | 452 | 408-500 | |

BPM: beats per minute; BRPM: breaths per minute.
Source: Own elaboration.

## Discussion

Multiple controlled clinical trials evaluate RMT tolerance and the occurrence of adverse events associated with this intervention in patients on MV. For example, Condessa *et al.*[7] and Martin *et al.*[10] report that this intervention was tolerable and safe in this population.

Marques-Tonella *et al.*,[23] in a study of 21 patients with tracheostomy and difficult weaning from MV, found that RMT, implemented using an electronic device, caused changes in respiratory rate, mean blood pressure, and oxygen saturation, without producing adverse effects. This result is consistent with those of the present study, despite differences in population and time of MV.

The present study showed that heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, and oxygen saturation increased significantly after completing the RMT session. This differs from the study conducted by Dos Santos-Pascotini *et al.*[12], who describe that RMT did not generate significant changes in tidal volume, respiratory rate, and heart rate after completing it in 14 patients with tracheostomy and difficult weaning from MV. It also differs from Bissett *et al.*,[8] who reported the same result for the variables heart rate, mean blood pressure, respiratory rate, and oxygen saturation in 10 individuals with tracheostomy and failed weaning from MV.

This may be associated with the differences of the study population, the RMT protocol and the total number of sessions received per patient since, in the present study, an RMT protocol with higher loads and longer duration was implemented, possibly resulting in less residual fatigue between training sessions[22] and a greater response in the values of the variables evaluated compared to other RMT protocols with high loads and short duration.[24,25] The 62 patients analyzed here only received a total of 159 sessions since they had a short period of MV after entering the study, so the number of RMT sessions was probably insufficient for them to adapt to the activity.[25-27]

In this study, the physiological variables evaluated remained in the safety range,[28,29] since the maximum values reached in each of these variables did not surpass the limit beyond which physical exercise is contraindicated in this population, even though there were significant increases in heart rate, respiratory rate, systolic and diastolic blood pressure, and oxygen saturation.[30]

When analyzing the physiological changes in patients according to the number of RMT sessions performed, no significant differences were found. This result can be explained, on the one hand, by the small sample size used in the present study, which in turn was its greatest limitation, and, on the other, by the distribution of the number of RMT sessions per participant (between 1 and 14 sessions), considering that they were exposed to MV only for a short period once it was determined that they met the inclusion criteria since the effect of RMT depends largely on its duration, as reported by Seynnes *et al.*[31], who point out that a minimum of 10 days of muscle training is required to increase the strength of the limb muscles, achieving an important clinical impact that also applies to inspiratory muscles.[32] However, some authors have reported that it takes about 14 days to achieve significant changes in muscle strength.[20,31]

The main strengths of the study were the strategies implemented to reduce the possibility of information bias during the implementation of the intervention protocol in the main study, including quality control of the measurement instruments and of the information collection and analysis processes.

Despite the limitation of the sample size, the results of this research are relevant because they allow considering RMT as a fundamental part of physical therapy in the ICU. They also provide evidence of the physiological changes related to RMT and, consequently, they contribute to knowledge in the area of cardiopulmonary physical therapy. Moreover, this is the first study to evaluate physiological changes related to RMT in Colombia, so it is a framework for future research.

## Conclusions

RMT was a viable and tolerable therapeutic intervention in the study population since it generated significant increases in heart rate, respiratory rate, oxygen saturation, and systolic and diastolic blood pressure, without exceeding the limit beyond which physical exercise is contraindicated in this population.[30] However, no significant improvements were found in the variables analyzed when evaluating the impact of training according to its duration (number of sessions), so the findings reported here should be confirmed by new studies with larger samples and in patients where the duration of the RMT is longer.

## Conflicts of interest

None stated by the authors.

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# Effect of warm-up on hand grip strength in sedentary overweight women

*Efecto del calentamiento en la fuerza de agarre de mano en mujeres sedentarias con sobrepeso*

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## Abstract

**Introduction:** In recent years, handgrip strength assessment has gained special relevance in health. However, a standardized application protocol that includes warm-up procedures is required to measure it.
**Objective:** To compare the acute effects of four warm-up strategies on maximal handgrip strength (MHS) in sedentary overweight women.
**Materials and methods:** Single-blind, randomized, crossover study in which MHS was measured in 12 overweight women under the following conditions: i) no warm-up (control condition), ii) static stretching warm-up, iii) strength-based warm-up (i.e., resistance band exercise), and iv) isometric squeezing-ball warm-up for the forearm muscles. A Jamar dynamometer was used for the measurements, which were taken on four different days, at 48-hour rest intervals; three measurements were made per hand.
**Results:** MHS mean values were 23.8 and 24.9 kg without warm-up, 20.3 and 21.4 kg after stretching warm-up, 20.9 and 22.9 kg after strength-based warm-up, and 22.0 and 23.0 kg after squeezing-ball warm-up for non-dominant and dominant hand, respectively. No significant differences ($p>0.05$; one-way ANOVA) were observed between protocols, nor were there differences in MHS in relation to nutritional status, lean mass, or fat mass.
**Conclusion:** Warm-up is not required to measure MHS in overweight sedentary women when three measurements are made.
**Keywords:** Muscles; Body Fat; Women; Sarcopenia; Muscle Strength (MeSH).

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## Resumen

**Introducción.** En los últimos años se ha dado una mayor importancia a la medición de la fuerza máxima de agarre de mano, sin embargo para hacer esta medición se requiere un protocolo estandarizado de aplicación, incluyendo procedimientos de calentamiento.
**Objetivo.** Comparar los efectos agudos de cuatro tipos de calentamiento en la fuerza máxima de agarre de mano de mujeres sedentarias con sobrepeso.
**Materiales y métodos.** Estudio ciego, aleatorizado y cruzado en el que se midió la fuerza máxima de agarre de mano de 12 mujeres con sobrepeso bajo las siguientes condiciones: i) sin calentamiento (condición de control), ii) con calentamiento de estiramiento estático, iii) con calentamiento basado en la fuerza (p. ej., ejercicios con banda elástica) y iv) con calentamiento con bola terapéutica de compresión para los músculos del antebrazo. Para las mediciones se utilizó un dinamómetro Jamar y estas se realizaron en cuatro días diferentes y en intervalos de 48 horas de descanso; además, se hicieron tres intentos de medición por mano.
**Resultados.** Los valores promedio de fuerza máxima de agarre para la mano no dominante y dominante fueron 23.8kg y 24.9kg sin calentamiento, 20.3kg y 21.4kg con estiramiento, 20.9kg y 22.9kg con banda elástica y 22.0kg y 23.0kg con bola terapéutica, respectivamente. No hubo diferencias significativas ($p>0.05$; ANOVA de una vía) entre los protocolos, ni diferencias en la fuerza máxima de agarre de mano en relación con estado nutricional, masa magra o masa grasa.
**Conclusión.** No se requiere una sesión de calentamiento para medir la fuerza máxima de agarre de mano en mujeres sedentarias con sobrepeso cuando se realizan tres intentos de medición.
**Palabras clave:** Músculos; Mujer; Sarcopenia; Fuerza muscular (DeCS).

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## Introduction

Loss of muscle strength (dynapenia)[1] has a negative impact on morbidity and mortality.[2] Therefore, the timely assessment of muscle strength is fundamental in preventive medicine.[3]

The handgrip strength test is a validated and simple test used to assess muscle strength in several health-related contexts.[4-10] Despite its importance in clinical practice, there is a wide range of equipment and protocols to measure maximal handgrip strength (MHS).[11] Particularly, the effects of warming-up before performing MHS tests have not been described yet.

A warm-up is generally intended to generate an increase in muscle temperature, facilitating increased blood flow, optimizing metabolic responses,[12,13] reducing muscle viscosity (i.e. smoother contraction), and increasing nerve conduction velocity.[14] By extension, the search for an optimal muscle temperature range that limits fatigue as much as possible whilst maximizing performance[12-15] seems prudent. Commonly, warm-up protocols tend to reflect the experience of individual researchers and practitioners, and most studies are performed in athletes.[16]

Controlled studies about the effects of warm-up on maximal performance are particularly scarce, maybe due to the unwillingness of voluntary subjects to complete a maximal effort without warm-up (i.e. control condition). However, among the studies investigating the effect of warm-up protocols on muscle performance (e.g., maximal strength), conflicting results have arisen and some of them show an increase in performance after general, specific,[17] or combined warm-up,[18] while others have not.[16]

Considering the lack of studies addressing the effects of warm-up on sedentary overweight women and MHS, as well as the clinical relevance of MHS in community-health programs,[19] a standardized protocol of application is required. The aim of this study was to compare the acute effects of different warm-up strategies on MHS in sedentary women since it has been suggested that different warm-up protocols may have an impact on MHS.

## Materials and methods

### Ethical considerations

This study (study protocol No. 103- 2018) was approved by the Institutional Review Board of the Department of Physical Activity Sciences, Universidad de Los Lagos, as stated in Minutes DECAF2016/3, issued on April 25, 2016. The participants who agreed to take part in the study signed an informed consent form, after being explained about the risks and benefits derived from their participation. The study was conducted according to the ethical principles for medical research involving human subjects established in the Declaration of Helsinki 2013.[20]

### Subjects and procedures

A public call was made in a local University to recruit sedentary overweight women willing to participate in a randomized single-blind crossover study. A total of 12 women were recruited (age: 21.1±2.0 years; fat mass: 38.1%±8.4%; see Table 1 for more characteristics), and completed four different measurement protocols to assess MHS, with 48h of rest between each.

**Table 1.** Baseline characteristics of the sample.

| Variables | Mean | σ |
|---|---|---|
| Body mass (kg) | 64.5 | 9.1 |
| Height (m) | 158.3 | 8.4 |
| Body mass index (kg/m²) | 26.3 | 3.9 |
| Body fat (kg) | 24.8 | 7.3 |
| Lean mass (kg) | 22.1 | 3.3 |
| Water (L) | 29.8 | 4.0 |
| Lean mass left hand (kg) | 2.1 | 0.4 |
| Lean mass right hand (kg) | 2.1 | 0.4 |
| Fat mass left hand (kg) | 1.8 | 0.7 |
| Fat mass left hand (kg) | 1.8 | 0.7 |

σ: standard deviation.
Source: Own elaboration.

To be included in the study, participants were required to: i) be over 18 years old, ii) be sedentary (weekly physical activity level = 600 MET-min/week),[21] iii) be free of cardiovascular, pulmonary or skeletal muscle diseases,[22] and iv) have fat mass >30% of total body mass. All experimental procedures were performed under controlled and standardized conditions in the Laboratory of Human Performance at the university where the study was conducted, always at the same time of day, with the same temperature, humidity, rest time (i.e., sleep hours before testing), menstrual cycle phase, and hours after the last meal. According to previous recommendations, height (Bodymeter 206, SECA, Germany to 0.1cm), body mass and body composition (InBody120, tetrapolar 8-point tactile electrodes system, model BPM040S12F07, Biospace, Inc., USA, to 0.1kg) were measured.[23]

### Measurement of handgrip strength

The test was applied according to previous recommendations.[24] To assess MHS, an adjustable digital dynamometer was used (Jamar®, PLUS+, Sammons Preston, Patterson Medical, Illinois, United States). After randomly assigning the order of dominant and non-dominant hand assessment, three trials were performed to achieve maximal voluntary isometric handgrip strength (MVIHS) for both dominant and non-dominant hands, with 2 minutes of rest between trials.

For each trial, subjects were asked to exert 5 seconds of maximal effort, while receiving standardized verbal motivation. Subjects completed each trial while sitting up straight on a chair. The hip, knee, and elbow were flexed to a 90° angle and the shoulder was abducted and neutrally rotated. The forearm was in a neutral position and the wrist was slightly extended (0° to 30°). Subjects performed the test with a horizontal cylinder using the digital grip dynamometer in position 2, while the evaluator lightly held its base. The best result (in kg) of the three trials for each hand was chosen for statistical analysis.

### Warm-up protocols

Four randomly selected warm-up protocols (Table 2) were applied for the forearm muscles of both the dominant and non-dominant hands as follow: i) no warm-up (control condition), during which subjects remained seated comfortably for three minutes before testing;

ii) static stretching warm-up, in which subjects carried out static stretching of the forearms flexors and extensors muscles for a total of 5 sets of 5 seconds each;[25] iii) strength (i.e. elastic band-based) warm-up, during which subjects completed two sets of 10 repetitions for the forearm flexor muscles for a duration of 2.5 seconds for each contraction[26] using an elastic band (THERA Band™; medium intensity, blue color) and 30 seconds to 1 minute of rest between sets; and iv) isometric therapeutic squeezing-ball warm-up, during which subjects completed 1 grip per 2.5 seconds (for a total of 20 repetitions) on a therapeutic squeeze ball.[27] The Borg Rating of Perceived Exertion was used to measure intensity during warm-ups to standardize it across all conditions, always with a score between 3 and 6 points. After the warm-ups, 3 minutes elapsed before testing MHS.

**Table 2.** Characteristics of the warm-up protocols.

| Warm up | Exercises | Sets | Repetitions | Rest between sets | Rest after warm-up |
|---|---|---|---|---|---|
| No warm-up | - | - | - | - | - |
| Static stretching | Static flexion of wrist | 5 | 5 seconds | 30 seconds | 3 minutes |
| | Static extension of wrist | 5 | 5 seconds | 30 seconds | |
| Elastic band | Dynamic flexion of wrist | 2 | 10 | 30 seconds | 3 minutes |
| Isometric therapeutic squeezing-ball | Squeeze and release | 1 | 20 | 30 seconds | 3 minutes |

Source: Own elaboration.

### Statistical analysis

All values are reported using means and their corresponding standard deviations. The Shapiro-Wilk and Levene's tests yielded non-significant values for all data. To determine the effects of the conditions on MHS, absolute mean differences between conditions were compared using a repeated measures analysis of variance, with Fisher post hoc procedures. The α level was set at $p<0.05$ for statistical significance, with Cohen's *d* representing effect size (ES) interpreted as <0.2=trivial; 0.2-0.6=small; >0.6-1.2=moderate; >1.2-2.0=large; >2.0-4.0 = very large; >4.0=extremely large). The reliability of the assessments was determined using the intra-class correlation coefficient. All measurements yield values ≥0.9.

## Results

The MHS mean values for the non-dominant and dominant hand were 23.8kg and 24.9kg after no warm-up, 20.3kg and 21.4kg after the stretching warm-up, 20.9kg and 22.9kg after the strength warm-up, and 22.0kg and 23.0kg after the squeezing-ball warm-up, respectively (Figure 1). No significant differences ($p>0.05$; ES<0.2) were observed among warm-up protocols.

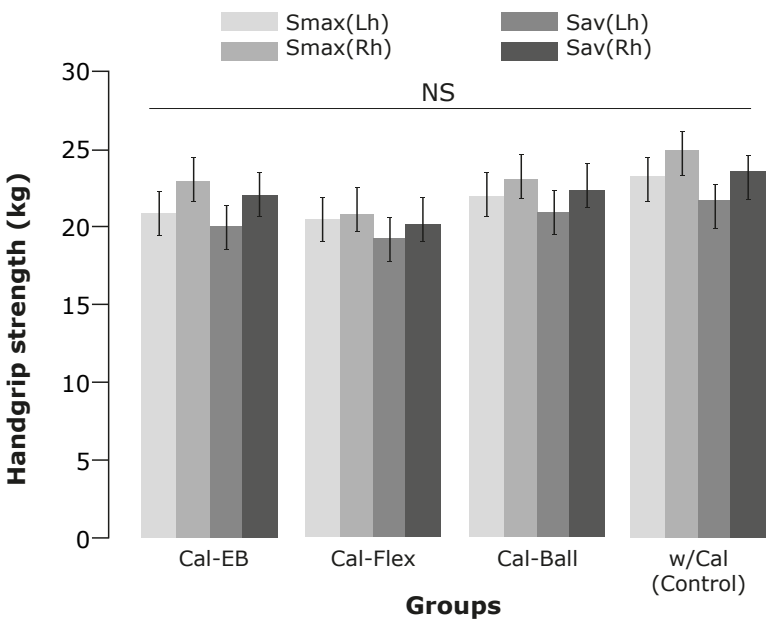


**Figure 1.** Maximal handgrip strength of dominant and non-dominant hands in obese sedentary women after no warm-up, stretching warm-up, strength warm-up, and squeezing-ball warm-up. Lh: left hand; Rh: right hand; Cal-EB: strength warm-up; Cal-Flex: stretching warm-up; Cal-Ball: squeezing-ball warm-up; w/Cal: no warm-up.
* Sav: mean maximal strength values from three measurement trials.
† Smax: Denotes maximal strength value from three measurement trials.
‡ NS: non-significant differences within-groups and between groups.
Source: Own elaboration.

Regarding the maximal strength value obtained from the 3 MHS trials (Smax in Figure 1) and the mean strength value obtained from the 3 MHS trials (Sav in Figure 1), no significant differences were observed between values ($p>0.05$; $ES<0.2$).

## Discussion

The aim of this study was to compare the effects of different warm-up protocols on MHS. The main findings suggest that the 3 randomly selected warm-up protocols had no effect on MHS in a sample of 12 sedentary overweight women. Moreover, a reduced MHS trend was observed in the participants after performing a static stretching-based warm-up.

Regarding static stretching in warm-up routines, Behm *et al.*,[28] in a study about the effects of static stretching warm-up on the strength of quadriceps muscles, reported a significant 12% maximal isometric strength decrease. Similar results have also been described for the pectoralis major and the triceps brachii muscles.[29] In this sense, the results reported in the present study are in agreement with the aforementioned findings[28,29] since static stretching of forearm flexor and extensor muscles, regardless of hand dominance, negatively affected MHS in sedentary overweight women. Several factors may help to explain the impairment in MHS after static stretching, such as alterations in the mechanical components of muscle contraction,[30] decreased muscle activation,[28] or both.[30]

In the current study, compared to the control condition, there were no improvements in MHS after the warm-up with elastic band. This finding is contrary to the results of a study conducted by Tilley & Macfarlane,[31] where an increase in swing performance was demonstrated in elite male golfers after a warm-up with a rubber band. In male judokas, a warm-up with an elastic band allowed them to improve performance in the jerk test when compared to a control condition.[32] Moreover, Mina *et al.*,[33] observed an increase in maximal squat strength in men after a warm up with an elastic band. In addition, in a study conducted by Aandahl *et al.*[34] an increase in the maximal kick speed in martial arts fighters was observed leading the authors to conclude that this increase was due to greater recruitment of higher order motor units, greater synchronization of the motor units and low presynaptic inhibition.

However, the performance-enhancing factors observed in previous studies[31-34] were found in athletes, not in a sedentary population as in the present study. Notably, the aforementioned studies[31-34] usually analyzed the effect of elastic band warm-ups on large muscle groups in multi-joint exercises, which differ from the muscle groups analyzed in our study. Therefore, these methodological elements (i.e., sedentary vs. athletes; small muscle group vs. large muscle group; single-joint vs. multi-joint) could help explain the difference between the results found in this work and those previously published.[31-34]

Current results show that the specific warm-up with a therapeutic ball (squeezing-ball warm-up) had no effect on MHS when compared to the control condition. A specific warm-up involves skill exercises that demonstrate equivalency with the targeted motor task.[35] It seeks to increase performance[36] via increases in muscle temperature, reductions in muscle viscosity and greater nerve conduction velocity.[14] In a study conducted by Andrade *et al.*,[37] the effects of a general warm-up, a specific warm-up and a combined warm-up on explosive muscle performance were compared, finding improvements in squat jump and drop jump after a specific jump-based warm-up. Similarly, in a study conducted in volleyball players, an improvement in countermovement vertical jump was observed after a specific warm-up protocol based on jump exercises.[38]

It is worth noting that the improvements in jumping performance after specific jump-based warm-ups were observed in large muscle groups. Smaller muscles, such as the forearm, are composed of a significant number of slow-twitch muscle fibers that require a low motor unit firing frequency (i.e., 5 to 30Hz), unlike other larger muscle groups.[39] Such slow-twitch fibers are easily excitable[40] and so require lower levels of stimulation to achieve maximal activation and, therefore, maximal strength. Consequently, as forearm muscle activation in hand-grip tasks is relatively easier[41] compared to larger muscle groups, a specific warm-up may not add to the performance of such muscle group during hand-grip tasks.

It should be stressed that no differences were observed in MHS after dynamic (elastic band) and isometric (static stretching; isometric therapeutic squeezing-ball) warm-up protocols. Such observation seems to be contrary to the findings of a previous study,[42] where a dynamic warm up, when compared to static-stretching warm up, improved power and agility (T-shuttle run, medicine-ball underhand throw for distance, and 5-step jump) in male and female military cadets. However, the methodological differences between the studies, such as the participant's characteristics (females vs. mix sample of male and females), physical fitness level (low vs. high), type of performance test (maximal isometric strength vs. dynamic power test), among others, should be considered.

In this regard, the American College of Sport Medicine indicated that more controlled studies are needed to substantiate the effectiveness of warm-up protocols.[43] The lack of consensus may be partially related to the different methodological issues previously reported, as the effect of warm-up may vary according to such aspects.[13] Moreover, most studies on warm-up strategies have been conducted in athletes.[13] In this sense, the present results expand the limited knowledge available about the effect of different warm-up protocols on the MHS of sedentary overweight women.

### Limitations, strengths, and practical applications

A limitation of the study was its sample size, as it may not have allowed obtaining statistically significant findings. Future studies should aim to replicate the current findings with a greater sample size. Additionally, to better understand the underlying mechanisms of different warm-up protocols, future research should include biomechanical as well as physiological measures related to the responses of forearm muscles to different warm-up protocols in sedentary overweight women.

## Conclusion

Warm-up of the forearm muscles does not acutely increase isometric MHS in sedentary overweight women

in the dominant, or the non-dominant hands. Three isometric trials, without warm-up, allows achieving MHS with high reliability, serving as a time-efficient measurement protocol with high applicability in clinical practice.

## Conflicts of interest

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# Changes in anthropometric parameters and physical fitness in older adults after participating in a 16-week physical activity program

*Cambios en los parámetros antropométricos y la condición física en adultos mayores luego de participar en un programa de actividad física de 16 semanas*

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## Abstract

**Introduction:** Physical activity is important for achieving healthy aging.
**Objective:** To analyze changes in anthropometric parameters and physical fitness among Chilean older adults after participating in a 16-week physical activity program and to evaluate whether there were differences in relation to their baseline nutritional status or not.
**Materials and methods:** Pre-experimental quantitative study. The study population consisted of 176 older adults (155 women and 21 men) distributed in three groups: normal weight (n=56), overweight (n=67) and obese (n=53). The following variables were evaluated: body mass index (BMI), waist circumference (WC), waist-to-height ratio (WHR) and physical fitness.
**Results:** Significant decreases between pre- and post-measurements were found for WC (p<0.001), BMI (p=0.015), and WHR (p<0.001). Improvements were observed in the following tests: chair stand (p<0.001), arm curl (p<0.001), 2-min step (p<0.001), chair sit-&-reach (p=0.018) and back scratch (p=0.014). Regarding BMI, significant changes were observed between normal weight vs. overweight participants (p=0.001) and between normal weight vs. obese participants (p=0.001).
**Conclusion:** Older adult participants that regularly attended the physical activity program were able to reduce their WC, BMI and WHR, and also improved their physical-functional performance on the chair stand, arm curl, 2-min step, chair sit-&-reach and back scratch tests. In addition, anthropometric parameters and physical fitness also improved regardless of their baseline nutritional status.
**Keywords:** Exercise; Anthropometry; Physical Fitness; Aging; Public Health (MeSH).

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## Resumen

**Introducción.** La actividad física es de gran importancia para lograr un envejecimiento saludable.
**Objetivos**. Estudiar los cambios en los parámetros antropométricos y la condición física de adultos mayores (AM) chilenos después de 16 semanas de participación en un programa de actividad física, y evaluar las diferencias en relación con su estado nutricional inicial.
**Materiales y métodos.** Estudio pre-experimental cuantitativo. Población: 176 AM (155 mujeres y 21 hombres) distribuidos en 3 grupos: normopesos (n=56), sobrepesos (n=67) y obesos (n=53). Se evaluaron las siguientes variables: índice de masa corporal (IMC), perímetro de cintura (PC), índice cintura-estatura (ICE) y condición física.
**Resultados.** Se observaron reducciones significativas en PC (p<0.001), IMC (p=0.015) e ICE (p<0.001), y mejoras en las siguientes pruebas: sentarse y levantarse de una silla (p<0.001), flexiones del codo (p<0.001), dos minutos de marcha (p<0.001), flexión del tronco en silla (p=0.018) y juntar las manos tras la espalda (p=0.014). Se encontraron diferencias significativas respecto al IMC entre participantes normopesos y sobrepesos (p=0.001), y entre normopesos y obesos (p=0.001).
**Conclusión.** Los AM que participaron regularmente en el programa de actividad física lograron reducir su PC, IMC e ICE y mejorar su rendimiento físico-funcional en las pruebas de sentarse y levantarse de una silla, flexiones de codo, dos minutos de marcha, y flexibilidad del tren inferior y superior. Además, sus parámetros antropométricos y su condición física mejoraron independientemente de su estado nutricional inicial.
**Palabras clave:** Ejercicio físico; Antropometría; Condición física; Envejecimiento; Salud pública (DeCS).

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## Introduction

Physical activity (PA) plays a fundamental role in achieving healthy aging.[1-4] All over the world, public and private institutions have implemented programs fostering the regular practice of PA in older adults.[1,2,5-7] However, in Chile, and despite the fact that the link between PA and health condition has been recently pointed out,[8,9] PA programs for older adults are limited.[10] The Older Adults in Motion program (*Adulto Mayor en Movimiento* in Spanish), created by the National Sports Institute, is one of the most important PA programs in the country and aims at promoting active aging.[11]

There is another older adults-oriented PA program, the More Independent Older Adults Program (*Programa Más Adultos Mayores Autovalentes* in Spanish), which has been implemented by the Chilean Ministry of Health to improve quality of life among older adults through health and self-care training and functional stimulation activities.[12] These governmental efforts are of great importance for the Chilean population, provided that, according to the most recent National Health Survey, 76.8% and 94% of the population over the age of 65 years are overweight and have sedentary lifestyles, respectively,[13] while only 15.8% are physically active.[14]

These government initiatives have scarce follow-up, measurement and socialization of results among the community.[15] Without a doubt, this relates to the difficulty of developing a research protocol that follows rigorous technical and methodological principles that could add value to the scientific community[1] and could show the effects of initiatives in real practice contexts.[16,17]

Evaluating older adults participating in government-designed PA programs is necessary considering the high levels of sedentarism and obesity in this population, as well as the lack of information on the impact that these programs have on their health status.[15] With this in mind, the present study was designed to examine possible changes in anthropometric parameters and physical fitness among Chilean older adults after participating in a 16-week PA program. Moreover, we evaluated whether differences varied by baseline nutritional status. Based on the literature,[1,7] it was hypothesized that participating regularly in a PA program may be associated with the decrease in waist circumference (WC), body mass index (BMI) and waist-to-height ratio (WHR), and in the improvement of physical fitness in older adults, regardless of their baseline nutritional status.

## Material and methods

A pre-experimental (one-group pretest–posttest design) study with a quantitative approach was conducted.

### Participants

Participants were selected using convenience sampling. The initial sample consisted of 312 people of both sexes aged between 60 and 85 years (mean=71.03 years) that attended the National Sports Institute's Older Adults in Motion Program in the Araucanía region, Chile. The inclusion criteria were: a) being a program participant for >6 months; b) being >60 years of age; c) ability to understand and follow instructions in context through simple commands; d) being independent according the Ministry of Health;[18] and e) attending at least 80% of the program sessions during the second measurement. Exclusion criteria were a) having a disabling disease; b) having musculoskeletal injuries that hindered normal physical performance; or c) having permanent or temporary contraindications for PA. A total of 176 older adults (mean height=1.52m) met the inclusion criteria. Participants were classified as normal weight, overweight or obese before the intervention based on their body mass index (BMI).

All participants were informed of the aim of the investigation and signed an informed consent authorizing the use of their data for scientific purposes. The research protocol was reviewed and approved by the Scientific Ethics Committee of the Universidad Autónoma de Chile (Minutes No. 06-2016 - 14/04/2016) and the principles of the Declaration of Helsinki were followed for its development.[19]

### Anthropometric parameters

Anthropometric assessments were made by measuring standing height using a stadiometer (Seca model 220, USA, 0.1cm accuracy). Bodyweight was measured with a digital scale (Scale-tronix, USA; 0.1kg accuracy), while WC was obtained using a measuring tape (Sanny, Brazil, 0.1cm accuracy). BMI was calculated by dividing body weight by squared standing height (kg/m$^2$), and participants were classified according to their nutritional status as normal weight (<27.9 kg/m$^2$); overweight (28-31.9 kg/m$^2$) and obese (>32 kg/m$^2$), according to the recommendations of the Pan American Health Organization[20] and the Ministry of Health[18] for classification of older adults. The waist-to-hip ratio (WHR) was measured by dividing WC by standing height.[21]

All measurements were performed according to the International Society for the Advancement of Kinanthropometry (ISAK)[22] by a level II (technical error of measurement: 0.8%) and a level III (technical error of measurement: 0.7%) ISAK anthropometrists. Test-retest reliability was assessed using the interclass correlation coefficient (ICC), with values between 0.93 and 0.98 for all measurements.

### Physical fitness measurements

Physical fitness measurements followed the Senior Fitness Test (SFT) protocol, previously described and validated for independent-living adults without health problems between 60 and 94 years of age.[23] The following tests were included: a) chair stand test to assess the strength of the lower body, counting the number of repetitions made in 30s; b) arm curl test to assess the strength on the upper body, using a 3lb (women) and 5lb (men) dumbbell, counting the number of repetitions made in 30s; c) 2-minute step to assess aerobic fitness, recording the number of knee elevations; d) chair sit-&-reach test to assess the flexibility of the lower-body, measured in cm; e) back scratch test to assess flexibility on the upper-body, measured in cm; and f) timed up-and-go test to assess agility and dynamic balance, surrounding a cone at 8ft (2.44m) and recording time in seconds.

An experienced researcher conducted each test after a 15min warm-up, which included joint mobility drills and aerobic exercises. ICC was between 0.72 and 0.94 for all physical fitness test measurements.

### Physical activity workshops description

The Older Adults in Motion Program was implemented in the Araucanía region in March 2015.[11] The program

was free for participants, was offered two or three times per week (180min weekly) in different social venues, and targeted independent-living persons aged 60 years or older.[10,11]

The program had a training load progression in terms of intensity and number of repetitions for muscle strength and muscle endurance exercises. The duration of the sessions was between 60min (three times per week) and 90min (two times per week). A typical session included a 10-to-15min warm-up, consisting of joint mobility exercises and low intensity aerobic exercises. It was followed by 10 to 15min of muscle strength and muscle endurance exercises for biceps, triceps, deltoids, latissimus dorsi, quadriceps, hamstrings, buttocks and gastrocnemius muscles, in combination with 10 to 15min of aerobic exercise, agility and dynamic balance, using elastic bands, canes, 2kg medicine-balls and chairs. Then, participants performed 20 to 30min of healthy dance using music with a beat rate no higher than 120 beats per minute. Finally, the sessions ended with a 10 to 15min cool down with dynamic and static flexibility exercises. Each workshop was led by a physical education teacher, responsible for carrying out and designing the activities of the PA sessions.

### Statistical Analysis

The Statistical Package for Social Science (SPSS) version 23.0 was used for all analyses. The means and standard deviations were calculated for anthropometric and physical fitness measurements. Furthermore, the distribution of normality and homogeneity of variance were calculated using the Kolmogorov-Smirnov and Levene's tests, respectively. To compare anthropometric parameters and physical fitness before (pre) and after (post) the 16-week PA program, the paired student's t-test was used when the variables had a normal distribution, and the Wilcoxon test when they did not have a normal distribution. To compare pre- and post-change according to nutritional status (normal weight, overweight and obese), the Kruskal-Wallis test with Dunn's post hoc (not parametric) was applied. Effect size (ES) was calculated with Cohen's *d*,[24] considering a small (0.20-0.49), moderate (0.50-0.79), or large (>0.80) effect. In all cases, a value of $p<0.05$ was considered statistically significant.

Standard errors of measurement (SEM) and minimal detectable change (MDC) were calculated for all anthropometric parameters and physical fitness tests. The SEM were calculated using the following equation: $SEM=SD \times (\sqrt{1} - ICC)$. In this equation, SD is the standard deviation of the measure, and ICC is the interclass correlation coefficient (test-retest reliability). MDC were calculated for the body weight, WC, BMI, WHR, chair stand test, arm curl test, 2-minute step test, chair sit-&-reach test, back scratch test and up-and-go test using the 95% confidence interval. The formula used for calculating MDC was $MDC=1.96 \times \sqrt{2} \times SEM$. In this equation, SEM was calculated as described previously. The 1.96 in the MDC equation represents the z-score at the 95% confidence level.

## Results

Table 1 shows the pre- and post-program anthropometric parameters. Significant decreases with a small effect size were observed in men, women and overall sample for WC ($p=0.022$ in men; $p<0.001$ in women and overall sample; $ES<0.30$ in men, women and overall sample), BMI ($p<0.05$ in men, women and overall sample; $ES=0.20$ in men) and WHR ($p=0.004$ in men, $p<0.001$ in women and overall sample; $ES=0.35$ in men, $ES=0.28$ in overall sample). No significant changes in body weight were observed. On the other hand, WC showed a higher change than the MDC in men, compared to women and overall sample (men and women together), while, for BMI, the change was greater than the MDC in men only.

**Table 1.** Anthropometric parameters in older adults after 16 weeks of participation in a physical activity program.

| Anthropometric parameters | | Pre-test | Post-test | p-value | Change % | SEM | MCD | Effect Size |
|---|---|---|---|---|---|---|---|---|
| | | Mean (σ) | Mean (σ) | | | | | |
| Body weight (kg) | Overall (n=176) | 70.19 (12.56) | 70.02 (12.35) | 0.473 * | -0.24 | 0.25 | 1.39 | 0.01 |
| | Women (n=155) | 68.93 (12.39) | 68.76 (12.27) | 0.538 * | -0.29 | 0.25 | 1.38 | 0.01 |
| | Men (n=21) | 79.51 (9.73) | 79.26 (8.58) | 0.625 * | -0.31 | 0.19 | 1.22 | 0.64 ** |
| Waist circumference (cm) | Overall (n=176) | 93.75 (11.10) | 90.96 (11.47) | <0.001 * | -2.98 | 0.78 | 2.44 | 0.25 ‡ |
| | Women (n=155) | 92.83 (11.00) | 89.97 (11.40) | <0.001 * | -3.08 | 0.88 | 2.60 | 0.26 ‡ |
| | Men (n=21) | 100.59 (9.52) | 98.24 (9.31) | 0.022 * | -2.34 | 0.57 | 2.09 | 0.25 ‡ |
| Body mass index (kg/m2) | Overall (n=176) | 30.18 (4.62) | 29.91 (4.47) | 0.015 * | -0.89 | 0.23 | 1.33 | 0.08 |
| | Women (n=155) | 30.22 (4.76) | 29.98 (4.65) | 0.022 * | -0.79 | 0.14 | 1.05 | 0.07 |
| | Men (n=21) | 29.87 (3.42) | 28.44 (2.70) | 0.039 * | -4.78 | 0.21 | 1.26 | 0.20 ‡ |
| Waist-to-height ratio | Overall (n=176) | 0.62 (0.07) | 0.59 (0.07) | <0.001 † | -4.84 | 0.00 | 0.19 | 0.28 ‡ |
| | Women (n=155) | 0.62 (0.06) | 0.59 (0.07) | <0.001 † | -4.84 | 0.00 | 0.19 | <0.001 |
| | Men (n=21) | 0.61 (0.06) | 0.59 (0.06) | 0.004 † | -3.28 | 0.00 | 0.17 | 0.35 ‡ |

σ: standard deviation; SEM: standard error of measurement; MCD: minimal detectable change.
* Student's t-test for related samples.
† Wilcoxon test.
‡ small.
** moderate.
Source: Own elaboration.

Table 2 shows the pre- and post-program SFT parameters. Significant improvements between the pre-and-post measurements were observed in men, women and overall sample for the chair stand ($p<0.001$ in women and overall sample; ES=0.35 in men, ES>0.80 in women and overall sample), arm curl ($p=0.001$ in men, $p<0.001$ in women and overall sample; ES=1.16 in men, ES<0.80 in women and overall sample), 2-minute step ($p=0.003$ in men, $p<0.001$ in women and overall sample; ES=0.71 in men, ES>0.80 in women and overall sample), chair sit-&-reach ($p<0.05$ in women and overall sample), and back scratch ($p<0.05$ in women and overall sample) tests. No significant changes in the timed up-and-go test were observed. In addition, the arm curl and the 2-minute step tests showed a higher change than the MDC in men, women and the overall sample. The chair stand test showed a higher change than the MDC in women and overall sample, while the chair sit-&-reach test showed a decrease in men with higher change than the MDC.

**Table 2.** Physical fitness of older adults after 16 weeks of participation in a physical activity program.

| Physical fitness test | | Pre-test | Post-test | p-value | Change % | SEM | MCD | Effect Size |
|---|---|---|---|---|---|---|---|---|
| | | Mean (σ) | Mean (σ) | | | | | |
| Chair stand test (repetitions) | Overall (n=176) | 15.54 (3.44) | 18.74 (4.13) | <0.001 † | 20.59 | 0.69 | 2.30 | 0.84 †† |
| | Women (n=155) | 15.33 (3.38) | 18.79 (4.18) | <0.001 † | 22.57 | 0.48 | 1.93 | 0.91 †† |
| | Men (n=21) | 17.09 (3.57) | 18.38 (3.89) | 0.081 * | 7.55 | 1.01 | 2.78 | 0.35 ‡ |
| Arm curl test (repetitions) | Overall (n=176) | 21.84 (4.42) | 25.65 (5.76) | <0.001 † | 17.44 | 0.84 | 2.54 | 0.74 ** |
| | Women (n=155) | 21.81 (4.64) | 25.52 (5.86) | <0.001 † | 17.01 | 0.65 | 2.24 | 0.70 ** |
| | Men (n=21) | 22.04 (2.29) | 26.57 (5.02) | 0.001 * | 20.55 | 0.54 | 2.04 | 1.16 †† |
| 2-minute step test (repetitions) | Overall (n=176) | 94.05 (23.36) | 115.18 (22.95) | <0.001 † | 22.47 | 4.91 | 6.14 | 0.91 †† |
| | Women (n=155) | 92.34 (23.77) | 114.36 (22.66) | <0.001 † | 23.85 | 4.40 | 5.81 | 0.95 †† |
| | Men (n=21) | 106.66 (15.23) | 121.19 (24.72) | 0.003 † | 13.62 | 3.78 | 5.39 | 0.71 ** |
| Chair sit-&-reach test (cm) | Overall (n=176) | 3.17 (7.81) | 4.07 (7.81) | 0.018 † | 28.39 | 0.94 | 2.68 | 0.11 |
| | Women (n=155) | 3.15 (7.58) | 4.61 (7.89) | <0.001 † | 46.35 | 0.48 | 1.92 | 0.19 |
| | Men (n=21) | 3.38 (9.55) | 0.05 (5.94) | 0.083 † | -52.07 | 1.74 | 3.65 | 0.42 ‡ |
| Back scratch test (cm) | Overall (n=176) | -8.28 (9.04) | -6.95 (9.60) | 0.014 † | 16.06 | 0.90 | 2.64 | 0.14 |
| | Women (n=155) | -7.63 (8.75) | -6.27 (9.16) | 0.017 † | 17.82 | 0.56 | 2.07 | 0.15 |
| | Men (n=21) | -13.00 (9.92) | -11.98 (11.43) | 0.512 * | 8.55 | 1.53 | 3.43 | 0.10 |
| Up-and-go test (s) | Overall (n=176) | 5.32 (1.07) | 5.25 (0.85) | 0.261 † | -1.13 | 0.16 | 1.11 | 0.06 |
| | Women (n=155) | 5.38 (1.10) | 5.30 (0.86) | 0.122 † | -1.48 | 0.15 | 1.07 | 0.08 |
| | Men (n=21) | 4.81 (0.70) | 4.91 (0.70) | 0.401 * | 2.08 | 0.12 | 0.96 | 0.14 |

σ: standard deviation; SEM: standard error of measurement; MCD: minimal detectable change.
* Student´s t-test for related samples.
† Wilcoxon test.
‡ small.
** moderate.
†† large.
Source: Own elaboration.

Figure 1 shows a significant decrease among normal weight participants in WC ($p=0.039$) and WHR ($p=0.022$), and a significant decrease in WC ($p<0.001$), BMI ($p<0.001$) and WHR ($p<0.001$) in the overweight and obese participants. Multiple comparisons of pre-post program changes between groups according to their baseline nutritional status showed a significant difference ($p<0.001$) for BMI only. The post-hoc test showed differences between normal weight versus overweight ($p=0.001$) and between normal weight versus obese ($p=0.001$) groups.

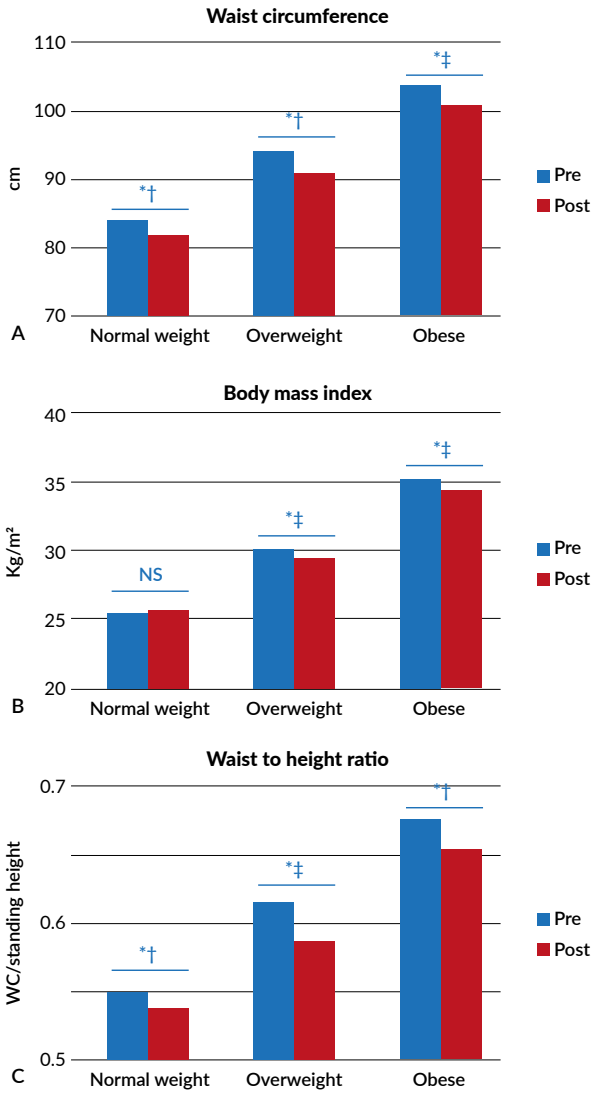


**Figure 1.** Changes in anthropometric parameters of older adults after 16 weeks of participation in a physical activity program by baseline nutritional status. A: Waist circumference; B: Body mass index; C: Waist-to-height ratio.
WC: waist circumference; NS: not significant.
* Significant differences between pre-and-post measurements ($p<0.05$).
† Paired Student's t-test.
‡ Wilcoxon test.
Source: Own elaboration.

Figure 2 shows a significant improvement among the normal weight and obese groups for the chair stand ($p<0.001$), arm curl ($p<0.001$) and 2-minute step ($p<0.001$) tests. In the case of the overweight group, significant improvements were seen for the chair stand ($p<0.001$), arm curl ($p<0.001$), 2-minute step and chair sit-&-reach ($p=0.036$) tests. When comparing the pre-post program changes between the normal weight, overweight and obese groups, no significant differences were observed for the SFT measurements.

## Discussion

In this study, changes in anthropometric parameters and physical fitness in a group of Chilean older adult participants was assessed after 16 weeks of participation in a PA program. Differences based on participants' baseline nutritional status were also determined. Results obtained here show that, regardless of baseline nutritional status and sex, there was an improvement in the anthropometric parameters and physical fitness of all participants. However, greater improvement was observed in women and in the overweight and obese groups. The findings reported here are in agreement with those described in a study conducted in a Chilean primary healthcare center with a sample of healthy older women who participated in a 12-week training intervention involving combined exercises, in which improvements in WC, muscle strength, flexibility, and balance were reported.[25]

BMI decreased significantly among women, men, the overall sample and in the overweight and obese groups after completing the program, although most of older adults maintained their basal nutritional status classification. A similar work among Argentinian older adults has shown decreases in the prevalence of overweight/obesity after a 12-month intervention from 49.3% to 31%.[26] Similarly, the WC and the WHR decreased significantly post-program in all groups (women, men, overall sample, normal weight, overweight and obese). Similar findings were shown in a study of Colombian older adults.[27]

WHR has been used to a lesser extent among older adults even though relevant scientific evidence has positioned it as a better risk marker compared to other measurement indexes such as WC and BMI.[28] As stated in other works,[10] using only nutritional status and cardiometabolic risk classification, without considering the continuous values of BMI, WC, and WHR, could underestimate the specific modifications among participants. Therefore, all of them should be used jointly to minimize possible errors.

The SFT performance improved in all groups with no differences by nutritional status. In particular, the chair stand (except for men) and arm curl tests showed significant changes in all older adult groups, similar to what was reported among Chilean older adults in the central[25] and northern[29] regions. Our findings are important given that strength in older adults relates to higher independence for performing daily activities,[10,30] and its increase may improve the quality of life of older women.[31-34]

The 2-minute step test improved significantly in all groups from 94 to 115 repetitions, and differences were greater than those shown in a study conducted with Colombian older adults that improved steps from 70 to 83 repetitions.[27] The relevance of this finding is that a recent review by Witard *et al.*[2] emphasized aerobic resistance as a key component, not only of cardiovascular health but also of muscle strengthening and sarcopenia protection in older adults. Similarly, in Chilean older women,[35] cardiorespiratory fitness was shown to be related to improved cardiovascular health.

Regarding chair sit-&-reach and back scratch tests, only significant improvements in the pre-and-post measurements were found in women, the overall sample, and among the overweight group in the chair sit-&-reach test; on the other hand, improvements were observed in women and the overall sample for the back scratch test. Other publications have reported significant improvements on the chair sit-&-reach test[25] and back scratch test[25,27] among older

adults after 12 weeks of intervention. It is probable that the low scoring in the chair sit-&-reach and back scratch tests demonstrated by older adults relates to the increase in rigidity of the cartilage and tissues, a phenomenon typical of the aging process, which decreases the articular movement range, and therefore, reduces flexibility.[10,27]

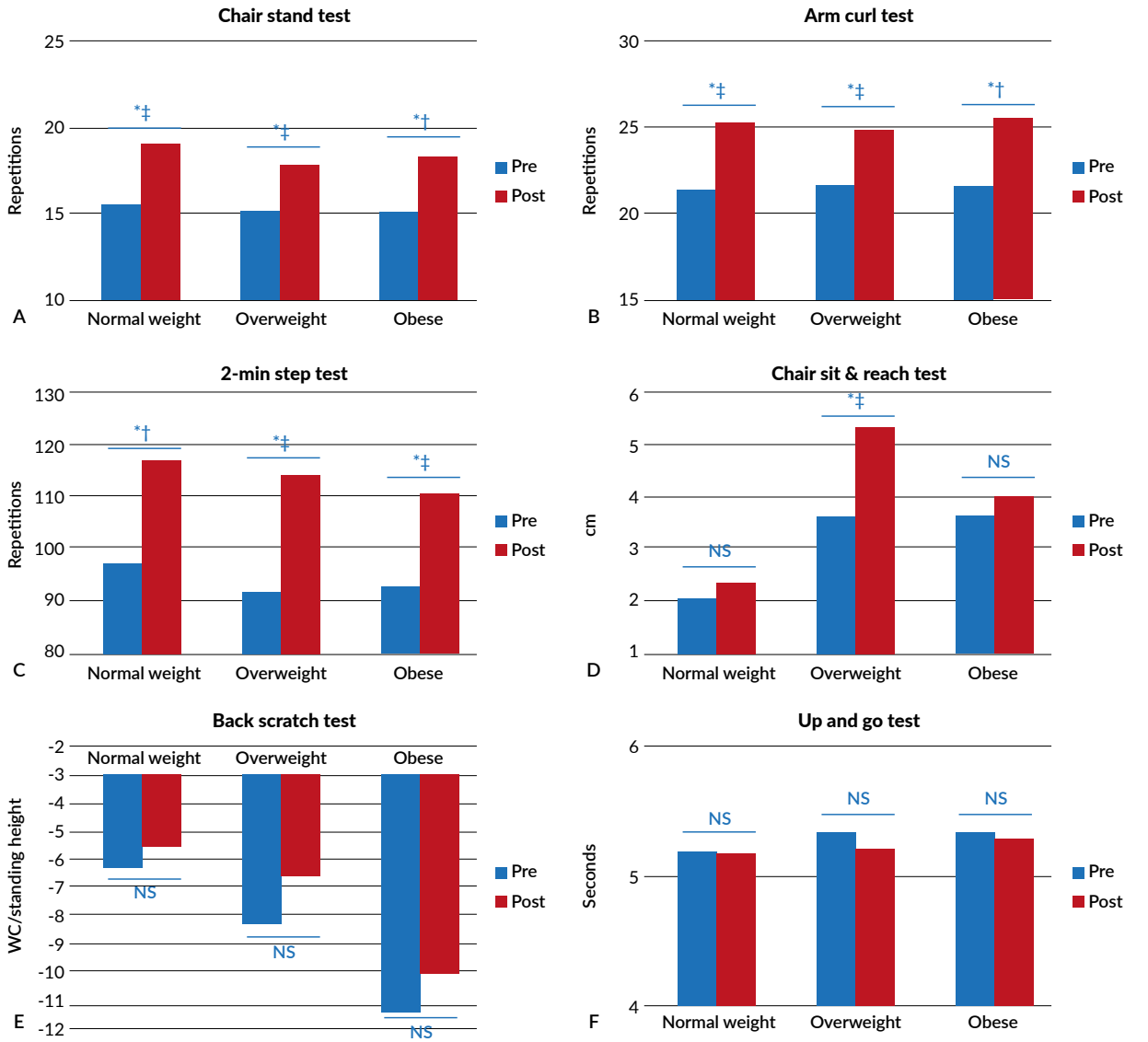


**Figure 2.** Changes in physical fitness in older adults after 16 weeks participation in a physical activity program by baseline nutritional status. A: Chair stand test; B: Arm curl test; C: 2min step test; D: Chair sit-&-reach test; E: Back scratch test; F: Up-and-go test.
NS: not significant.
* Significant differences between pre-and-post measurements ($p<0.05$).
† Paired Student's t-test.
‡ Wilcoxon test.
Source: Own elaboration.

The up-and-go test showed no significant improvement in any group after the program. Contradictory results are reported among older adults following a 12-week program of combined exercises.[25] However, the reaction time of all groups evaluated (except for men) improved after the program, which was equal to or higher than the one expected for their age and sex. This could be auspicious since this capacity is related to a lower risk of falling in older adults.[5,6]

Although this study shows how beneficial PA programs are for improving anthropometric parameters and physical fitness in all groups of older adults, the poor adherence to the program (56.4%) and the lack of technical orientations that guide teachers to develop their program[11] are concerning. Despite this, the activities planned for the program seem to stimulate physical-functional capacities successfully and improve anthropometric measures of older adults regardless of their nutritional status. In this sense, the public institutions in charge of PA programs oriented towards older adults should reinforce strategies to retain the beneficiaries of these initiatives and develop technical/methodological manuals for the

professionals that carry out the sessions, since PA is a key element for the promotion of healthy aging.

It should be noted that, according to these results, an overweight/obese status would not limit the improvement of the physical fitness of older adults since they responded equally to similar PA stimuli compared to normal weight participants. Physical inactivity has been described as a greater risk for mortality than excess weight.[36] On the other hand, physical fitness is a protective factor for several diseases.[37] Therefore, older adults that are physically active, regardless of their nutritional status, could decrease their mortality risk even more if they improve their physical fitness.[36,37]

Some of the main strengths of this study are the relatively large sample size of older adults that participated in the PA program; the fact that older adults participants were evaluated in a community-based setting; and, the simplicity of the measurements, which means that the methodology could be replicated and implemented in other PA initiatives for older adults. Likewise, the costs required for conducting this type of intervention are very low, and it could be used in large population groups, such as those found in community centers, preventive health units, back-to-school events, among others.

The limitations to this study include the non-probabilistic selection of the sample, which restrains the external validity of the results, and the reduction of the sample size, which went from 312 at the beginning of the study, to 176 in the end. Despite of these limitations, this study provides input that supports government actions that encourage healthy aging.

## Conclusion

Older adults that took part regularly in a PA program decreased their WC, BMI and WHR, and improved their physical-functional performance on the chair stand, arm curl, 2-minute step, chair sit-&-reach, and back scratch tests. Anthropometric parameters and physical fitness improved regardless of their baseline nutritional status. We recommend that governmental and non-governmental institutions encourage the practice of PA in older adults, as well as in middle-aged adults, to provide longevity with health and quality of life for this portion of the population.

## Conflicts of interest

None stated by the authors.

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# Association between high blood pressure and fitness and fatness in adolescents

*Presión arterial alta asociada con condición física y adiposidad en adolescentes*

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## Abstract

**Introduction:** Excess adiposity is considered the most important risk factor for high blood pressure (HBP) in children and adolescents.
**Objectives:** To explore the association between HBP and overweight (OW) and abdominal obesity (AO), mediated by cardiorespiratory fitness (CRF). To analyze the combined effect of excess adiposity and CRF on HBP among a sample of school-aged children from Montería, Colombia.
**Materials and methods:** Cross-sectional study conducted in a sample of 546 adolescents aged between 11 and 18 years from 14 randomly selected schools in Montería. Blood pressure, anthropometric, and fitness measures were evaluated by trained personnel using standardized protocols and instrumentation. The association of HBP with fitness and fatness was analyzed using logistic regression models.
**Results:** HBP was associated with OW, AO and low CRF. The inclusion of CRF in this model did not attenuate the association between HBP and OW and between HPB and AO. Adolescents with higher adiposity and low CRF were more likely to have HBP compared with those with lower adiposity and high CRF. Moreover, it was found that excess adiposity and low CRF had an additive effect on the risk for HBP among the sample.
**Conclusion:** HBP is a prevalent condition in children and adolescents from Montería, Colombia. HBP is significantly associated with OW, AO, and low CRF; therefore, it is necessary to implement initiatives to promote healthy habits aimed at this population in order to reduce the incidence rate of HBP in Colombian adolescents.
**Keywords:** Cardiovascular Diseases; Adiposity; Obesity (MeSH).

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## Resumen

**Introducción.** El exceso de adiposidad es considerado como el factor de riesgo más importante para la presión arterial alta (PAA) en niños y adolescentes.
**Objetivos**. Explorar la asociación entre PAA y sobrepeso (SP) y obesidad abdominal (OA), mediada por condición física cardiorrespiratoria (CFC), y analizar el efecto combinado de la adiposidad excesiva y la CFC en la PAA en una muestra de escolares de Montería, Colombia.
**Materiales y métodos.** Estudio transversal realizado en 546 adolescentes con edades entre 11 y 18 años de 14 escuelas seleccionadas aleatoriamente en Montería. Se evaluó la presión arterial, los indicadores antropométricos y la condición física; las mediciones fueron realizadas por personal capacitado mediante el uso de protocolos e instrumentos estandarizados. La asociación de PAA con condición física y adiposidad fue analizada a través de modelos de regresión logística.
**Resultados.** Se encontró una asociación entre PAA y SP, OA y baja CFC. La inclusion de la CFC en el modelo no atenuó la asociación entre PAA y SP y entre PAA y OA. Los adolescentes con mayor adiposidad y baja CFC fueron más propensos a presentar PAA que aquellos con menor adiposidad y alta CFC. Además, se observó que la presencia de adiposidad excesiva y baja CFC aumenta el riesgo de desarrollar PAA.
**Conclusión.** La PAA es una condición prevalente en niños y adolescentes de Montería, además se encontró una asociación estádisticamente significativa entre PAA y SP, OA, y baja CFC, por lo que es necesario que en el país se implementen estrategias que promuevan hábitos saludables en escolares y permitan reducir la tasa de incidencia de PAA en esta población.
**Palabras clave:** Enfermedades cardiovasculares; Adiposidad; Obesidad (DeCS).

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## Introduction

High blood pressure (HBP) is a critical risk factor for cardiovascular disease,[1] and it is one of the main leading causes of premature mortality in Latin America.[2] In the Americas region, the most recent estimations indicate that HBP affects 26.3% of males and 19.7% of females.[3] Specifically in Latin America, the prevalence of HBP ranges from 9 to 29%,[4] and in Colombia, 34.3% of males and 26.5% of females suffer from this condition.[3] Multiple epidemiological studies have been carried out to follow up the development of this disease from childhood into adulthood.[5]

In the last decade, the presence of HBP in children and adolescents has increased.[6] Previously considered a risk factor for adult populations, it is now reaching important proportions among teenagers. For instance, Ostchega *et al.*[7] documented an increase in HBP prevalence between 1994 (11.6%) and 2002 (13.9%) among adolescents aged 13 to 17 years. Similarly, a study conducted in León, Mexico, found a prevalence of 20.7% among adolescents aged 12 to 15 years.[8] HBP results from an interaction of genetic factors and several environmental factors[9] that appear early during childhood, including excessive sedentary behaviors (i.e., playing video games and watching television for long periods),[10] and accessibility to fast food and sugary drinks,[11] thus increasing cardiovascular risk factors.

Accelerated urbanization processes in Latin America have been associated with the high burden of non-communicable diseases.[12] In fact, the prevalence of overweight among adolescents in Colombia increased from 12.5% in 2005 to 15.5% in 2010 and 17.9% in 2015.[13] In adition, since 1998, cardiovascular disease is the main cause of death in the department of Córdoba, located in the Caribbean region of the country.[14]

Poor fitness and excess adiposity during childhood and adolescence are closely correlated to HBP in adulthood.[15,16] Actually, excess adiposity is considered a major risk factor for HBP in children and adolecents.[17] However, the independent effects of poor physical fitness and excess adiposity are masked because they often occur in combination; hence, it is unclear what condition exerts greater influence on cardiovascular risk factors.[18] In this regard, it has been documented that cardiorespiratory fitness (CRF) may attenuate the effect of excess adiposity on blood pressure.[15] This study explores the association between HBP and overweight (OW) and abdominal obesity (AO), analyzes whether these associations are mediated by CRF, and assesses the combined effect of excess adiposity and CRF on HBP among a sample of adolescents from Montería, in the department of Córdoba, Colombia.

## Materials and methods

This is a school-based, cross-sectional study carried out in the city of Montería, Colombia, in 2008. Montería's population is close to 382 000 inhabitants, and some estimations show that nearly half of the population has a low socioeconomic status, 11.5% has not received a formal education, and 39.5% is below the poverty line.[19] This scenario negatively impacts children's and adolescents' health status and leads to an increased risk of developing chronic diseases.

### Sampling design

The study included 546 adolescents aged 11 to 18 years from Montería, Colombia. The study design, and other design characteristics, were reported in a previous paper.[22] Based on the school records of the municipality, 14 schools were randomly selected, and considering the proportion of the size of each school for the sample frame (13 413 students registered), 578 students were randomly selected. Only the students who gave their informed assent and whose parents signed the informed consent form required to take part in the study were finally included for analysis (n=546). The study protocol was reviewed to ensure it complied with the ethical principles for medical research involving human subjects outlined by the Declaration of Helsinki,[20] and the administrative, technical and scientific standards regarding health research established by Resolution 8430 of 1993 issued by the Colombian Ministry of Health.[21] Moreover, the Central Research Committee of the Universidad de Córdoba granted its approval for the development of this research by means of the unnumbered minutes issued on August 23, 2007.

### Measurements

Eight physical education teachers were trained to obtain blood pressure and anthropometric measurements (height, weight, and waist circumference), conduct the fitness test (20m shuttle run test), and administer questionnaires to the participants. To ensure reliability, each measurement was made by the same teacher.

### Outcome variable

Systolic and diastolic blood pressure was measured by auscultation with a standard aneroid sphygmomanometer (Welch Allyn®) and using an upper arm cuff suitable for use in children. The blood pressure measurement protocol was followed according to the National High Blood Pressure Education Program recommendations.[23] HBP was defined as mean systolic blood pressure and diastolic blood pressure at or above the 90$^{th}$ percentile for sex, age, and height.[23]

### Anthropometric measures

Height (SECA® stadiometer) and weight (Health-O-Meter® scale) were assessed as per standardized protocols. Body mass index (BMI) percentiles were computed using the Centers for Disease Control and Prevention (CDC) growth charts.[24] Based on the sex and age reference, overweight was identified in those students with a BMI percentile equal or greater than the 85$^{th}$ percentile.[24]

Waist circumference was measured following the standardized protocol with a measuring tape. The reading was taken at the end of a normal breath. The waist-to-height ratio (WHtR) was calculated as height (cm) divided by waist circumference (cm). Abdominal obesity (AO) was defined as a WHtR value above 0.5.[25]

### Fitness test

Cardiorespiratory fitness (CRF) was measured using the multi-stage fitness test,[26] which is useful to estimate aerobic capacity ($VO_2$ max). Participants were asked to run a distance of 20m, with a progressive increase in the level of intensity marked by a sound that indicated rate increments. Participants had to run from one line to another according to the sound. The test finished when the student did not reach the 3m zone placed ahead of each 20m line at the moment of the audio signal for two consecutive times. The validity and reliability of this test have been already reported.[27] FITNESSGRAM® standards by sex and age were used to classify participants into two levels: high CRF for those who met the CRF standards for healthy fitness zone, and low CRF for those who did not.[28]

### Physical activity, sedentary behaviors, and dietary intake measures

The physical activity (PA) and dietary behavior questionnaires of the Global School-based Student Health Survey (GSHS-2006) were administered to the sample of students. The GSHS was developed by the World Health Organization and has been used in Latin American countries such as Colombia, Venezuela, Peru, Ecuador, Chile, and Argentina.[29] This tool includes questions about PA, eating, and sedentary behaviors such as use of television, computers and videogames.

PA was measured with the question: During the past 7 days, on how many days were you physically active for at least 60 minutes per day? Response choices included: 0 days, 1 day, 2, 3, 4, 5, 6, and 7 days. These responses were dichotomized as physically active for those who engaged in PA during 7 days, and inactive for the rest of answers.

In addition, students reported how much time they spent watching TV during a typical school day. Seven choices were provided (I do not watch TV during school days, less than 1 h/day, 1 h/day, 2 h/day, 3 h/day, 4 h/day, 5 or more h/day). Responses were dichotomized as high TV viewing time (≥2 h/day) and low TV viewing time (<2h/day).[30]

The frequency of fruit and vegetable consumption was measured with two separate questions: During the past 30 days, how many times per day did you eat fruits/vegetables? For both questions, response options included: I did not eat fruits/vegetables during the past 30 days, less than one time per day, 1 time per day, 2, 3, 4, and 5 or more times per day. The answers to both questions were added and participants were categorized into high frequency of fruit and vegetable consumption, if the adolescent reported a frequency of combined fruit and vegetable consumption of 5 or more servings per day.[31]

#### *Sociodemographic covariates*

Information about age and sex were collected. School type, private or public, was utilized as a proxy for socioeconomic status.

### Data analysis

The descriptive characteristics of the sample were analized through t-test and chi-square tests. Participants were grouped into 4 fitness categories for each adiposity measure (OW and AO) and CRF levels. The 1st category was the reference group, comprised of the participants with normal adiposity and high CRF; the 2nd category included adolescents with normal adiposity and low CRF; the 3rd category was made up of participants with high adiposity and high CRF; and the 4th category had high adiposity and low CRF.

The association between HBP and predictors was analyzed using logistic regression models. Strength of association was calculated with odds ratios (OR) and the corresponding confidence intervals (95%). All models were studied separately for OW and AO. The confounding variables included in the models were area of residence (urban and rural), type of school (public or private), sex, CRF, PA level, TV viewing time, and consumption of fruits and vegetables. The combined effect of excessive adiposity and CRF on HBP was analyzed using logistic regression models for OW and AO for the three defined categories, separately, to compare them with the reference group. Analyses were conducted with the STATA statistical software, V.10.0.

## Results

Subject characteristics were stratified by sex and are presented in Table 1. Compared with girls, boys had significantly higher values in height ($t=5.4$; $p<0.001$), weight ($t=2.2$; $p<0.01$), systolic ($t=6.7$; $p<0.001$), and diastolic blood pressure ($t=3.2$; $p<0.001$), BMI ($t=-0.65$; $p<0.01$), CRF ($t=-3.8$; $p<0.001$), and number of days per week of PA ($t=0.65$; $p<0.001$). HBP was identified in 20.3% of students, being more prevalent in girls (25% vs. 15.8%, $\chi^2=7.1$; $p<0.01$). Low CRF was found in 41% of the students, being significantly more frequent in boys (61.1% vs 20.1%, $\chi^2=94.8$; $p<0.01$). OW was found in 15.2% of the adolescents, AO in 13.7%, and there were no significant differences in the prevalence of OW and AO between girls and boys. The results indicate that 92.5% of the participants are physically inactive, while 80.4% reported high TV viewing times and 47% reported low frequency of consumption of fruits and vegetables.

Table 2 shows the prevalence of HBP according to some specific characteristics and its bivariate associations. Boys (OR: 0.6; 95%CI: 0.4-0.9) and adolescents who live in rural areas (OR: 0.6; 95%CI: 0.4-1.0) were less likely to have HBP. Adolescents with OW (OR: 2.3; 95%CI: 1.4-3.9), AO (OR: 2.8; 95%CI: 1.6-4.7), and low CRF (OR: 1.5; 95%CI: 1.0-2.3) were significantly more likely to have HBP. There were no significant bivariate associations between HBP and school type, physical inactivity, TV viewing time, and fruits and vegetables consumption.

**Table 1.** Sample characteristics.

| Variables | Overall (n=546) | Girls (n=268) | Boys (n=278) | p-value |
|---|---|---|---|---|
| | x̄ (σ) | | | |
| Age (years) | 14.9 (1.9) | 14.9 (1.9) | 14.9 (1.9) | 0.75 |
| Height (cm) | 157 (10.2) | 154 (7.2) | 159 (11.9) | 0.001 |
| Weight (kg) | 49.3 (10.5) | 48.2 (8.5) | 50.5 (12.1) | 0.01 |
| Systolic Blood Pressure (mmHg) | 109 (11.5) | 106 (10.3) | 112 (11.7) | 0.001 |
| Diastolic Blood Pressure (mmHg) | 69 (9.1) | 68 (8.5) | 71 (9.3) | 0.001 |
| BMI (kg/m²) | 19.8 (2.8) | 20.1 (2.9) | 19.5 (2.7) | 0.007 |
| Waist circumference (cm) | 70.3 (8.0) | 70.3 (7.7) | 70.2 (8.2) | 0.89 |
| Waist-to-height ratio | 0.45 (0.05) | 0.44 (0.06) | 0.45 (0.05) | 0.09 |
| $VO_2$ max ($mL^{-1}/kg^{-1}/min^{-1}$) | 41.8 (6.6) | 43.7 (6.0) | 40.0 (6.5) | 0.001 |
| Physical activity (days per week) | 2.9 (2.0) | 2.5 (2.0) | 3.2 (2.0) | 0.001 |
| TV viewing time (hours per day) | 3.0 (1.6) | 3.0 (1.7) | 3.0 (1.6) | 0.81 |
| Variables | % | | | |
| High blood pressure (%) | 20.3 | 25 | 15.8 | 0.008 |
| Overweight * (%) | 15.2 | 16.4 | 14 | 0.44 |
| Abdominal obesity † (%) | 13.7 | 14.9 | 12.6 | 0.43 |
| Low CRF ‡ (%) | 41 | 20.1 | 61.1 | 0.001 |
| Physical inactivity **(%) | 92.5 | 94.4 | 90.6 | 0.09 |
| High TV viewing time †† (%) | 80.4 | 80.6 | 80.2 | 0.91 |
| Low frequency of consumption of fruits and vegetables ‡‡ (%) | 46.9 | 51.1 | 42.8 | 0.05 |

x̄: mean; σ: standard deviation.
* Defined using the CDC 2000 CDC growth charts.[24]
† Defined using a waist-to-height ratio cutoff of 0.5.[25]
‡ Defined using the FITNESSGRAM® cutoffs values.[28]
** Being active for at least 60 minutes a day for 7 days before the survey.
†† Those who reported TV viewing times of 2 or more hours per day.
‡‡ Those who reported consuiming less than 5 portions of fruits and vegetables per day.
Source: Own elaboration.

**Table 2.** Prevalence of high blood pressure and bivariate associations with potential correlates (n=546).

| Variables | | % | High Blood Pressure | | |
|---|---|---|---|---|---|
| | | | Prevalence (95%CI) | OR (95%CI) | p-value |
| Area (%) | Urban | 69.8 | 22.6 (18.4 - 26.8) | 1 | 0.049 |
| | Rural | 30.2 | 15.1 (9.6 - 20.6) | 0.6 (0.4 - 1.0) | |
| School type | Public | 84.8 | 20.9 (17.2 - 24.7) | 1 | 0.396 |
| | Private | 15.2 | 16.9 (8.7 - 25.0) | 0.8 (0.4 - 1.4) | |
| Sex (%) | Female | 49.1 | 25.0 (19.8 - 30.2) | 1 | 0.008 |
| | Male | 50.9 | 15.8 (11.5 - 20.1) | 0.6 (0.4 - 0.9) | |
| Overweight * | No | 84.8 | 17.9 (14.4 - 21.4) | 1 | 0.001 |
| | Yes | 15.2 | 33.7 (23.5 - 44.0) | 2.3 (1.4 - 3.9) | |
| Abdominal obesity† | No | 86.3 | 17.6 (14.2 - 21.1) | 1 | 0.001 |
| | Yes | 13.7 | 37.3 (26.3 - 48.4) | 2.8 (1.6 - 4.7) | |
| Cardiorespiratory fitness ‡ | High | 59.0 | 17.4 (13.2 - 21.5) | 1 | 0.042 |
| | Low | 41.0 | 24.5 (18.9 - 30.2) | 1.5 (1.0 - 2.3) | |
| Physical activity level ** | Active | 7.5 | 17.1 (6.0 - 28.8) | 1 | 0.591 |
| | Inactive | 92.5 | 20.6 (17.1 - 24.1) | 1.3 (0.5 - 2.9) | |
| TV viewing time (%) | <2 hours | 19.6 | 22.4 (14.5 - 30.4) | 1 | 0.547 |
| | ≥2 hours | 80.4 | 19.8 (16.1 - 23.6) | 0.9 (0.5 - 1.4) | |
| Fruits and vegetables consumption | ≥5 portions per day | 53.1 | 20.0 (15.4 - 24.6) | 1 | 0.839 |
| | <5 portions per day | 46.9 | 21.0 (15.7 - 25.7) | 1.0 (07 - 1.6) | |

OR: odds ratio; CI: confidence interval.
* Defined using the CDC 2000 Growth Charts.[24]
† Defined using a waist-to-height ratio cutoff of 0.5.[25]
‡ Defined using FITNESSGRAM® cutoffs values.[28]
** Being active for at least 60 minutes a day for 7 days before the survey.
Source: Own elaboration.

The logistic regression analysis results of the association between HBP and OW and AO, as well as other potential correlates, are depicted in Figure 1. Results show that HBP was associated with OW (adjusted odds ratio (AOR): 2.3; 95%CI: 1.4-3.9) (Model 1). Model 2 shows that HBP was associated with OW (aOR: 2.1; 95% CI: 1.3-3.6) and low CRF (AOR: 2.0; 95%CI: 1.3-3.1). Also, HBP was associated with AO in Model 1 (aOR: 2.7; 95%CI: 1.6-4.6) and in Model 2 (aOR: 2.4; 95%CI: 1.4-4.1). The inclusion of CRF in Model 2 did not attenuate the association of HBP with OW and AO.

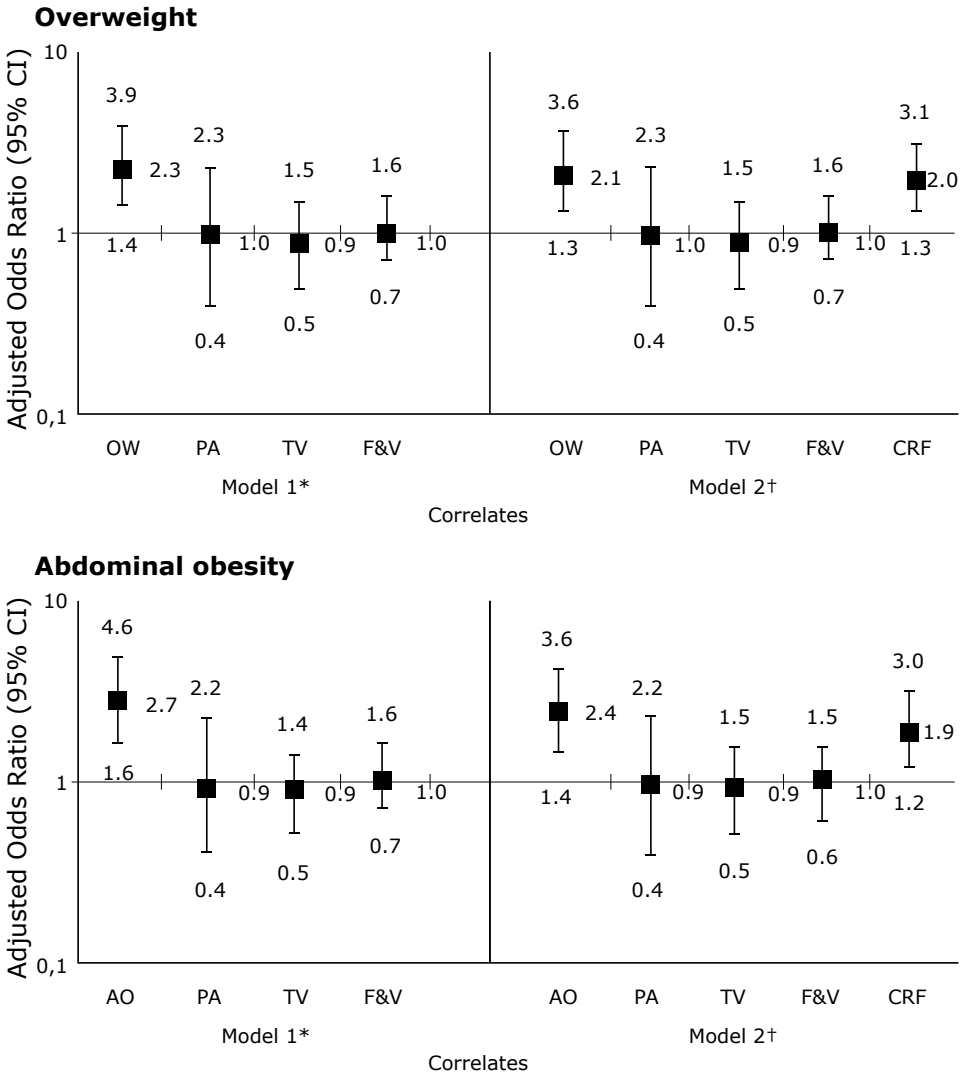


**Figure 1.** Logistic regression analysis of the association between high blood preassure and overweight, abdominal obesity, cardiorespiratory fitness, and other potential correlates.
OW: overweight; PA: physical activity; TV: television viewing time; F&V: fruits and vegetables consumption; CRF: cardiorespiratory fitness; AO: abdominal obesity; CI: confidence interval.
* Adjusted by residence area, school type, sex, overweight, physical activity, TV viewing time, and frequency of fruits and vegetables consumption.
† Adjusted by the correlates included in Model 1 + cardiorespiratory fitness.
Source: Own elaboration.

Figure 2 presents the results of the combined effect of adiposity and CRF. Students with normal weight and low CRF (AOR: 2.2; 95%CI: 1.2-3.7), and those with OW and low CRF (AOR: 5.6; 95%CI: 2.6-12.1) were significantly more likely to have HBP compared with the reference group, that is, those with normal weight and high CRF. Concerning AO, students with no AO and low CRF (AOR: 1.9; 95%CI: 1.2-3.3) and those with AO and low CRF (AOR: 6.2; 95%CI: 3.0-13.1) were significantly more likely to have HBP compared with the reference group. Models in Figure 2 were adjusted by residence area, school type, sex, physical activity, TV viewing time, and fruits and vegetables consumption.

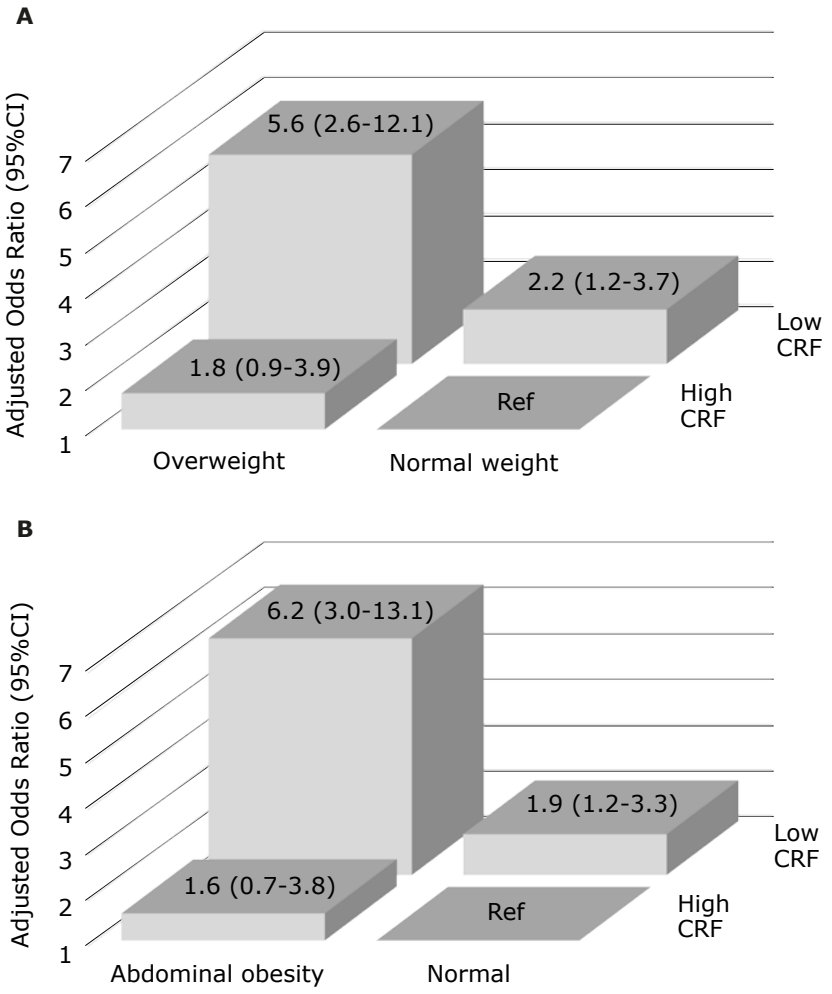


**Figure 2.** Logistic regression analysis of the association between high blood preassure and combined categories of adiposity and cardiorespiratory fitness. A: Combined categories of overweight and cardiorespiratory fitness; B: Combined categories of abdominal obesity and cardiorespiratory fitness.
CRF: cardiorespiratory fitness; CI: confidence interval.
Source: Own elaboration.

## Discussion

This study assessed the cross-sectional associations between HBP and OW, AO, and CRF in a cohort of 546 adolescents. It was found that HPB was positively associated with OW, AO, and low CRF. Also, in this study, an additive effect of high adiposity and low CRF was found. These findings contribute to understanding the relationship between excessive adiposity and low CRF, yielding an important health-related outcome such as blood pressure level in childhood, which suggests that a high CRF may attenuate the association between excessive adiposity and blood pressure in adolescents.

In this sample, HBP is a prevalent health condition, especially among adolescents with low CRF, OW, and AO. Thus, the scope of prevention initiatives in this regard should also consider that the prevalence of HBP is partly associated with the increasing prevalence of childhood obesity.[32] The present study fount that HBP prevalence was higher compared to studies conducted in other cities from Latin America that have used similar methods (5.2% in Medellín, Colombia,[33] and 4.7% in Santiago de Cuba, Cuba),[34] and similar to the prevalence reported in León, Mexico (20.7%)[8] and in the U.S. (20.6%).[35]

It should be noted that HBP prevalence in the present sample occurs with lower prevalence of overweight (15.2%) compared to the prevalence of overweight in Mexican (22%)[8] and North American children (33%);[35] however, the latter study, the authors used a 95$^{th}$ percentile as a criterion for detecting HBP instead of the 90$^{th}$ percentile used here. This could indicate that the current population is more sensitive to excess adiposity, which has been explained by fetal programming.[36] However, the associations between HBP and OW found in this study did not have the magnitude reported previously by Rodriguez *et al.*,[37] where obese adolescents were 3.5-4 times more likely to develop HBP than non-obese adolescents.

These results are consistent with previous studies. For instance, HBP has been found to be associated with high waist circumference[38] and OW[35,39] in children and adolescents. Moreover, different studies have reported a beneficial association between CRF and blood pressure.[40] In this study, behavioral risk factors such as PA, sedentary

behavior, and frequency of fruit and vegetable consumption, were not associated with HBP. Previous studies have suggested that CRF seems to relate more strongly to cardiovascular disease risk factors than to components of objectively measured PA in youth.[41]

From this perspective, it would be expected that low central adiposity and high CRF, independently, lead to a lower blood pressure level. However, in this study, HBP was more prevalent in girls than in boys, but boys had a higher prevalence of low CRF. In addition, there were no statistically significant differences in the prevalence of AO bewtween girls and boys. These findings may indicate that sex alters the interaction between fitness, fatness, and HBP. In this regard, Ruiz *et al.*[42] reported that adiposity is associated with high blood pressure only in the group of children with the lowest level of CRF. Consequently, these findings suggest a complex interdependency between sex, central adiposity, and CRF and their associations with blood pressure level.

Moreover, these findings are relevant to public health. The high prevalence of HBP points to an adverse impact on children's health due to the increased risk of short- and long-term negative health outcomes. Consequently, interventions should be focused on behavioral approaches that involve diet, sedentary behaviors and PA as main factors to reduce excess adiposity and increase CRF.

The results of this study have some limitations that should be mentioned. Firstly, the cross-sectional nature of the study does not allow establishing causal relationships between HBP, OW, AO, and CRF. However, it is not biologically plausible that HBP could lead to OW or AO. In fact, multiple intervention studies have reported the benefits of weight loss on blood pressure reduction in children .[43] Secondly, in this study, dietary sodium and family history of hypertension or cardiovascular disease were not considered; it is known that sodium is an important predictor of HBP and that heredity plays a role in high blood pressure among children.[23] Thirdly, the risk of misclassification may be of particular concern, but this risk was minimized by measuring blood pressure three times. Finally, behavioral information could be biased since it was gathered through self-report.

On the other hand, the strengths of the study include the representativeness of the sample and the inclusion of both urban and rural areas, as well as the fact that this is one of the few studies exploring these types of associations in the Colombian school population.

## Conclusion

These findings show that HBP is a prevalent condition in children and adolescents from Montería. Furthermore, HBP is significantly associated with OW, AO, and CRF. These results have public health relevance, considering that, in Colombia, OW among adolescents keeps reaching unexpected proportions and, therefore, a rise of blood pressure levels is anticipated. For this reason, it is necessary to implement initiatives to promote healthy habits aimed at this population to reduce the incidence of new HBP cases in adolescents. Longitudinal and intervention studies and their translation into practice are needed in order to understand better the relationship between blood pressure and central adiposity and fitness.

## Conflict of interest

None stated by the authors.

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# Clinical and epidemiological profile of patients in the chronic phase of Chagas disease treated at a reference center in Southeastern Brazil

*Perfil clínico y epidemiológico de pacientes chagásicos en fase crónica atendidos en un centro de referencia del sudeste de Brasil*

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## Abstract

**Introduction:** After implementing measures to control vector transmission by *Triatoma infestans* in Brazil, the number of new cases of Chagas disease (CD) decreased. Currently, the American continent has an annual incidence of 28 000 cases, but a large number of older adults are still affected by the chronic phase of this disease.
**Objective:** To characterize the clinical and epidemiological profile of patients in the chronic phase of CD treated at a reference center located in the state of São Paulo, Brazil.
**Materials and methods:** A cross-sectional, descriptive study was conducted based on the analysis of the medical records of 62 patients in the chronic phase of CD and treated at the Hospital das Clínicas de Marília.
**Results:** No significant differences were found regarding sex, age and time of diagnosis. Cardiac problems were the most reported clinical sign. A significant difference was observed in the case of the indeterminate form of the disease, which was more predominant in males. In addition, functional classification B1 of CD was more common in women, while B2 predominated in men.
**Conclusion:** A late diagnosis of CD may increase the chances of presenting digestive complications. However, the classic manifestations of the disease and its comorbidities can be successfully managed as long as comprehensive (multidisciplinary) medical care is provided, since this would help delay the course of the disease and, consequently, improve the patients' quality of life.
**Keywords:** *Trypanosoma cruzi;* Chagas Disease; Complications; Neglected Diseases (MeSH).

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## Resumen

**Introducción.** Luego de la implementación de medidas de control de la transmisión vectorial por *Triatoma infestans* en Brasil, hubo una reducción en el número de nuevos casos de la enfermedad de Chagas (EC). Actualmente, en el continente americano la incidencia anual de EC es de 28 000 casos, pero cabe señalar que aún existe una gran cantidad de adultos mayores que padecen los síntomas y signos de la fase crónica de esta enfermedad.
**Objetivo.** Caracterizar el perfil clínico y epidemiológico de pacientes chagásicos en fase crónica atendidos en un centro de referencia ubicado en el estado de São Paulo, Brasil.
**Materiales y métodos.** Estudio transversal y descriptivo. Se analizaron las historias clínicas de 62 pacientes chagásicos crónicos atendidos en el Hospital das Clínicas de Marília.
**Resultados.** No hubo diferencias significativas con respecto a sexo, edad y tiempo de diagnóstico. Los problemas cardiacos fueron el signo clínico más reportado. Se observó una diferencia significativa en el caso de la forma indeterminada de la enfermedad, siendo más predominante en los hombres. Por otra parte, el estadio B1 fue más frecuente en las mujeres, mientras que el estadio B2 fue predominante en los hombres.
**Conclusión.** El diagnóstico tardío de la EC puede aumentar la probabilidad de presentar complicaciones digestivas. Sin embargo, las manifestaciones clásicas de esta enfermedad y sus comorbilidades pueden ser controladas siempre que se cuente con atención médica integral (multidisciplinar), ya que de esta forma se retrasa su evolución y, en consecuencia, se mejora la calidad de vida de estos pacientes.
**Palabras clave:** *Trypanosoma cruzi;* Enfermedad de Chagas; Perfil epidemiológico; Comorbilidad; Enfermedades desatendidas (DeCS).

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## Introduction

Worldwide, neglected tropical diseases (NTDs) are caused by protozoan, bacterial and helminth infections, and Chagas disease (CD) is one of the three most important NTDs caused by protozoa and transmitted by vectors.[1] In addition, it constitutes a major public health problem in Latin America, especially in endemic continental countries. Also, it has been estimated that approximately 6 million individuals are infected with *Trypanosoma cruzi* in 19 Ibero-American countries, with an annual incidence of 28 000 cases, in addition to the occurrence of sporadic cases of natural transmission in the United States.[2]

In 2006, the Southern Cone Intergovernmental Commission to Eliminate *Triatoma infestans* and Interrupt the Transmission of Transfusional Trypanosomiasis[3] (INCOSUR-Chagas) certified that Brazil had successfully interrupted vector-borne transmission of *T. cruzi* by *T. infestans* in all endemic states, the main *triatominae* in the country and the main responsible for the transmission of this infectious disease.[4] However, in Brazil, CD is still the main NTD in terms of morbidity and mortality, since, besides premature death, it also causes physical disability.[5,6] It has been estimated that 1.9 to 4.6 million people in the country are infected with *T. cruzi*, that is, 1.0 to 2.4% of its total population, and that out of these, approximately 540 000 to 1.8 million individuals have cardiovascular or digestive diseases. In addition, it has been reported that in Brazil, CD causes almost 6 000 deaths per year.[7,8]

There are two phases of CD: the acute phase and the chronic phase, and in both phases it can be symptom free, mild or severe. In the acute or initial phase, the infection can be severe in 3 to 5% of infected people, causing cardiac complications and may lead to sudden death.[9] In the chronic phase, 40 to 90% of people do not have symptoms, and their electrocardiograms (ECGs) will be normal or slightly altered, yet their serological and/or parasitological tests will be positive.[9,10] During the chronic phase, which may last decades or even the lifetime of the infected individual, most patients have no Chagas-related symptoms (a phase known as chronic indeterminate), but approximately 20% to 30% will develop *cardiac complications and digestive complications* affecting the esophagus and the colon.[8,9]

However, the clinical signs and the severity of CD may vary depending on the geographic area and the strain of the parasite.[11] Other comorbidities that may affect the severity of the infection and the development of these complications, such as diabetes mellitus and systemic hypertension, should be also considered.

In the Marília region, located in the state of São Paulo, Brazil, *T. cruzi* infection used to be highly prevalent. This situation was historically associated with coffee farming activities in rural areas and with the expansion of cities in the region as a result of the construction of railroads, which opened up unexplored territories of Western São Paulo.[12,13]

Thus, considering the high number of CD cases recorded in the region of Marília before the campaigns to eradicate the main vector of *T. cruzi* in this region were carried out, the present study aims to characterize the clinical and epidemiological profile of patients in the chronic phase of CD treated at a reference center of São Paulo (State), Brazil.

## Materials and methods

Cross-sectional descriptive study. The medical records of 62 patients in the chronic phase of CD treated at the Cardiology outpatient clinic of the Hospital das Clínicas de Marília between February and October 2016 were reviewed. This hospital is a referral health institution that provides cardiology care services to patients from all municipalities belonging to the DRS IX-Marília-SP (Regional Health Department IX-Marília-São Paulo) area.

The following variables were analyzed: sex, age, time elapsed after the disease was diagnosed, symptoms and clinical signs of CD, associated comorbidities, electrocardiographic alterations, medications used by the patients, and cardiac alterations based on ECGs results. Functional classification of CD followed the Second Brazilian Consensus on Chagas Disease guidelines[8]: B1, cardiac involvement without congestive heart failure (CHF), altered ECG, and left ventricular ejection fraction (LVEF) ≥45%; B2: cardiac involvement without CHF, altered ECG, and LVEF <45%; C: altered ECG and compensated heart failure (HF); D: altered ECG and refractory HF.

For age analysis, patients were classified into two groups: adults aged <60 years and those aged between 60 to 84 years.

Continuous numerical variables were described using central tendency (mean) and dispersion (standard deviation) measures. Categorical numerical variables were described using absolute (f) and relative (%) frequencies and were dichotomized based on the following options: presence (1) or absence (0) of clinical manifestations or alterations. A student's' t test and a Fisher's exact test were performed to compare means between men and women, and to determine the association between qualitative variables, respectively. Also, the Spearman's rank correlation coefficient was used to analyze the correlation between categorical variables. A logistic regression analysis was used to verify the effect and odds ratio of the independent variables on the probability of occurrence of the different types of clinical manifestations of CD. The percentage of variation in the probability of the dependent variable explained by the variation of the independent variables in the logistic regression model was analyzed by means of Nagelkerke's $R^2$. All statistical analyses were performed using the IBM SPSS Statistics Software for Windows, version 19.0 (Armonk, NY: IBM Corp.). A significance level of 5% was considered for all analyses.

Before participating in the study, all individuals signed a free and informed consent form. Also, the study was conducted following the ethical principles for medical research involving human subjects established by the Declaration of Helsinki[14] and in accordance with the research ethics standards outlined by Resolution 466 of December 12, 2012, issued by the National Health Council of Brazil.[15] This research was approved by the Research Ethics Committee of Famena - Faculdade de Medicina de Marília (Faculty of Medicine of Marília) as stated in the CAAE (Certificado de apresentação para Apreciação Ética - Submission certificate for ethical evaluation) No. 11565712.8.0000.5413 (12/19/2012).

## Results

Participants' age ranged from 31 to 83 years, 24.2% were younger than 60 years old, and 75.8% older than

60. There were no significant differences between men and women and between age groups (Table 1).

**Table 1.** Distribution of patients in the chronic phase of Chagas disease treated at the Cardiology outpatient clinic of Hospital das Clínicas de Marília from February to October 2016 (n=62) according to sex and age group.

| Sex† | Age group† | f | % * | p-value |
|---|---|---|---|---|
| Female (n=32) | <60 years | 8 | 25.0 | 0.879 |
| | ≥60 years | 24 | 75.0 | |
| Male (n=30) | <60 years | 7 | 23.3 | |
| | ≥60 years | 23 | 76.7 | |

* Comparison of mean according to the student's' t test.
† Association between sex and age group according to the Fisher's exact test.
Source: Own elaboration.

In addition, the clinical manifestations of CD reported in the medical records that were reviewed are shown in Table 2.

**Table 2.** Clinical manifestations of Chagas disease in the study population (n=62) according to sex and age group.

| Clinical manifestations | Age group (years) | Sex | | | | p-value* |
|---|---|---|---|---|---|---|
| | | Female | | Male | | |
| | | f | % | f | % | |
| Cardiac complications | <60 | 6 | 75.0 | 5 | 71.4 | 1 |
| | ≥60 | 19 | 79.2 | 15 | 65.2 | 0.341 |
| Esophageal complications | <60 | 1 | 12.5 | 0 | 0 | 1 |
| | ≥60 | 4 | 17.4 | 3 | 11.1 | 0.689 |
| Intestinal complications | <60 | 0 | 0 | 0 | 0 | - |
| | ≥60 | 6 | 26.1 | 2 | 7.4 | 0.121 |
| Indeterminate (asymptomatic) | <60 | 2 | 25.0 | 2 | 28.6 | 1 |
| | ≥60 | 2 | 8.7 | 7 | 30.4 | 0.072 |

* A p-value ≤0.05, obtained after performing the Fisher's exact test, was considered as a significant association.
Source: Own elaboration.

The analysis of the association between age, sex, comorbidities, functional class of CD, and electrocardiographic alterations in the study population is shown in Table 3. The main comorbidity was systemic hypertension (SH), followed by dyslipidemia and diabetes *mellitus*. Alzheimer's disease was not reported, and only one woman had a rheumatic disease. Electrocardiographic alterations such as anterosuperior left bundle branch block (ALBBB), altered ventricular repolarization, first-degree atrioventricular block, ventricular extrasystole, atrial fibrillation, left bundle branch block, and volume overload of the left atrium are not shown in Table 3 because they were reported in only one case each, making any statistical analysis impossible. It is noteworthy that despite these alterations were statistically assessed, they were not relevant for the final results of the study.

**Table 3.** Association between age, sex, comorbidities, functional classification of Chagas disease and electrocardiographic alterations in the study population (n=62).

| Comorbidity, functional class of CD, and electrocardiographic alterations | Age group | Sex | | | | p-value* |
|---|---|---|---|---|---|---|
| | | Female | | Male | | |
| | | f | % | f | % | |
| SH | <60 | 0 | 0 | 3 | 42.9 | 0.077 |
| | ≥60 | 20 | 83.3 | 9 | 39.1 | 0.003* |
| DM | <60 | 1 | 12.5 | 0 | 0.0 | 1 |
| | ≥60 | 7 | 30.4 | 2 | 7.4 | 0.013* |
| DYS | <60 | 0 | 0.0 | 1 | 14.3 | 0.467 |
| | ≥60 | 10 | 41.7 | 8 | 34.8 | 0.766 |
| Functional class B1 | <60 | 5 | 62.5 | 4 | 57.1 | 1 |
| | ≥60 | 15 | 65.2 | 6 | 26.1 | 0.019* |
| Functional class B2 ' | <60 | 1 | 12.5 | 1 | 14.3 | 1 |
| | ≥60 | 1 | 4.3 | 6 | 26.1 | 0.048* |
| Functional class C | <60 | 0 | 0 | 0 | 0 | NA† |
| | ≥60 | 2 | 8.3 | 3 | 13.0 | 0.666 |
| RBBB | <60 | 1 | 12.5 | 0 | 0.0 | 1 |
| | ≥60 | 7 | 30.4 | 3 | 11.1 | 0.286 |
| Pacemarker | <60 | 2 | 25.0 | 0 | 0.0 | 0.467 |
| | ≥60 | 5 | 20.8 | 3 | 13.0 | 0.701 |
| RBBB+ALBBB | <60 | 2 | 25.0 | 0 | 0.0 | 0.467 |
| | ≥60 | 4 | 17.4 | 0 | 0.0 | 0.109 |
| AVR | <60 | 1 | 12.5 | 1 | 14.3 | 1 |
| | ≥60 | 3 | 13.0 | 3 | 13.0 | 1 |

CD: Chagas disease; SH: systemic hypertension; DM: diabetes *mellitus*; DYS: dyslipidemia; RBBB: right bundle branch block; ALBBB: anterosuperior left bundle branch block; AVR: altered ventricular repolarization.
* A p-value ≤0.05, obtained after performing the Fisher's exact test, was considered as a significant association.
† Functional classification C was not observed in patients under 60 years of age.
Source: own elaboration.

The correlation analysis between type of clinical manifestation of CD, functional class of CD, electrocardiographic alterations, and time of diagnosis, described in Table 4, showed that the longer the time elapsed since the diagnosis was made, the higher the probability of having esophageal and intestinal complications. It should be noted that only values with significant correlations were included. The following codes were used to interpret the correlation: presence of manifestations or alterations (1) or absence of manifestations or alterations (0), as mentioned in the methodology.

**Table 4.** Correlation between type of clinical manifestation of Chagas disease, functional class of Chagas disease, electrocardiographic alterations, and time of diagnosis in the study population (n=62).

| Functional class, electrocardiographic alterations and time of diagnosis | Cardiac manifestation | Esophageal manifestation | Intestinal manifestation | Indeterminate manifestation |
|---|---|---|---|---|
| Functional class B1 | 0.619† | | | -0.523† |
| Functional class B2 | 0.264† | | | |
| RBBB+ALBBB | | | | |
| RBBB | 0.297† | | | -0.251† |
| RBBB+VE | | | | |
| RBBB+VE+AF | | 0.333† | | |
| Time elapsed since diagnosis | | 0.439† | 0.319† | |

RBBB: right bundle branch block; ALBBB: left bundle branch block; VE: ventricular extrasystole; AF: atrial fibrillation.
† a p-value ≤0.05 indicates a significant correlation by the Spearman's correlation coefficient.
Source: Own elaboration.

Table 5 shows the binary logistic regression analysis for the independent variables that showed a significant correlation (Table 4) with the clinical manifestations controlling the effect of sex and age group. However, variables with a Nagelkerke's $R^2$ correlation coefficient >0.30 were considered for the regression analysis. The following codes were used to interpret the regression analysis: presence of clinical manifestations (1) or absence of clinical manifestations (0), sex (0=female; 1=male); age group (0: <60 years; 1: ≥60 years).

**Table 5.** Logistic regression analysis of the effect of independent variables in increasing the probability of occurrence of any clinical manifestation of Chagas disease.

| Variables | | B | Wald p-value* | Exp(B) | IC 95% for Exp(B) | | $X^2$ p-value | Nagelkerke's $R^2$ |
|---|---|---|---|---|---|---|---|---|
| Dependent | Independent | | | | Lower | higher | | |
| Cardiac manifestation | B1 | 21.53 | 0.998 | <0.001 | <0.0001 | >1 | 0.0001† | 0.545 |
| | Age group | 0.65 | 0.495 | 1.92 | 0.29 | 12.56 | | |
| | Sex | 0.28 | 0.710 | 1.32 | 0.31 | 5.70 | | |
| | Constant | -0.84 | 0.380 | 0.43 | | | | |
| Esophageal manifestation | TD | 0.19 | 0.005* | 1.21 | 1.06 | 1.39 | 0.002 † | 0.411 |
| | Age group | -0.04 | 0.978 | 0.97 | 0.07 | 12.44 | | |
| | Sex | -0.24 | 0.801 | 0.78 | 0.12 | 5.23 | | |
| | Constant | -6.05 | 0.002* | 0.00 | | | | |
| Intestinal manifestation | TD | 0.14 | 0.008* | 1.15 | 1.04 | 1.27 | 0.002 † | 0.336 |
| | Sex | -1.20 | 0.201 | 0.30 | 0.05 | 1.90 | | |
| | Constant | -4.34 | 0.002* | 0.01 | | | | |
| Indeterminate (asymptomatic) | B1 | -21.04 | 0.998 | 0.0001 | 0.001 | 0.00001 | 0.0001 † | 0.487 |
| | Age group | -1.48 | 0.138 | 0.23 | 0.03 | 1.61 | | |
| | Sex | 0.70 | 0.391 | 2.01 | 0.41 | 9.91 | | |
| | Constant | 0.36 | 0.701 | 1.44 | | | | |

B1: functional classification B1; TD: time of diagnosis (in years); B (regression coefficient); $\chi^2$: Chi-square; $R^2$: Nagelkerke's percentage of variation in the probability of the outcome explained by the model; Exp (B): odds ratio.
* a p-value ≤0.05 indicates a significant effect of each independent variable by the Wald test.
† A p-value ≤0.05 means a significant effect of the model on the variation of the probability of the outcome taking place. The effect was measured using the Chi-square ($\chi^2$) statistic.
Source: Own elaboration.

Regarding the association between the time of diagnosis and the probability of developing clinical manifestations of CD, it was observed that for every year elapsed since the diagnosis was made, the probability of having a digestive complication increases (Figure 1). In this regard, the probability of developing an esophageal complication is 1.21 times higher for every year elapsed since the diagnosis of CD was made (Figure 1A) (p=0.005).

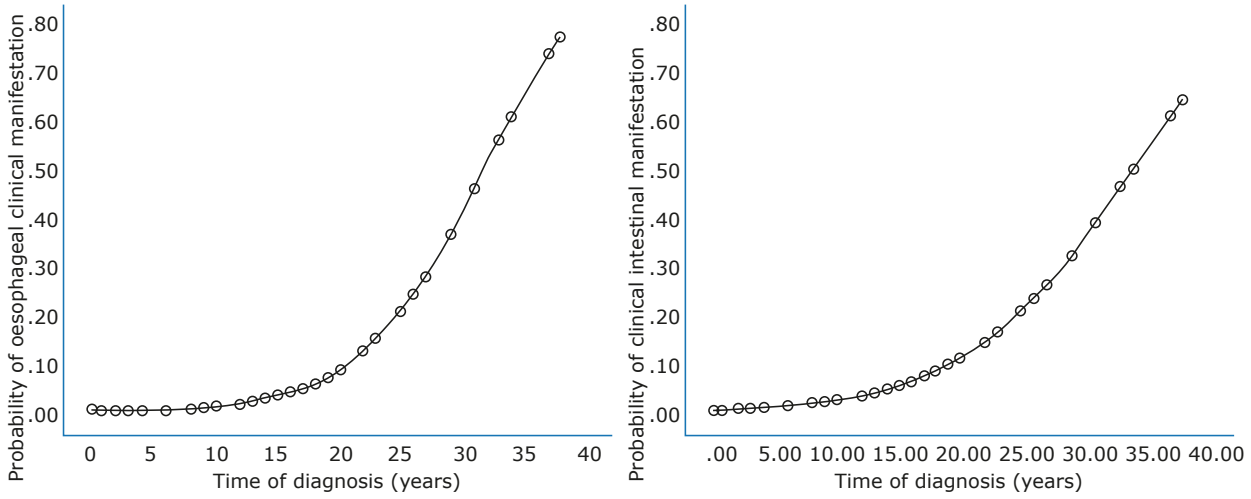


**Figure 1.** Effect of time of diagnosis on the probability of occurrence of the clinical manifestations analyzed. Figure A: esophageal complications; Figure B: intestinal complications.
Source: own ellaboration.

Regarding the medications used by the study population, 49 patients (79.03%) used at least one medication. Of these, 25 (40.32%) used diuretics; 21 (33.87%), Beta blockers; 16 (25.80%), antiarrhythmic drugs; 15 (24.19%), angiotensin-converting enzyme (ACE) inhibitors; 12 (19.35%), statin; 9 (14.51%), angiotensin II receptor blockers and spironolactone; 7 (11.29%), calcium channel blockers and metformin; 4 (6.45%), glibenclamide, and 3 (4.80%), doxazosin.

## Discussion

In Brazil, the success of the *T. infestans* eradication campaigns has led to a massive decrease in the number of new acute cases of CD; somehow, CD remains a major public health problem.[4,8]

The impact of the control measures to interrupt the transmission of *T. cruzi* by the main vector in the country has been described in several studies. For example, Luquetti-Ostermayer *et al.*[16], in a serological survey conducted from 2001 to 2008, reported there were no *T. cruzi* infection cases in children under the age of five years. In addition, in the state of São Paulo, thanks to the reduction of new acute cases of CD and the reduction of the number of triatomines in its area, the transmission of the disease has been controlled for more than four decades.[17,12]

Similar to what other authors have described[17,18], in the present study, 75.8% of the patients were aged over 60 years. In this regard, Bertanha *et al.*[18] state that increased longevity in patients with CD in Brazil is associated with the current technological advances that have been achieved in terms of CD treatment, given the needs of the new epidemiological profile of Brazilian people as a consequence of the accelerated demographic growth of the elderly in the country.

It should be noted that in our study, four elderly patients were diagnosed with CD within four years before conducting the study. Somehow, despite the fact there were no reports of cardiac or digestive complications suggesting CD, or positive serological tests for CD in their medical records before being referred to the Cardiology service of the Hospital das Clínicas de Marília, it is assumed that these individuals were already in the indeterminate chronic phase of the disease, and their diagnosis was confirmed in our service once they started experiencing CD-related signs and symptoms. However, a recent infection by vector transmission of *T. cruzi* in these four patients by species of the *Triatominae* family such as *Triatoma sordida*[19] cannot be ruled out, since this is the most prevalent *Triatominae* species found in the region where this study was conducted, that is, the state of São Paulo.[20]

On the other hand, in the group of adults <60 years old, a 31-year-old patient had been diagnosed with CD 3 years before conducting the study. Yet, according to the medical record, the patient was born in the state of Bahía, and then moved to the state of São Paulo and settled in the region of Marília one year after the diagnosis was made. Also, due to the absence of information regarding a possible *T. cruzi* infection or any blood transfusion the patient may have received, congenital CD or transmission of the infection via blood transfusion were ruled out. However, since the patient was a farmer, it is possible to assume this was a case of vector-borne transmission, provided that in some municipalities of the State of Bahía there are still residual outbreaks of *T. infestans*.[21]

In this regard, Brum-Soares *et al.*[11], in a study carried out in the state of Amazonas, reported that 14 patients aged 7 to 36 years tested positive for CD. This reinforces the need to keep working on vector control, to verify blood transfusions processes, and to pay close attention to other routes of transmission, such as oral (food-borne), which currently is one of the most frequent routes of transmission.[22]

In the present study, there were no statistically significant differences regarding sex between age groups, which is a similar finding to those reported by Borges-Pereira *et al.*[23] and Silva *et al.*[24] in studies carried out in Piauí and Bahía, respectively. In these studies, vector-borne transmission within households was observed in these regions before vector control measures were strengthened. However, in studies conducted in the northern region of Brazil, Brum-Soares *et al.*[11] and Beltrão-Teixeira & Carvalho-de Oliveira[25] found that *T. cruzi* infection was more

frequent in men, concluding that CD is associated with the occupation of the infected person, for in this region the disease is mainly transmitted to people who work in the natural habitats of triatomines, and thus are more exposed to the vector transmission route of the disease.

Although in the present study the average time elapsed since the patients were diagnosed with CD was 17 years, this period does not provide accurate information of the exact moment in which the onset of the clinical manifestation of CD occurred, because in many patients' medical records there are reports of tiredness, dysphagia, or constipation that, in some cases, were made before the diagnosis of chronic CD was confirmed by serologic tests.

In our study, cardiac complications were the most frequent clinical manifestation of CD, affecting 72.58% patients, yet no statistical difference between genders was found. These results are similar to those of Almeida *et al.*[26] and dos Santos-Pereira *et al.*[27] who described that cardiac complications were reported in 88.50% of patients in the chronic phase of CD from Campinas (São Paulo) and in 65.30% of those living in the state of Ceará, respectively. However, these results greatly differ from those by Mota *et al.*[28], who found that, in Brazil, 30% of these patients developed any cardiac alteration.

The predominance of cardiac complications observed in our study might be explained by the *T. cruzi* strains present in the state São Paulo, where Y and Famema strains have been isolated in patients in the chronic phase of CD, as described by Silva & Nussenzweig[29] and Martins *et al.*[30] in 1953 and 2003, respectively. Cardiac tissue tropism has been reported for both strains, although experimental studies conducted using these two strains have found differences regarding virulence and pathogenicity between them. Likewise, cardiac tissue tropism has been described in the strains found in other states of Brazil, such as the state of Bahia[31], so it is possible to say that the 31-year-old patient included in our study, but who was born in the region of Bahía, may have been infected with any of these strains.

Furthermore, the diversity of *T. cruzi* strains present in the State of São Paulo, and their ability to cause infection, added to the early diagnosis of complications related to CD and the early onset of treatment might explain why 48.40% patients were classified in functional classes B1 and B2 of CD, and 8.10%, in class C. Also, functional class B1 was more frequent in women, while B2 predominated in men, with statistically significant differences, which is in agreement with the findings of the study by Guariento *et al.*[32], in which men with the disease had a worse prognosis

Based on the ECG results, the cardiac conduction system was affected in patients with altered ECG. Right bundle branch block was the most frequent cardiac alteration, followed by the need to have a pacemaker implanted. In addition, although cardiac complications were more frequent in women, there was no statistically significant difference between sexes, as reported by other studies.[24, 27,33]

Treatments used to minimize the clinical signs and symptoms of CD, such heart rate alterations, probably caused by the destruction of the parasympathetic nervous system[34] included the prescription of β-blockers and antiarrhythmic drugs in 33.87% and 25.80% of these patients, respectively. In addition, most of the patients included in the present study were using diuretics (40.32%) and antihypertensives (24.19%), as SH was the most prevalent comorbidity in individuals in the >60 years age group. In this sense, several studies have described an association between CD and hypertension.[17,18,35] Out of these patients, 71.80% had cardiac complications, thus confirming that having SH and CD leads to the worsening of the heart function.[36]

The predominance of SH in females in the >60 years age group presented a significant difference in relation to men, which may be explained by the higher survival rate of women in the general population, and by the hormonal and biological changes that they undergo during menopause.[37] Most of the times, these changes result in an increased body mass index,[38] which in turn increases the risk of high blood pressure, together with other comorbidities such as dyslipidemia, diabetes, in addition to the infection by *T. cruzi*. In our study, dyslipidemia was reported in 38.30% of patients in the elderly group (>60 years) and was the second most frequent comorbidity, yet no significant difference was observed between genders, which is similar to the findings of Pereira,[39] who reported this condition was observed in 21% of the individuals included in their study.

Furthermore, 12.9% of our patients had diabetes *mellitus*, which is similar to the prevalence found by Bertanha *et al.* (10.4%).[18] Also, in our study, the majority of patients in the elderly (>60 years) group were women (75.0%), and 30.4% of them had diabetes *mellitus*. According to some authors, patients in the chronic phase of CD may develop diabetes *mellitus* due to the excessive production of free radicals caused by *T. cruzi* infection, which may lead to insulin resistance,[40] and due to dysautonomia,[41] a condition that can occur in these patients.

Confirming the biological characteristics of the *T. cruzi* strains existing in the Marília region, the indeterminate form of the disease was the second most prevalent type of CD in the study population, followed by the intestinal and esophageal manifestations types. However, the linear relationship analysis showed that the time of diagnosis can significantly influence the probability of developing the classic manifestations of CD. This finding is consistent with that of Beltrão-Teixeira & Carvalho-de Oliveira[25] who reported that about 10% of patients with CD-related cardiac complications will eventually develop gastrointestinal manifestations such as megacolon and megaesophagus. However, the intensity of the immune response that occurs in parasite-host interactions is inherent to each patient.

## Conclusion

A late diagnosis of CD may increase the chances of presenting digestive complications. However, the classic manifestations of the disease and its comorbidities can be successfully managed as long as comprehensive (multidisciplinary) medical care is provided, since this would help delay the course of the disease and, consequently, improve the patients' quality of life.

## Conflicts of interest

None declared by the authors.

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# A new approach to teaching anatomy: modified Caldwell-Luc procedure

*Un nuevo enfoque de enseñanza anatómica: técnica Caldwell-Luc modificada*

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## Abstract

**Introduction:** Knowing eye morphology is crucial for the training of medical students; however, learning about the anatomy of the eye is limited to virtual models and illustrations that do not accurately portray the orbital cavity and its contents. In this sense, the use of dissection techniques has shown to improve the learning of the morphology of any anatomical structure.
**Objective:** To modify the Caldwell-Luc procedure using a simultaneous superior approach that allows access to all the extrinsic structures of the eye contained in the orbital cavity, and thus facilitate its study in situ.
**Materials and methods:** Based on a thorough literature review, dissection practices were performed first with pig eyes to gain the necessary experience, and then the dissection was carried out by planes on a human corpse: the maxillary bone was cut and a horizontal cut was made at the base of the skull.
**Results:** By dissecting all the extrinsic muscles of the eye it was possible to visualize the nerves (cranial pairs), their branches and vascular structures from an upper and lower perspective of the orbit.
**Conclusion:** The successful application of the modified Caldwell-Luc procedure described in this study is a better tool for teaching and learning about the anatomy of the eye, as it allows observing as many of the surrounding structures of the eye in situ as possible, and provides an opportunity to improve students' anatomical dissection skills.
**Keywords:** Orbit; Anatomy; Dissection; Learning (MeSH).

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## Resumen

**Introducción.** Conocer la morfología ocular es crucial para la formación de estudiantes de medicina; sin embargo, el aprendizaje de la anatomía del ojo está limitado a modelos virtuales e ilustraciones que no ofrecen una impresión real de la cavidad orbitaria y su contenido. Al respecto, se ha demostrado que el uso de técnicas de disección mejora el aprendizaje morfológico de cualquier estructura anatómica.
**Objetivo.** Modificar la técnica Caldwell-Luc con un abordaje superior simultáneo que permita acceder a todas las estructuras extrínsecas del ojo contenidas en la cavidad orbitaria y, de esta forma, facilitar su estudio *in situ*.
**Materiales y métodos.** Basándose en una revisión exhaustiva de la literatura, primero se realizaron prácticas de disección con ojos porcinos para adquirir la experiencia necesaria y luego se procedió a realizar la disección por planos en un cadáver humano: se llevó a cabo el corte del hueso maxilar y el corte horizontal en la base del cráneo.
**Resultados.** La disección de todos los músculos extrínsecos del ojo permitió observar los nervios (pares craneales) con sus ramos desde una perspectiva inferior y superior de la cavidad orbitaria.
**Conclusión.** La aplicación satisfactoria de la técnica modificada de Caldwell-Luc descrita en el presente estudio constituye una mejor herramienta para la enseñanza y el aprendizaje de la anatomía ocular, ya que esta permite observar la mayor cantidad de estructuras anexas del ojo *in situ* y ofrece una oportunidad para mejorar las habilidades en disección anatómica de los estudiantes.
**Palabras clave:** Órbita; Anatomía; Disección; Aprendizaje (DeCS).

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## Introduction

The human eye is an organ constituted by an assembly of lenses with the capacity to capture light and convert it into electrical impulses, which are transformed into images by the brain.[1] These impulses are transmitted to the visual cortex, located at the back of the head, by a set of nerve fibers called optical pathways.[2] The movements of the eyeball in the orbital cavity occur thanks to the extrinsic muscles, which are innervated by the common ocular motor, trochlear, abducens, and trigeminal nerves, cranial pairs that relay sensitive information.[1]

Eyes are the organ that makes possible the sense of sight and, therefore, they are necessary to interact properly with the environment. For this reason, health professionals (optometrists, ophthalmologists, and general practitioners) involved in their care must learn in a practical and correct way their anatomy during their training.

There is currently controversy among anatomists as to whether dissection is the best method for teaching this scientific discipline.[3] In recent decades, this method has gained detractors because of the limitations that professionals and students face when they need to perform dissection procedures, such as the difficult access to cadavers and legal restrictions on their use.[4,5] Nevertheless, corpse dissection continues to be the preferred method for teaching and learning anatomy.[6]

With this in mind, the present research revisits this classic method and proposes an innovative modification of the Caldwell-Luc procedure, a surgical intervention indicated for treating chronic sinusitis and odontogenic maxillary sinusitis,[7,8] to facilitate the learning of the structures surrounding the eye among health professionals. To this end, this study sought to modify the Caldwell-Luc procedure with a simultaneous superior approach that allows access to all the extrinsic structures of the eye contained in the orbital cavity and, in this way, facilitate its study in situ.

## Materials and methods

Descriptive study. First, pig eyes were dissected so the students could gain the necessary experience to carry out the dissection in a human corpse. Then, the orbital cavity contents were dissected by planes in a human cadaver based on an exhaustive review of the literature in the ClinicalKey, PubMed, LILACS, and SciELO databases, as well as in textbooks of human anatomy and embryology.

The procedures were performed in the Human Anatomy Laboratory of the Faculty of Health Sciences at the Universidad de Ciencias Aplicadas y Ambientales U.D.C.A by the research group using the necessary biosafety tools. The following materials were used: dissection instruments; scalpel blades # 10, 11, 15, 18, 23 and 25; two pig heads (preserved with formalin and glycerin in the laboratory); Stryker® autopsy saw (model 810 - BD001) for cutting bones; visual protection equipment and a Nikon® D-5500 camera with 17mm lens.

Before performing the anatomical dissection of the human orbital cavity, students practiced the procedure on two pig heads, which were purchased in the Quirigua neighborhood marketplace; this is to make clear that no animal sacrifices were performed. It should be noted that pigs were used because of the anatomical similarities between its eyes and human eyes.[3] A cut was made in the maxillary bone of one of the heads, while the eyeball was dissected keeping this bone intact in the other one. The purpose was to determine which of the two procedures allowed visualizing a larger amount of structures.

Then, the modified Caldwell-Luc technique was utilized in the human orbital cavity, as described in 1972 by Walter.[9] Two incisions were made, one on the face midline from the forehead, going through the nasal dorsum and the nasolabial fold until the upper lip, and the other from the medial region to the lateral region, starting from the cut made on the midline until the right auricle. Then, the frontal belly of the occipitofrontal muscle and the orbital and palpebral portions of the orbicularis oculi muscle were exposed. Subsequently, the subcutaneous and muscle tissues were removed from the surface of the zygomatic and maxillary bones to expose these bone structures and, therefore, visualize the infraorbital artery, the infraorbital vein, and the infraorbital nerve.

Afterwards, using the autopsy saw, a 2cm square cut was made on each side and the bone block was removed to see the infraorbital artery, the infraorbital vein, and the infraorbital nerve. Then, the subcutaneous tissue from the orbit was dissected and removed to improve the visualization of the extrinsic structures contained in this cavity.

In addition, a cut was made beginning at the base of the skull, crossing the minor wing of the sphenoid bone, continuing through the anterior cranial fossa to the frontal bone at the base of the skull, and then continuing around the anterior cranial fossa with a lateral cut up to its limit with the middle cranial fossa; finally, an anterior cut was made until the initial point of the first cut was reached. A bony piece of the skull was left free to approach the structures contained in the orbital cavity from an upper view, so these structures were cleaned and separated for proper identification.

The original Caldwell-Luc procedure was modified by performing a surgical resection of the maxillary bone and the medial edge of the zygomatic bone, that is, where this bone articulates with the maxillary bone. Another cut was made at the base of the skull on the limit between the orbital cavity and the superciliary arch. Once the common tendinous ring was dissected, the ophthalmic artery was identified.

### Ethical and legal considerations

This study was conducted following the ethical principles set forth in the Declaration of Helsinki[10] and the ethical standards established in Resolution 485 of 2002 issued by Instituto de Medicina Legal y Ciencias Forenses, which regulates the procedures for the destination of corpses and anatomical components obtained from them for teaching and research purposes.[5] Likewise, the provisions of Decree 1546 of 1998, which establish that scientific institutions and hospitals may use unclaimed cadavers, as well as organs or anatomical components obtained from them for teaching and research purposes, were taken into account.[11]

All guidelines and parameters that ensure due respect for human corpses and their use to support and expand medical, surgical and scientific knowledge established in articles 47 and 48 and the principles for biomedical research on animals set forth in article 87 of Resolution 8430 of 1993, issued by the Colombian Ministry of

Health,[12] were followed. Also, according to this resolution, since the study was conducted on a corpse in the dissection hall, it is considered to be free of risk.[12]

## Results

The structures contained in the orbital cavity of both pig heads were exposed (Figure 1). This practice allowed the students to obtain the necessary skills to carry out the dissection in the human cadaver.

During the procedure, it was determined that cutting the maxillary bone facilitates the approach to the orbital cavity since it allows identifying the structures contained in this cavity and dissecting them in a more practical way.

By dissecting the human corpse, it was possible to observe the frontal belly of the occipitofrontal muscle and the orbital and palpebral portions of the orbicularis oculi muscle, as well as the infraorbital artery, the infraorbital vein, and the infraorbital nerve (Figure 2).


**Figure 1: Dissection performed on pig heads.** A: pig's head with resection of the maxillary bone; B: pig's head with complete maxillary bone.
Source: Document obtained during the study.

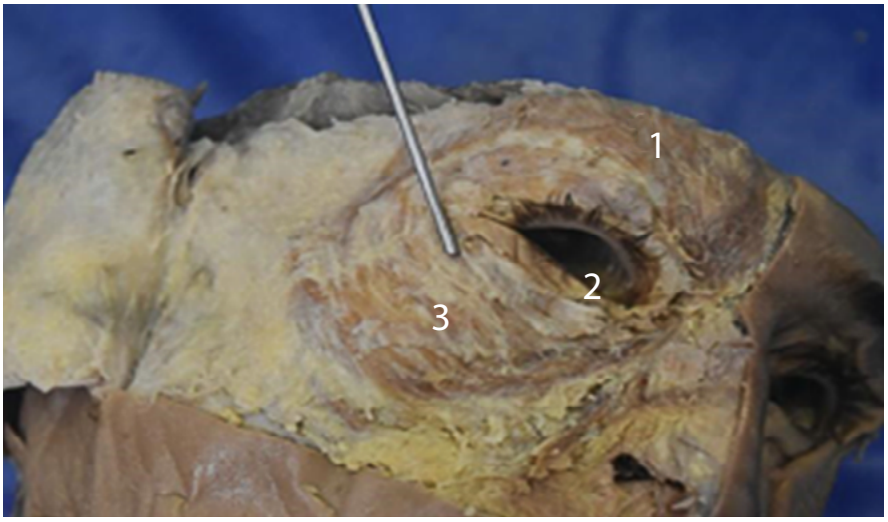


**Figure 2.** Cuts made in the skin on the sagittal midline of the face and transversally up to 2 cm below the right auricle. 1: frontal belly of the occipitofrontal muscle; 2: palpebral portion of the orbicularis oculi muscle with complete detachment of the skin covering it; 3: orbital portion of the orbicularis oculi muscle.
Source: Document obtained during the study.

The square cut made in the middle third of the zygomatic bone, that is, where this bone articulates with the maxillary bone (Figures 3 and 4), and in both lateral portions of the right half of the maxillary bone, that is, in the articular proximity with the zygomatic bone, allowed visualizing the infraorbital artery, vein and nerve, and the occipitofrontal and orbicular muscles of the eye. This cut is one of the modifications made in the present study to the original procedure proposed by Caldwell-Luc in 1972[9] and to other modified procedures that preserved the original approach.

Another modification to the original technique and its variants in the present study was a cross section made at the base of the skull to allow the observation of the infraorbital artery, infraorbital vein and infraorbital nerve, and the common tendinous ring, which reaches the orbital cavity from the cranial cavity. After this cut was made, the following structures were visible: the eyeball; the lacrimal gland; the lacrimal vein; the frontal nerve; the frontal sinus; the olfactory bulb; the pituitary gland and pituitary stalk; the levator palpebrae superioris muscle; the superior, oblique, medial and lateral rectus muscles; the oculomotor (III cranial pair), trochlear (IV cranial pair) and abducens (VI cranial pair) nerves; and the lacrimal, frontal and nasociliary branches of the ophthalmic nerve (V1) of the trigeminal nerve (V cranial pair) (Figure 5).

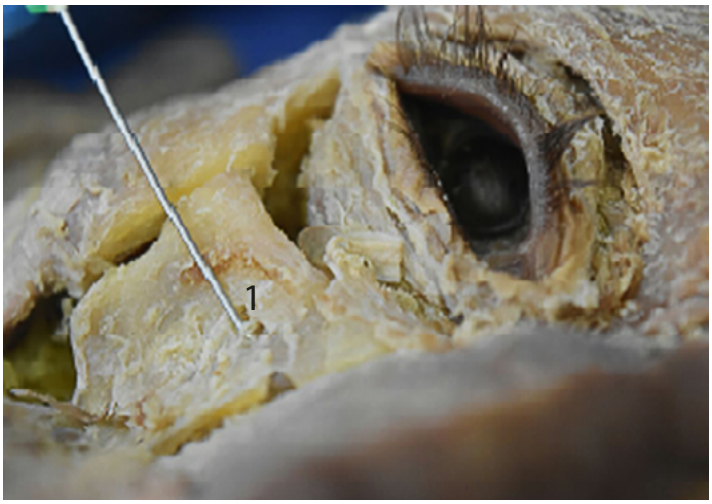


**Figure 3.** Square cut made in the zygomatic bone. 1: infraorbital nerve passing through the infraorbital foramen after the dissection of the anatomical structures.
Source: Document obtained during the study.

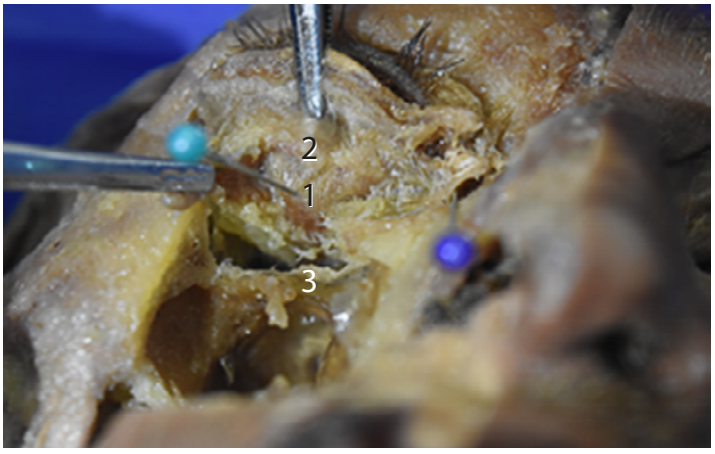


**Figure 4.** Cutting and resection of the square block of the zygomatic bone with anteroinferior view of the orbital cavity. 1: inferior rectus muscle; 2: inferior oblique muscle; 3: infraorbital nerve.
Source: Document obtained during the study.

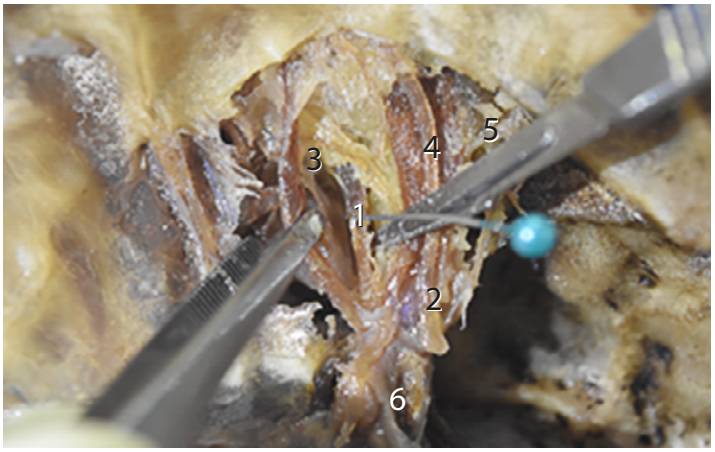


**Figure 5.** Upper view after making the cross section at the base of the skull. 1: medial rectus muscle; 2: superior oblique muscle; 3: levator palpebrae superioris muscle; 4: superior rectus muscle; 5: lateral rectus muscle; 6: ophthalmic nerve.
Source: Document obtained during the study.

## Discussion

Currently, the Caldwell-Luc procedure is not being used for the purpose for which it was initially intended since minimally invasive procedures are preferred. With this technique, indicated for treating chronic sinusitis, the sinuses are approached through the oral cavity.[13,14] Multiple modifications have been made to the original version, so it has become a dissection technique that preserves the morphology of the orbital cavity structures and provides a real and accurate perspective of their location.

In 2003, Gönül *et al.*[15] proposed an anatomical model for the study of the morphology of the orbital floor that encouraged the creation of other models based on the Caldwell-Luc procedure. At the University of Costa Rica, Rodríguez-Vargas & Guevara-Arroyo[16] proposed an anatomical model to visualize, in a more precise manner, the vascular and nervous structures of the orbital floor, in which the musculature is lifted until finding the bony structures. Then, a part of the zygomatic bone and the maxillary bone are removed precisely under the orbital cavity, and the vascular and nervous structures of the anterior segment of the orbital roof are dissected.

In contrast with the original Caldwell-Luc procedure and the modifications proposed by Gönül *et al.*[15] and Rodríguez-Vargas & Guevara-Arroyo,[16] in the present study, a variation in the way of approaching the anatomical structures of the face and a cross section at the base of the skull in the superciliary arch were performed. The cross section was added to remove the anterior cranial fossa from the base of the skull to approach the structures of the orbital cavity from an upper view in an axial plane, as seen in Figure 5.

The proposed modification is based on a complete dissection of all the structures attached to the orbital cavity while advancing in depth, that is, skin, subcutaneous cellular tissue, muscles, bones, nerves and blood vessels, favoring learning of the cranial morphology and the extrinsic structures of the eye. Therefore, the modification proposed in this research is a new technique and a model for studying the anatomy of the orbital cavity and its contents.

The authors do not think that there were study limitations; however, they agree with Mora-Villate *et al.*[3] that the study of the orbital cavity morphology can be difficult since it is limited to virtual models and illustrations that do not offer a real impression of this structure and its contents. This shortcoming is solved by our proposal, as it has been proven that the use of dissection techniques improves the morphological learning of any anatomical structure.[3] Table 1 compares the original Caldwell-Luc procedure and previous modifications, and describes the relevance of the findings of this study.

**Table 1.** Comparison of the Caldwell-Luc procedure and related modified dissection techniques.

| Technique (year) | Approach | Objective | Access | Target dissection structures | Modification and innovation | Additional structures found |
|---|---|---|---|---|---|---|
| Original technique[9] | Surgical | Paranasal sinuses | Oral cavity, canine fossa | Maxillary sinuses | Original surgical procedure | Infraorbital nerve. Face and gums preserved |
| Gönül *et al.*[15] (2003) | Anatomical study | Maxillary sinuses | Transmaxillary approach | Maxillary sinuses | Modification | Face and nerves preserved |
| Rodríguez-Vargas & Guevara-Arroyo[16] (2013) | Anatomical study | Orbital floor | Transmaxillary approach | Orbital floor structures | Modification and innovation: resection of the maxillary and zygomatic bones | Rectus and inferior oblique muscles, infraorbital nerve |
| Muñoz-Castaño *et al.* (2018) * | Anatomical study for the teaching-learning process | Extrinsic structures of the eye contained in the orbital cavity | Bone resection, dissection with transmaxillary and transfrontal approach | Rectus muscles of the eye, levator palpebrae superioris, gland and oblique muscles, nerve structures | Modification and innovation: resection of the maxillary and zygomatic bones, cross section at the base of the skull | All extrinsic structures of the human eye, vascular and nerve structures of the face and base of the skull |

* Technique proposed by the authors of this study.
Source: Own elaboration based on [13], [15] and [16].

## Conclusion

The successful application of the modified Caldwell-Luc procedure described in the present study is a better tool for teaching and learning ocular anatomy. It allows observing many appendages of the eyes in situ and offers an opportunity to improve students' anatomical dissection skills.

## Conflicts of interest

None stated by the authors.

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# Validation of the FACT-Lym scale to measure quality of life in Colombian patients with lymphoma

*Validación de la escala FACT-Lym para la evaluación de la calidad de vida en pacientes colombianos con linfoma*

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## Abstract

**Introduction:** Instruments for measuring quality of life must be validated before being used in different cultural contexts. There is a specific scale (FACT-Lym) to assess health-related quality of life (HRQOL) in patients with lymphoma, but it has not been validated in Colombia yet.
**Objective:** To determine the clinimetric properties of the FACT-Lym scale in Colombian patients with lymphoma.
**Materials and methods:** A validation study of a scale was conducted based on the classical test theory. The FACT-Lym scale was administered to 301 patients diagnosed with different types of lymphomas and treated at the National Cancer Institute of Colombia, and their sociodemographic and clinical data were recorded. The statistical analysis included exploratory factor analysis, confirmatory factor analysis, construct validity, internal consistency, test-retest reliability and sensitivity to change.
**Results:** The exploratory factor analysis confirmed a two-factor structure of the scale, while the confirmatory analysis showed adequate adjustment of the model. Internal consistency was measured using the Cronbach's alpha coefficient (>0.8 on the global scale and on each of the factors). Correlation values significantly different from zero were found between the FACT-Lym scale and the FACT-G scale domains. No significant changes were observed in any domain of the FACT-Lym scale after the completion or suspension of treatment.
**Conclusions:** The validation of the FACT-Lym questionnaire in Colombia showed it has a consistent factorial structure and adequate reliability. However, its sensitivity to change should be verified by evaluating its performance in other patient groups.
**Keywords:** Quality of Life; Lymphoma; Surveys and Questionnaires; Validation Studies (MeSH).

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## Resumen

**Introducción.** Los instrumentos para medir la calidad de vida se deben validar antes de ser utilizados en diferentes contextos culturales. En la actualidad existe una escala específica (FACT-Lym) para medir la calidad de vida en pacientes con linfoma, sin embargo esta no ha sido validada en Colombia.
**Objetivo.** Establecer las propiedades clinimétricas de la escala FACT-Lym en pacientes colombianos con linfoma.
**Materiales y métodos.** Se realizó un estudio de validación de escalas según la teoría clásica de test. Se aplicó la escala FACT-Lym a 301 pacientes del Instituto Nacional de Cancerología diagnosticados con diferentes tipos de linfoma y se registraron sus datos sociodemográficos y clínicos. El análisis estadístico incluyó análisis factorial exploratorio, análisis factorial confirmatorio, validez de constructo, consistencia interna, confiabilidad test re-test y sensibilidad al cambio.
**Resultados.** El análisis factorial exploratorio confirmó una estructura de dos factores de la escala, mientras que el análisis confirmatorio mostró un adecuado ajuste del modelo estructural. La consistencia interna se midió con el coeficiente alfa de Cronbach (>0.8 en la escala global y en cada uno de los factores). Se encontraron valores de correlación significativamente diferentes a cero entre la FACT-Lym y los dominios de la escala FACT-G. No se observaron cambios significativos en ninguno de los dominios de la FACT-Lym luego de completar o suspender el tratamiento.
**Conclusiones.** La validación de la escala FACT-Lym en Colombia mostró que esta tiene una estructura factorial consistente y una adecuada confiabilidad. Sin embargo, su sensibilidad al cambio debe verificarse evaluando su desempeño en otras poblaciones.
**Palabras clave:** Calidad de vida; Linfoma; Encuestas y cuestionarios; Estudios de validación (DeCS).

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## Introduction

According to the World Health Organization (WHO), cancer is one of the leading causes of morbidity and mortality in the world, with 8.8 million deaths reported in 2015.[1] Lymphomas are a type of hematological malignancy with highly variable immunophenotypes, clinical and histological features and genetic abnormalities.[2] They are classified into two groups: Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL),[3] and about 500 000 diagnoses of NHL are made worldwide every year.[4]

As per the 2018 report by the Global Cancer Observatory (GCO), NHL had an incidence of 2.8% with 1 353 273 cases over a 5-year period (2013-2018), while HL had an incidence of 0.44% with 275 947 cases over a 5-year period (2013-2018).[5] In Colombia, as reported by the *Fondo Colombiano de Enfermedades de Alto Costo* (High Cost Diseases Fund), 7 507 and 1 770 patients over the age of 18 were diagnosed with NHL and HL, respectively, between 2015 and 2016.[6]

Although the clinical presentation of both types of lymphoma is similar, prognosis varies according to the subtype.[7] In NHL patients, the relative survival rate is 70% and 60% at 5 and 10 years, respectively,[8] while survival in HL patients depends on the stage of the disease: the relative 5-year survival rate is 90% for stages I and II, 80% for stage III, and about 65% for stage IV.[9,10] Advances in clinical and therapeutic management of patients with lymphoma, such as autologous and allogeneic stem cell transplants, improve progression-free survival in this disease.[11,12]

Even though lymphoma patients have specific concerns that generate physical, social, psychological, and functional deterioration,[13] to date, in Colombia there are no valid instruments that allow assessing health-related quality of life in this population. Quality of life is considered an outcome of cancer treatment and is used as a measure of well-being in patients with this disease.[14] The WHO describes quality of life as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns."[15,p3] To assess an individual's quality of life, it is necessary to take into account their subjective perceptions of health, their emotional response to the different situations they face, as well as their level of job satisfaction, their interpersonal relationships and their life purpose.[16] With this in mind, the concept of quality of life allows us to obtain information about the impact of the disease and its treatment on both the physical and emotional aspects of patients' lives.

According to the American Society of Clinical Oncology,[17] quality of life should be considered a priority outcome of treatment in oncology patients. Therefore, it should be considered for the development of clinical practice guidelines and the evaluation of new technologies for therapeutic purposes.

The scales suggested to measure quality of life in cancer patients include the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (EORTC QLQ-C30),[18] which is the most widely used instrument in this population,[19] and the Quality of Life Patient/Cancer Survivor Version (QOL-CSV) scale, designed based on an instrument to evaluate pain management in cancer patients.[20,21] On the other hand, the 36-Item Short Form Health Survey (SF-36), elaborated in the United States, seeks to evaluate the positive and negative states of health, and their implications in the quality of life of patients with different types of diseases.[22,23]

One of the few scales that measure quality of life in patients with lymphoma is the Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym) scale, developed by the Functional Assessment of Chronic Illness Therapy (FACIT) organization in 2005.[24] The literature reports on the original validation, carried out in 2013, and the validation carried out the same year in Greece;[25] however, the latter is partial as it does not take into account all the clinimetric properties of the instrument. The FACT-Lym scale is made up of the items included the generic module of the FACT-G scale[26,27] and by 15 specific items for physical and emotional symptoms of patients with lymphoma. These scales have been designed to be used both in clinical interviews and for self-administration.[28]

Due to the importance of evaluating quality of life in patients with lymphomas and the unavailability of adequately validated instruments to do so in Colombia, the objective of this study was to establish the clinimetric properties of the FACT-Lym scale in Colombian patients with lymphoma.

## Materials and methods

A validation study of scales following the classical test theory was carried out using the FACT-Lym questionnaire. Authorization from the FACIT organization, which was in charge of translating the scale into Spanish, was obtained before beginning with the study. The owners of this instrument do not authorize making new adaptations in Spanish since they already have one in this language, so no cross-cultural adaptation was required.

The sample was selected by convenience and 301 patients who met the following inclusion criteria were included: being >18 years old, verbally agreeing to participate, having a diagnosis of lymphoma at any stage confirmed by histology with or without treatment, and being treated at the *Instituto Nacional de Cancerología* (National Cancer Institute) between 2016 and 2018 in outpatient, inpatient, or emergency services. Patients with cognitive or sensory impairments that prevent understanding the questionnaire were excluded.

To estimate sample size, the PASS® program was used and all the components of the scale validation process were considered. The exploratory and confirmatory factor analysis was performed on a sample of 301 patients, taking into account the recommendation of MacCallum & Hong[29] of having at least 300 sample observations, using the PASS® program and including all the components of the scale validation process. To estimate concurrent validity, a sample size of 163 patients was calculated considering a Pearson's correlation coefficient of 0.2 for the null hypothesis ($H_0$) and 0.4 for the alternative hypothesis ($H_a$). To estimate the reliability of the instrument, and using the test-retest method, a sample size of 64 patients was defined, assuming a Lin correlation coefficient of agreement of 0.6 and 0.7 for $H_0$ and $H_a$, respectively.[30,31] To estimate the internal consistency of the scale, a sample size of 85 patients was established, taking Cronbach's alpha coefficient values of 0.5 and 0.7 for $H_0$ and $H_a$, respectively, and bearing

in mind that the FACT-Lym scale has 15 items.[32,33] Finally, in the sensitivity analysis, sensitivity to change was determined based on information from the study conducted by Hlubocky *et al.*,[24] in which, an effect size of -0.87 on the overall score of the FACT-Lym subscale was observed with sample sizes of at least 14 patients.

### Description of the questionnaire

The FACT-Lym instrument has two modules: one generic and one specific for lymphomas, consisting of 27 and 15 items, respectively. Its domains are physical well-being (7 items), social/family well-being (7 items), emotional well-being (6 items), functional well-being (7 items) and specific symptoms and concerns related to lymphoma (15 items). Each item has a scoring scale between 0 and 4, with 5 answer options (nothing, a little, some, a lot and very much). These instruments are designed by the FACIT organization in such a way that higher scores indicate a better level of quality of life for the patient in the final score.[34,35] The scale was completed by staff trained in its administration.

### Statistical analysis

Sociodemographic and clinical data were analyzed by means of descriptive statistics. They are presented using percentages, as well as means and medians with their corresponding standard deviations (SD) and interquartile ranges (IQR). The scale was validated according to classical test theory.

Content validity of the instrument was estimated through an exploratory factorial analysis, which allowed establishing the validity of its construct and, additionally, its domain structure. For the exploratory factorial analysis, the main components of the scale were analyzed based on the polychoric correlation matrix once the possible factorization of the matrix was defined with the Bartlett's test of sphericity and the Kaiser Meyer-Olkin (KMO) test, and the number of factors to be analyzed was determined using the optimal coordinate and the parallel analysis methods.[36] To determine the factorial structure, a presence of >0.3 factor loadings was taken into account. The ultimate solution factors were established by applying orthogonal and oblique rotations.[37]

Confirmatory factor analysis was performed using a polychoric correlation matrix and an asymptotic covariance matrix. Model fitting was evaluated using the following criteria with the specified values, which indicate a proper model fitting: ratio $\chi^2$/ degrees of freedom ($\chi^2$/gL: values <3), root mean square error of approximation (values <0.08), non-standard fit index (values >0.9), goodness of fit index (values >0.9), comparative fit index (values >0.9) and standardized root mean square residual (values <0.08).

The assessment of concurrent validity was performed by calculating Spearman's correlation coefficients[38] between the FACT-Lym and FACT-G scale domain scores. The internal consistency of the instrument was analyzed by means of Cronbach's alpha coefficient, which was estimated for the entire scale, for its domains and, also, when each of the items was removed.

To estimate the reliability of the instrument, the test-retest method was used to evaluate the data after administering the questionnaire for the second time to 64 patients, which took place 4 to 10 days after the first time. The data from the second administration were analyzed by means of the Lin's concordance correlation coefficient. Finally, sensitivity to change was measured by comparing the scores obtained before starting the treatment scheme and after its completion or suspension, and was tested using the paired t-test with a two-tailed test and considering a significance level of 5% for hypothesis testing. The statistical analysis procedures were carried out with the R software.

### Ethical considerations

The ethical principles for biomedical research established in the Declaration of Helsinki[39] were followed. According to Resolution 8430 of 1993 of the Ministry of Social Protection, this study is classified as low risk.[40] The study was approved by the Ethics Committee of the Instituto Nacional de Cancerología through Minutes No. 015 of August 21, 2015.

## Results

As for the sociodemographic variables, the average age was 56.7 years (SD=16.4 years), 54.82% were women and 61.4% were classified in the socioeconomic strata 1 and 2 (Table 1). It should be noted that in Colombia, socioeconomic status is classified into strata that range between 1 and 6, being 1 the lowest and 6 the highest (Table 2).

**Table 1.** Socio-demographic characteristics of the study population.

| Variables | | n | % |
|---|---|---|---|
| Sex | Female | 165 | 54.82 |
| | Male | 136 | 45.18 |
| Marital status | Single | 73 | 24.5 |
| | Common-law marriage | 73 | 24.25 |
| | Married | 104 | 34.55 |
| | Divorced | 20 | 6.64 |
| | Widower | 31 | 10.30 |
| Socioeconomic Stratum | 1 | 73 | 24.25 |
| | 2 | 112 | 37.21 |
| | 3 | 100 | 33.22 |
| | 4 | 15 | 4.98 |
| | No data | 1 | 0.33 |
| Occupation | Home | 92 | 30.56 |
| | Unemployed | 66 | 21.93 |
| | Freelancer | 53 | 17.6 |
| | Employed | 48 | 15.95 |
| | Retired | 34 | 11.30 |
| | Student | 8 | 2.66 |

**Table 1.** Socio-demographic characteristics of the study population. (continued)

| Variables | | n | % |
|---|---|---|---|
| Place of origin | Bogotá D.C. | 174 | 57.81 |
| | Cundinamarca | 47 | 15.61 |
| | Boyacá | 28 | 9.3 |
| | Tolima | 20 | 6.64 |
| | Atlantic Coast | 11 | 3.65 |
| | Eastern Plains and Amazon | 12 | 3.98 |
| | Other | 9 | 2.99 |

Source: Own elaboration.

**Table 2.** Socioeconomic strata in Colombia according to the National Administrative Department of Statistics

| Stratum | Description |
|---|---|
| 1 | Low-low. Beneficiaries of home utility subsidies. |
| 2 | Low. Beneficiaries of home utility subsidies. |
| 3 | Middle-low. Beneficiaries of home utility subsidies. |
| 4 | Middle. They are not beneficiaries of subsidies, nor do they pay surcharges; they pay exactly the amount that the company defines as the cost for providing home utilities. |
| 5 | Middle-high. They pay surcharges (contribution) on the value of home utilities. |
| 6 | High. They pay surcharges (contribution) on the value of home utilities. |

Source: Elaboration based on the data issued by National Administrative Department of Statistics.[41]

With respect to the clinical variables, 256 patients (85%) were diagnosed with NHL and 45 with HL (14.9%). 19.6% of patients were in stage IVb of the disease, 16% in stage IV, 9% in stage IIIb, 7.67% in stage IIb, and 4% in stage I. Of the total amount of patients, 270 (90%) had received chemotherapy; 47 (15.6%), biological therapy; 22 (7.33%), palliative care; and 19 (6.33%), autologous transplant.

## Description of FACT-Lym scale scores and items

After applying the scale scoring algorithm, it was found that the items with the highest scores reached a median of 3. The items that had a lower median and, therefore, influenced a lower level of quality of life were: "I feel pain in certain parts of my body", "I have trouble sleeping at night", "I get tired easily", "I worry about getting infections" and "I am concerned about having new symptoms associated with the disease." Table 3 describes the scores and items on the FACT-Lym scale.

**Table 3.** Characteristics of the scores and items on the scale.

| ID | Item | Median | IQR |
|---|---|---|---|
| BRM3 | I have episodes of fever that bother me | 3 | 1 |
| LYM1 | I am bothered by the itching | 3 | 1 |
| ES3 | I get night sweats | 3 | 1 |
| P2 | I feel pain in certain parts of my body | 2 | 2 |
| HI8 | I have difficulty concentrating | 3 | 1 |
| C2 | I am losing weight | 3 | 1 |
| GA1 | My appetite has decreased | 3 | 1 |
| LYM2 | I have trouble sleeping at night | 2 | 1 |
| LEU1 | I feel discomfort because of the lumps I have in some parts of my body | 3 | 1 |
| BMT6 | I get tired easily | 2 | 2 |
| N3 | I am worried about getting infections | 2 | 2 |
| LEU6 | I am concerned about having new symptoms associated with my disease | 2 | 2 |
| LEU4 | Because of my illness, it is difficult for me to plan for the future | 3 | 1 |
| BRM9 | I have emotional ups and downs | 3 | 1 |
| LEU7 | I feel isolated from other people because of my illness or treatment | 3 | 1 |

ID: identifier; IQR: interquartile range.
Source: Own elaboration.

## Exploratory factor analysis

The results obtained with the Bartlett's test of sphericity ($\chi^2$ (105) = 1632.935; $p<0.005$) and the KMO test (0.879) allowed concluding that the matrix had an adequate structure for factor analysis. Given the amount of eigenvalues >1 and the characteristics of the eigenvalue sediment graph, and based on the results obtained with the parallel analysis and optimal coordinate methods , it was concluded that bi-factor analysis was the most suitable to perform the exploratory factor analysis. From the value of each factor loading and according to the interpretability of the different factor solutions, an orthogonal rotation (varimax) was selected. The uniqueness values were below 0.60. Table 4 presents the factor structure of the subscale, in which two domains are differentiated: one of symptoms specific to the disease and one related to patient concerns.

**Table 4.** Factor structure of the specific subscale (FACT-Lym).

| ID | Item | Factor 1 | Factor 2 | Uniqueness |
|---|---|---|---|---|
| BRM3 | I have episodes of fever that bother me | 0.77 | | 0.40 |
| LYM1 | I am bothered by itching * | 0.75 | | 0.43 |
| ES3 | I get night sweats * | 0.68 | | 0.48 |
| P2 | I feel pain in certain parts of my body * | 0.68 | | 0.48 |
| HI8 | I have difficulty concentrating * | 0.60 | 0.44 | 0.45 |
| C2 | I am losing weight * | 0.60 | 0.43 | 0.46 |
| GA1 | My appetite has decreased* | 0.59 | 0.47 | 0.46 |
| LYM2 | I have trouble sleeping at night * | 0.57 | 0.31 | 0.58 |
| LEU1 | I feel discomfort because of the lumps I have in some parts of my body * | 0.55 | 0.31 | 0.59 |
| BMT6 | I get tired easily * | 0.55 | 0.42 | 0.52 |
| N3 | I am worried about getting infections † | | 0.87 | 0.24 |
| LEU6 | I am concerned about having new symptoms associated with my disease † | | 0.86 | 0.23 |
| LEU4 | Because of my illness, it is difficult for me to plan for the future † | 0.38 | 0.72 | 0.34 |
| BRM9 | I have emotional ups and downs † | 0.42 | 0.67 | 0.37 |
| LEU7 | I feel isolated from other people because of my illness or treatment † | 0.47 | 0.53 | 0.49 |

ID: identifier.
* Symptoms of the disease domain.
† Emotional and social component domain.
Source: Own elaboration.

## Confirmatory factor analysis

Figure 1 shows the characteristics model for the factorial structure of the FACT-Lym scale. The ovals represent the domains (emotional component and disease symptoms), and the rectangles represent the FACT-Lym scale items (each item is represented with its identifier). Dates marked with a single point indicate the causal relationship between the domain and each of the items, the arrows with double points represent the correlations between domains, and the arrows in dashed lines correspond to loadings that are set with a value of 1 to estimate the coefficients of the models. With respect to the estimators of the equation model, the following results were obtained: $\chi^2/gL=0.803$; RMSEA=0.000, NNFI=1.010, GFI=0.981; CFI=1 and SRMR=0.062, which showed proper fit of the internal structure of the model.

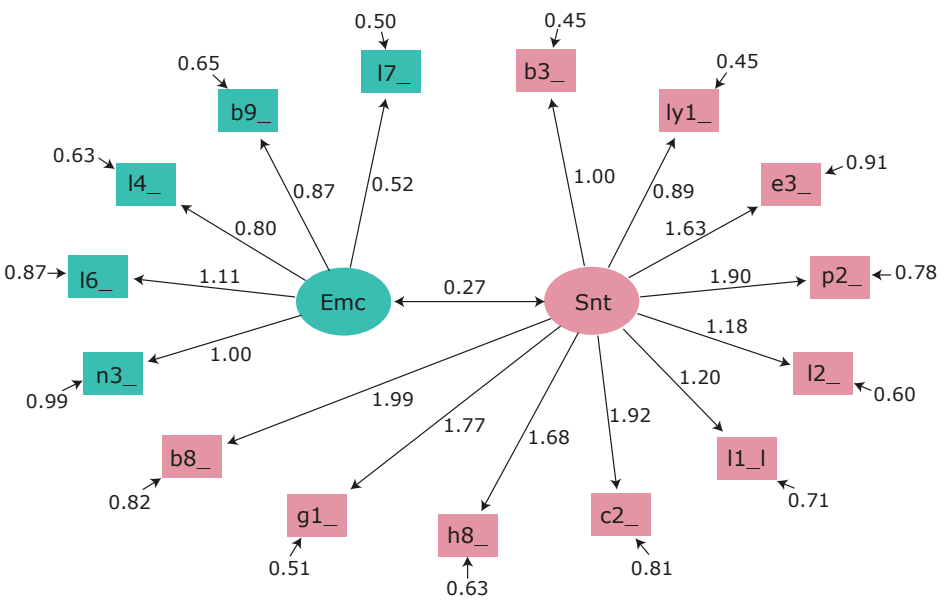


**Figure 1.** Characteristics of the factor structure of the FACT-Lym scale (system of structural equations).
Emc: emotional; Snt: symptoms.
Source: Own elaboration.

### Concurrent validity

Concurrent validity was assessed in 301 patients based on the scores obtained in the four domains of the FACT-G scale: physical well-being; social/family well-being; emotional well-being; and functional well-being. The values of the correlation coefficients were between 0.24 (correlation with social and family well-being) and 0.73 (physical well-being) (Table 5), so plausible values were considered in the correlation between the four domains of the FACT-G scale and the FACT-Lym subscale. All coefficients were significantly different from 0.

**Table 5.** Correlation between the four domains of the FACT-G scale and the FACT-Lym subscale.

| Pair correlations | | Spearman's correlation coefficient | 95%CI | |
|---|---|---|---|---|
| Physical | Lymphoma | 0.734 | 0.677 | 0.782 |
| Social | Lymphoma | 0.241 | 0.132 | 0.345 |
| Emotional | Lymphoma | 0.688 | 0.624 | 0.743 |
| Functional | Lymphoma | 0.497 | 0.407 | 0.578 |

Source: Own elaboration.

### Internal consistency

The scale had a coefficient α=0.882. The alpha values did not increase when any of the items were removed. Additionally, a coefficient of α=0.8 was found for the mood and/or worry domain and a coefficient of α=0.84 for the fitness domain.

### Reliability calculated with the test-retest method

The reliability of the instrument was evaluated in 64 patients, with an average of 7 days between the two evaluations (SD=1.8 days). The medians of the initial evaluation and subsequent measurement were 36 (IQR=11) and 37 (IQR=9), respectively; the difference between them was not significant (Wilcoxon-signed rank test: Z=-1.12, p=0.26). Lin's concordance correlation coefficient was 0.8 (95%CI: 0.78-0.92). Agreement limits obtained with the Bland-Altman method were between -11.45 and 9.3.

### Sensitivity to change

Sensitivity to change was analyzed with data from lymphoma patients between 30 and 60 days after completing or discontinuing treatment, either due to side effects or administrative procedures that did not allow for continuity. For patients treated with allogeneic or autologous stem cell transplants, sensitivity to change was evaluated between 90 and 120 days after the procedure. Table 6 shows the means obtained at each measurement for each domain, which were similar in the two evaluation moments. There were no statistically significant differences (p>0.05 in all paired t-tests performed); this trend is maintained for all subscales developed by the FACIT organization.

**Table 6.** Comparison of the scores between domains before and after the end or suspension of treatment.

| Domain | Measurement before end or suspension of treatment * Mean (σ) | Measurement after end or suspension of treatment* Mean (σ) |
|---|---|---|
| Physical | 20.46 (4.96) | 20.83 (5.94) |
| Social | 21.7 (5.98) | 19.4 (7.02) |
| Functional | 18.33 (4.67) | 18.46 (3.71) |
| Lymphoma | 30.56 (9.8) | 30.26 (9.34) |
| Emotional | 18.73 (4.05) | 18.46 (3.71) |

* The differences between means before and after the end or suspension of treatment were not significant (p>0.05).
Source: Own elaboration.

## Discussion

Health-related quality of life is a concept used to measure the general well-being of patients, which makes it necessary to have valid and reliable instruments to assess the psychosocial aspects of an individual and their influence on health status. Therefore, the FACT-Lym scale was validated in this study to evaluate quality of life in lymphoma patients since it had not been previously done in Colombia.

Most patients included in this study were women, which coincides with the data presented by the *Fondo Colombiano de Enfermedades de Alto Costo*,[6] which reports that the majority of lymphoma cases in the adult Colombian population occur in women. In terms of the clinical characteristics of the patients included, most were in advanced stages of the disease and had received chemotherapy. The most frequent subtype was NHL, which coincides with the data reported by the Global Cancer Observatory.[5]

Regarding the results obtained in the items of the scale, it has been suggested that the items: "I feel pain in certain parts of my body", "I have trouble sleeping at night", "I get tired easily", "I am worried about getting infections" and "I am concerned about developing new symptoms associated with the disease" may be associated with a lower quality of life in patients and, consequently, represent an important marker of quality of life in this population since the medians obtained for these items were low. However, further studies should be conducted using other methods, such as the Rasch model, to test this hypothesis.

The exploratory factor analysis showed that the FACT-Lym subscale has a simple structure consistent with the FACT-G scale; this analysis allowed establishing two domains: physical condition and specific concerns. Moreover, since the factor loading values were adequate and the uniqueness values were within the recommended ranges, it was concluded that all items in the FACT-Lym subscale are appropriately represented in the factorial structure, suggesting that there were no maladjusted or redundant items in the specific component of the scale.

In terms of internal consistency, the results obtained for the total scale and for each of the items indicated

that the FACT-Lym scale has adequate reliability, a result that is consistent with the study by Hlubocky *et al.*,[24] who reported alphas between 0.90, 0.93, and 0.95 on this subscale. With respect to sensitivity to change, no statistically significant differences were observed between the results before and after treatment; however, the differences found in the two measurement moments were very little, and no changes were observed in the other subscales of the FACT-G scale, an instrument that has already been validated and that has adequate sensitivity to change; therefore, it was concluded that the lack of differences is explained by the stability of the construct and not by a clinimetric defect of the scale

Finally, most of the patients included in the study had a low socioeconomic level. This could be a selection bias of the study because perceptions or interpretations related to the socioeconomic situation may have been excluded.

## Conclusions

The validation of the FACT-Lym scale in Colombia showed that it has a consistent factorial structure and adequate reliability. However, its sensitivity to change must be confirmed by evaluating the scale's performance in other populations.

## Conflicts of interest

None stated by the authors.

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# Narrative inquiry and quality of life in women with rheumatoid arthritis

*Indagación narrativa y calidad de vida en mujeres con artritis reumatoide*

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## Abstract

**Introduction:** Rheumatoid arthritis (RA) has a strong impact on work capacity and quality of life. The prevalence of RA is higher in women in their third and fourth decades of life. In order to understand how RA patients perceive their quality of life, it is necessary to consider their experiences and the meanings they give to their condition as chronic patients. This process also provides relevant information for implementing strategies that contribute to solving their needs and improving their quality of life.
**Objective:** To describe the perceptions of women with RA about their quality of life.
**Materials and methods:** Qualitative descriptive study conducted on a sample of 36 women diagnosed with RA who were administered in-depth interviews. Data were organized using the AtlasTI program; on the other hand, the narrative inquiry and the interpretive analysis were carried out according to Ricoeur and Benner, respectively.
**Results:** The narrative inquiry of the participants' stories allowed them to describe their quality of life as a state of well-being despite being affected by the disease. The analysis of the narratives told by the participants made evident the need for social security and protection, considering the multiple difficulties faced by people with RA in the current Colombian health system.
**Conclusion:** The results of this study may be regarded as a contribution to the humanization of health service delivery since they will allow health professionals to reflect on how to approach quality of life from a psychosocial and humanistic perspective.
**Keywords:** Rheumatoid Arthritis; Life Quality; Qualitative Research (MeSH).

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## Resumen

**Introducción.** La artritis reumatoide (AR) es una enfermedad que afecta la capacidad laboral y la calidad de vida; su prevalencia es mayor en mujeres entre la tercera y la cuarta década. Para comprender cómo los pacientes con AR perciben su calidad de vida, es necesario considerar sus experiencias y los significados que dan a su condición de enfermo crónico, además este proceso permite obtener información relevante para implementar estrategias que contribuyan a solucionar sus necesidades y mejorar su calidad de vida.
**Objetivo.** Describir las percepciones de mujeres con AR sobre su calidad de vida.
**Materiales y métodos.** Estudio descriptivo cualitativo realizado en una muestra de 36 mujeres diagnosticadas con AR a quienes se les realizaron entrevistas a profundidad. Los datos fueron organizados mediante el programa AtlasTI; la indagación narrativa y el análisis interpretativo fueron realizados de acuerdo con lo propuesto por Ricoeur y Benner, respectivamente.
**Resultados.** La indagación narrativa de los relatos de las participantes les permitió describir su calidad de vida como un estado de bienestar a pesar de que esta se ve afectada por la enfermedad. En el análisis de las narrativas se evidenció que la necesidad de protección y seguridad social es un fenómeno producto de las múltiples dificultades que las personas con AR afrontan en el actual sistema de salud de Colombia.
**Conclusión.** Los resultados reportados en este estudio pueden considerarse como un aporte para la humanización de la prestación de los servicios de salud, puesto que permitirán a los profesionales de la salud reflexionar sobre cómo abordar la calidad de vida desde un enfoque psicosocial y humanístico.
**Palabras clave:** Artritis reumatoide; Calidad de vida; Investigación cualitativa (DeCS).

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## Introduction

For patients with rheumatoid arthritis (RA), quality of life is a relevant concept that is directly related to the level of satisfaction they have with their lifestyle, beyond the physical consequences of the disease.[1,2]

RA affects the quality of life of the people who suffer from it, as well as their working potential and, therefore, their general well-being. In some cases, it can cause premature mortality, which is why it is considered a public health problem.[2] This disease is more common in women (with a female to male ratio of 3:1), particularly in their third to fourth decade of life.

Due to the great economic burden it generates for society, RA is considered a high-cost disease. In this regard, Birnbaum *et al.*[3] reported that it had a direct cost of $19.3 billion in the U.S. in 2005, money that was allocated to employers (33%), patients (28%), government (20%) and caregivers (19%).

Early diagnosis and timely initiation of treatment contribute positively to the quality of life and well-being of people with RA, as the perception of the disease improves, and life expectancy increases when the health condition is stable.[4]

Considering perceptions from a qualitative approach leads to comprehending the congruence or disparity between the opinions of the patient, the family, and the health care provider, which is useful to know the benefits and risks that are not detected using other study methodologies.[4,5] Likewise, recognizing the experiences and meanings that people give to their chronic illness allows understanding life from their point of view and learning relevant information to implement processes that help solve their needs and, therefore, improve their quality of life.

Exploring the narratives that describe the experience of living with a chronic disease allows, on the one hand, to know the perception that this type of patients have about the quality of life and, on the other hand, to make contributions to the development of a comprehensive, worthy and humanized care, represented in socially responsible and people-centered care.[6] In this sense, the objective of the present study was to describe the perceptions of women with RA about their quality of life.

## Materials and methods

Qualitative descriptive study in which a narrative inquiry methodology was implemented. It was used to conduct a phenomenological analysis based on the understanding of the contexts, facts, and truths that people exposed when asked about their experience as RA patients.[7]

To select the participants, all women with a diagnosis of RA who attended the outpatient service of the reference center where the study was conducted (in Bogotá D.C., Colombia) and had a HAQ (Health Assessment Questionnaire) score of 3 at the time of the interview, that is, markedly impaired functional capacity, and no cognitive impairments, were considered.

Data was collected through in-depth interviews according to the following questions: What is the meaning of the experience of living with the disease? Based on your experiences with arthritis, what has happened to your quality of life? What are the most important needs you have in your everyday life after being diagnosed with arthritis? Similarly, during the administration of the instrument, the participants were given a socio-demographic characterization card designed by the researchers so that they could fill it out and provide information on age, educational level, marital status, and occupation.

The interviews, which were conducted between March and September 2014, took between 18 and 60 minutes and were recorded, transcribed verbatim and transferred to the AtlasTi software. Immediately after the end of the interview, the researchers made a field journal reflection that was self-recorded and transcribed; at the end, 42 field journal notes were transcribed.

The interpretative analysis was carried out according to the method proposed by Benner[8] and following the guidelines for content analysis[9] and narrative inquiry[10] described below:

1. *Transcription of interviews.* Each interview was recorded and transcribed verbatim, line by line and individually, to capture the meanings contained in the narratives.
2. *Thematic analysis.* The narratives were read and reread in depth as many times as necessary to obtain a global interpretation and to establish the most relevant themes.
3. *Narrative analysis.* The life stories of the interviewees were considered for the interpretative analysis. All the narratives were included in a universe of perceptions where every situation shared by the participants was relevant. In addition, each patient's ideology, concerns, and opinions were deemed as the central input for narrative inquiry.
4. *Identifying patterns of meaning.* The aim was to discover the richness of the narrative meanings to understand the experiences of each patient.

The study followed the ethical principles for medical research on human subjects established by the Declaration of Helsinki[11] and the provisions on health research of Resolution 8430 of 1993;[12] in addition, it was approved by the Research Ethics Committee of the Faculty of Nursing of the Universidad Nacional de Colombia, as stated in Minutes No. 1 of January 24, 2011. Once patients were informed about the objective, possible risks, and procedures to be performed, and agreed to participate in the study, they signed an informed consent.

To keep the anonymity of the participants, each one was identified with the letter "p" and a number assigned according to the order in which they entered the project.

Finally, the authors report that this article derives from the doctoral thesis entitled *Calidad de vida y nivel de salud percibido en personas con artritis reumatoide* (Quality of life and perceived health level in people with rheumatoid arthritis).[13]

## Results

The sample was made up of 36 women between the ages of 32 and 76, of whom 15 were married, 7 were divorced, 9 were single, and 5 were widowers. The majority (n=27) of the participants had basic education, 5 had some technical studies and 4 had university studies. With respect to their occupation, 11 women were retired, 3 were unemployed, 10 were housewives, 6 were employees, and 6 said they were freelancers.

The women interviewed expressed through their experiences what living with RA means to them. Based on the analysis of these narratives, the stories were

classified into three categories: "Perception of quality of life for women living with RA", "Perception of lack of protection and vulnerability when living with RA" and "Care needs of people with RA". The characteristics of each of these categories, which are supported by some of the participants' stories, are described below:

### Perception of quality of life for women living with RA

According to their stories, the interviewees perceive their quality of life as an "optimal" state of well-being that allows them to live well despite the disability caused by RA. For these women, having a stable health condition, that is to say, having the disease under control, means not feeling pain, being able to handle the symptoms, facing crises in the best possible way, and feeling good and happy in spite of what they are going through.

> "Sometimes I can't go out because of the pain, but I try to stay active in my house regardless of the symptoms" (p2).
> "When pain crises and digestive discomfort occur, it is very difficult to manage the disease, but that is my life story, it is up to me to face this" (p4).
> "Trying to be happy and thinking that things will get better. It is not (sic) all the time, only when I eat meat or when I do housework" (p19).
> "In this situation, I can say that my life is visiting doctors and hospitals" (p8).

### Perception of lack of protection and vulnerability when living with RA

Lack of protection is perceived as a fact that represents the multiple difficulties faced by women with RA in the current health system. According to the interviewees, there is no timely, quality, and comprehensive treatment that considers this disease as a pathology that affects all aspects of the life of those who suffer from it.

> "Going through so many medical services, tests, medications [...] every doctor looks at one part" (p5).
> "I could not use public transport again, people are not supportive, there are no mechanisms to facilitate access to a pension or support for the expenses generated by specialized care when living outside the city" (p31).

This category also includes the concept of vulnerability, which was described by the interviewees as the perception of fragility in the context of a chronic disabling disease that forces a change in routines and lifestyle in a struggle to preserve autonomy.

> "This disease changes your life. You can no longer do the same things you did before; you have to learn to survive" (p33)

In this sense, suffering from this disease brings with it the perception of vulnerability at both the individual and social levels. Similarly, feeling as a burden to the family and not being able to accept reality are facts with which the interviewees live daily.

> "It is not easy to get used to see the deformity of the hands. Sometimes I dream with my life before using the wheelchair, I would like to go back to that time" (p7).
> "Not being able to exercise my role as a mother, losing my job, not having a pension, these things affect me a lot. It's like being broken" (p6).

### Care needs of people with RA

Study participants expressed multiple care needs, which can be interpreted as a lack of social support, affection, disease management skills, and social protection and security. In this sense, social relationships, especially with family and friends, are regarded as a need to maintain a social bond to deal with the disease and the main support to address uncertainty.

> "Talking or listening to my visiting relatives is very important [...] I don't leave the house much, but I am always communicating by phone or text" (p22).
> "The help and company of the family is fundamental to live with the disease every day" (p4).
> "I try to think calmly about my future, although I don't know what complications will happen later, or if one day I will wake up unable to get out of bed" (p17).

In addition to family and friends support, the interviewees talked about the need to be recognized as chronically ill and request help from the State.

> "I have had many disabilities in my job and my bosses think very little of my situation. They have not changed my duties and only hope that I will retire soon [...] Because of the disabilities, I almost lost my job and now I have many economic difficulties" (p23).
> "I feel unprotected, without any support from the state, I only count on my mother and she is already an old person" (p29).

According to the stories analyzed, it was also evident that the interviewees need to feel supported and loved even though their health condition affects their physical image, that is, they feel the need for affection. It was also important for them to manifest and channel their feelings and, in this way, strengthen their emotional state and mental health.

> "When I can, I vent to a neighbor. She is the only person I can talk to about my fear of being disabled [...] I am very concerned about my financial future, not being a productive person because of the damage to my hands" (p14).
> "When the days are of pain and inflammation, it takes time to assimilate that situation [...] it is a very overwhelming condition" (p9).
> "The company of my dog is fundamental [...] he accompanies me unconditionally" (p35).

Similarly, participants noted that, to participate in activities related to their health care, they must have appropriate and extensive knowledge of RA, its treatment, and the potential to improve their quality of life. In this regard, they stated, among other ideas, that they would like to participate in support groups to learn about the experiences of other people with the same disease, be aware of scientific advances in the treatment of RA and receive information on alternative therapies for its management.

"I would like to have a space to share with other sick people and learn tips so that the symptoms do not win" (p36).
"I want to learn relaxation techniques and exercises to do at home [...] I am interested in learning how to handle crises with tranquility, do some therapy" (p32).
"I would like to learn more about new treatments and medical advances" (p33).

Finally, in all the stories, the need for protection and social security perceived by the interviewees was evident, since these women have to face various difficulties to access health services in their daily lives, which evidences failures in the quality and timeliness of care.

"So many procedures that limit access [...] I always have to do lines again, they do not give me all the medications" (p8).
"I am authorized to pick the medication in one place, and it is delivered in another. So many trips cause me fatigue and pain [...] Every time I am assigned a control appointment, I see a new specialist" (p36).
"It is very frustrating when they do not authorize the appointment with a specialist, the continuity is lost. Medical appointments take more than four to six months" (p1).

## Discussion

The narratives of the interviewees reveal the condition of vulnerability that people with RA experience. They also reflect the burden that a chronic disease entails in terms of changes in their lifestyles and the way they deal with the symptoms and disability resulting from the progression of the disease, as well as the socialization problems caused by this situation.[14]

Social impact is evident in the costs of medication and travel (difficulties in accessing public transportation) and in the decrease in income due to job instability. These situations increase the perception of feeling a burden on the family, as stated by one of the participants when she said that not being able to work or fulfill her role as a mother affects her greatly. In this regard, some studies agree that RA affects both patients and their families, as daily routines, financial burdens, and relationships between family members and their primary roles are altered.[15-17]

Interviewees said that they experience feelings such as fear, anger, frustration, uncertainty, and sadness, which they avoid expressing in front of their loved ones. In this regard, Fallatah & Edge[18] point out that the scale of emotions experienced by both patients and families is not only evident during the diagnostic phase of the disease, but also when exacerbations and crises occur. For this reason, it is fundamental to explore this component and, in this way, generate spaces in which those suffering from RA can express what they are feeling and receive support for the resolution of their problems. The participants also expressed the need for more humanized care and invited to reflect on strategies that contribute to improving the quality of life from a humanistic perspective.

Concerning the perception of lack of protection, the impact of the difficult access to the health system[19] and, particularly, specialized care services, is evident, as it may generate complications and reduce opportunities to treat and mitigate systemic effects and joint damage.[20-22] In summary, it is clear that there is a need for more quality health services that provide more humane, timely, and comprehensive care.

Participants described quality of life as a state of well-being and happiness that allows them to "live well" despite the severity of their condition and the disabilities that can result from the disease.[23] According to them, in order to have proper care of the disease and meet their need for a better quality of life, active communication[24] between the treating health team and the patient is required.[25]

Slade *et al.*[26] state that trust is a determining factor for adherence to therapies and that consultations should, therefore, be oriented towards patient perceptions and interpretation of suggested guidelines. Also, Rees & Williams[27] point out that patients should be able to discuss their own perceptions of care actions (including lifestyle management) with a professional who is willing to listen and has the time to do so.

Since a patient's autonomy is the most reliable and accurate source of information about their physiological function and symptoms, it is also the focus of self-management interventions.[28] This shows the importance of developing comprehensive care focused on the particular needs of each person.

The analysis of the reports obtained revealed some needs that, when solved, can facilitate the confrontation of RA and all that it entails, which coincides with what Fallatah & Edge reported.[18] However, the multiple care needs involving social and emotional dimensions reflect the impact of coping with a chronic condition, a finding also reported by Withall *et al.*[29] Furthermore, the patients interviewed said that they are interested in participating in follow-up programs that strengthen their security and confidence, and in developing coping strategies with self-defined objectives.

According to the findings of this study, health care centers should consider people with chronic diseases as patients requiring continuous health care. Consequently, patients must move from a paradigm of individual health care to a comprehensive one, in which the capacities of each human being are recognized and strengthened, the difficulties resulting from the disease are mitigated, and not only the disease as such is valued but also the experience of each individual.

The limitation of this study is that it was conducted in a single rheumatology care center, which is why it is necessary to develop new research to expand knowledge about the experience of living with RA in a health system such as the Colombian system.

## Conclusions

The results of this study show the complexity of the impact that RA has on women's lives and can be considered as a contribution to the humanization of health service delivery. They should encourage health professionals to reflect on how to approach quality of life from a psychosocial and humanistic approach, as well as to understand the needs for care and accompaniment in the process of coping with the disease.

The interviewees expressed their desire to feel more informed and involved in their symptom control process and in the search for alternatives to achieve self-management considering their health condition. Therefore, research efforts must be directed towards

comprehensive and participatory care that allows RA patients to live the reality of their disease from a positive perspective.

## Conflicts of interest

None stated by the authors.

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# Exclusive breastfeeding counseling at Women and Children Friendly Institutions of Bogotá D.C., Colombia

*Consejería en lactancia materna exclusiva en Instituciones Amigas de la Mujer y la Infancia de Bogotá D.C., Colombia*

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## Abstract

**Introduction:** Exclusive breastfeeding is still limited in Colombia. Despite the strategies implemented to promote it, the goal established by the World Health Organization (WHO) regarding this practice is far from being achieved.
**Objective:** To describe the current situation of exclusive breastfeeding counseling at Women and Children Friendly Institutions (WCFI) of Bogotá D.C., Colombia.
**Materials and methods:** Cross-sectional descriptive study conducted in a sample of 76 counselors from 12 WCFI institutions who were administered a semi-structured questionnaire with open and closed questions. Descriptive statistics were used to analyze the numerical and categorical variables, and the NVivo 10 software was used to analyze the answers obtained through open questions.
**Results:** Qualified nurses and nursing assistants had the most contact with breastfeeding mothers (84% and 42% respectively). 91% of the participants had not been trained in exclusive breastfeeding counselling according to the WHO guidelines, while 60% of the sample considered that counseling only meant teaching and providing information to mothers on how to breastfeed.
**Conclusion:** Breastfeeding counseling training is focused on providing information on how to breastfeed, but not on developing counseling skills. Furthermore, there is no consensus among health staff that works as breastfeeding counselors about what exclusive breastfeeding counseling is.
**Keywords:** Counseling; Health Facilities; Breastfeeding; Health Personnel (MeSH).

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## Resumen

**Introducción.** En Colombia la práctica de la lactancia materna exclusiva es baja y, pese a las estrategias implementadas para promoverla, aún falta mucho para cumplir con la meta establecida por la Organización Mundial de la Salud (OMS).
**Objetivo.** Describir la situación actual de la consejería en lactancia materna exclusiva (CLME) en Instituciones Amigas de la Mujer y la Infancia (IAMI) de Bogotá D.C., Colombia.
**Materiales y métodos.** Estudio descriptivo transversal. La muestra estuvo constituida por 76 consejeros (miembros del personal en salud) de 12 IAMI, a quienes se les aplicó una encuesta semiestructurada con preguntas cerradas y abiertas. Para el análisis de las variables numéricas y categóricas se empleó estadística descriptiva y para analizar las respuestas obtenidas mediante preguntas abiertas se usó el software N-Vivo versión 10.
**Resultados.** Los enfermeros y los auxiliares de enfermería fueron los consejeros que tuvieron mayor contacto con las madres lactantes (84% y 42% respectivamente). El 91% de los participantes no contaba con formación en CLME según los lineamientos de la OMS, mientras que para el 60% la consejería significaba enseñar o brindar información a las madres sobre cómo lactar.
**Conclusión.** La formación en consejería en lactancia materna se centra en brindar información sobre cómo lactar, mas no en desarrollar habilidades de consejería; además, no hay un consenso entre el personal de salud que se desempeña como consejero en lactancia materna sobre lo que significa la CLME.
**Palabras clave:** Instituciones de salud; Lactancia materna; Personal de salud (DeCS).

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## Introduction

According to official figures, early initiation of breastfeeding (BF) and exclusive breastfeeding (EBF) up to the 6th month of life of the baby is not common in Colombia. Furthermore, the practice of EBF is actually decreasing: the 2010 National Nutritional Status Survey[1] reported that only 57% of babies started BF in the first hour after birth; the 2010 National Demographic and Health Survey[2] established that the median time of BF went from 2.2 months in 2005 to 1.8 months in 2010; and finally, the 2010 National Nutritional Status Survey[3] showed that the prevalence of BF went from 42.8% in 2010 to 36.1% in 2015.

One of the strategies implemented to promote BF in Colombia are the so-called Women and Child Friendly Institutions (IAMI by its acronym in Spanish), which are an adaptation of the program *Hospital Amigo de los Niños* (Children's Friendly Hospital). These institutions seek to encourage the practice of BF by fulfilling the *Ten Steps to Successful Breastfeeding* proposed by UNICEF.[4,5] These steps include breastfeeding counseling (BFC), an initiative implemented in the last 20 years to promote BF,[6,7] and its effectiveness is evident in the beginning, exclusivity, and duration of BF.[8-11]

In the IAMIs, counseling is regarded as a fundamental strategy for teaching mothers about the best way to feed their children, always taking into account what they feel and respecting their beliefs and needs.[12] Therefore, the health staff of these institutions are a fundamental actor for the fulfillment of the *Ten Steps*, from prenatal check-ups to hospital discharge, in what is called exclusive breastfeeding counseling (EBFC).

Colombia has guidelines that promote, protect, and support BF.[13,14] They specifically state that counseling should involve maternal and child care; however, the definition of said concepts and the way it should be done is not clear. In 2011, the relevance of the BFC was recognized, so the Ministry of Health and Social Protection of Colombia included the EBFC within the activities of health care and declared it as mandatory; this was ratified in 2018 through Resolution 3280.[15] Nevertheless, its execution has been challenging since the implementation of the IAMI initiative in health institutions authorized to provide maternal and child care is still very limited.[12,16]

Knowing how EBFC is being carried out and how it should be carried out based on the position of the health staff who have contact with the mothers in the IAMIs of Bogotá D.C., Colombia, makes it possible to strengthen and guide this strategy. Moreover, this could facilitate the provision of effective health care for pregnant and breastfeeding women, thus helping to improve the initiation and maintenance of EBF for the recommended 6 months. Therefore, the objective of this study was to describe the current situation of EBFC from the perspective of the health staff of the IAMIs in Bogotá D.C., Colombia.

## Materials and methods

This is a cross-sectional descriptive study conducted on a sample of 76 counselors (health staff members) from 12 of the 17 health institutions that were accredited as IAMI in 2014, in Bogotá D.C., who agreed to participate in the study. Participants were selected by each of the IAMI mother and child service coordination offices or nutrition offices according to the criteria described below:

*Inclusion criteria:* Having received training in BFC according to the WHO guidelines,[17] which were adopted by Colombia as a requirement for performing EBFC at the IAMI or having a minimum experience of 3 months as a BF counselor.

*Exclusion criteria:* Not serving as a BF counselor at the IAMIs at the time of the study.

Participating counselors worked in the following facilities: delivery rooms, neonatal units, maternity wards, pumping rooms, and outpatient clinics.

Data were collected at three different times through a semi-structured survey of 52 questions: between March 15 and May 30, 2015; between August 15 and October 30, 2015; and in January 2016. The instrument, which was completed by one of the researchers or self-administered by the participants in the presence of the researcher, included the following information: i) general information on the health institution and the breastfeeding counselor, ii) data on the EBFC training received by the counselor, iii) data on the methodology implemented to teach EBFC in the institution, and iv) counselor's knowledge of EBFC. The survey was designed based on the 2009 WHO Infant and Young Child Feeding Guidelines[17] and some conceptual aspects developed for the research. To validate it, a pilot test was carried out with health staff trained in BFC according to the WHO guidelines.[17]

To assess EBFC in the IAMI, both dependent and independent variables were considered. Dependent variables included the EBFC activities carried out during pregnancy, postpartum and hospital discharge; the material used in EBFC; the difficulties reported when carrying out the EBFC; and the participants' knowledge of EBFC. Independent variables included concerns and problems of the mother identified by the interviewees; information on the type of health institution and the training of the breastfeeding committee and the BF support group; and some data on the staff from the institution who provide support to breastfeeding mothers, such as type of work contract, working hours, data on training in counseling (time, topics, methodology), and time of experience as a counselor.

Once the questionnaire was administered, it was verified that it had been completed in full and clearly; then, a database was created with the collected information. The acronym of each IAMI was used to develop this database and each participating counselor's information was coded with an order number for each institution to keep the information confidential. To categorize the answers to the open questions, an analysis was made using the N-Vivo Software version 10, and to analyze the results of the numerical and categorical variables, descriptive statistics were used using averages, frequencies, and proportions.

The survey was conducted upon obtaining the informed consent from the participants. The study took into account the ethical principles for medical research on human subjects established by the Declaration of Helsinki[18] and the provisions on health research of Resolution 8430 of 1993 issued by the Colombian Ministry of Health.[19] In addition, the project was reviewed and approved by the ethics committees of the Faculty of Medicine of the Universidad Nacional de Colombia according to Minutes No. 152-15 of September 23, 2015, and of the Faculty of Sciences of the Pontificia Universidad Javeriana according to Minutes No. 089, endorsed in

Minutes No.152 and the reference document 2015/218 of December 15, 2015.

## Results

### EBFC in the IAMIs

Of the 17 accredited IAMIs in Bogotá D.C., only 12 accepted to participate in the study. These institutions (7 private and 5 public) provided care of different levels and served the population of both the contributory and subsidized insurance regimes. None of the participating IAMIs had a system for monitoring the practice of EBF among the mothers and only 42% (n=5) contacted some of the mothers by phone to ask whether or not they were breastfeeding; however, the information obtained in these calls was not systematized.

### EBF Counselors

In total, 76 questionnaires were administered at the participants' workplaces: 43 were self-completed and 33 were administered through a structured interview.

In terms of the characteristics of the participants, it was found that 99% (n=75) were female, 34% (n=26) had graduate studies, 72% (n=55) had a permanent employment contract, 68% (n=52) worked full time and 91% (n=69) had more than one year of work experience as a counselor.

91% of counselors had not received breastfeeding counseling training according to the WHO guidelines.[17] In this regard, 51 reported they had not been trained to work as breastfeeding counselors, and among those who claimed having been trained, only 12 said they had completed the WHO breastfeeding counseling training course (40 hours)[17]; however, out of these 12 counselors, 7 reported they had received training on counseling techniques related to the practical components of the course, including topics such as "how to approach nursing mothers", "how to counsel them" and "communication skills". Similarly, it was observed that the training in both topics received by those who reported being trained in counseling and the aspects they addressed when they were in contact with mothers had in common that they focused on the conceptual aspects of BF, the benefits, and the technique.

For 60% of those interviewed, BFC means teaching or giving information to the mother about breastfeeding, which they expressed with phases such as: "it is giving advice to the mother", "it is giving a talk to the mothers", "it implies having the knowledge and practice to educate and solve concerns", "teaching the mother how to feed her children, all the benefits that breastfeeding has, teaching them the correct positions, massage techniques." Furthermore, 95% said that breastfeeding is promoted through educational activities in which information materials such as brochures and primers are provided.

The health staff who had the most contact with the mothers during the breastfeeding process were nurses and nursing assistants (84% and 42%, respectively); in contrast, dietitian nutritionists (8%), general practitioners (6.6%) and other health professionals (speech therapists) (1.4%) had very little contact. Also, 71% of the nurses and nursing assistants had contact with the same mother more than once. The mothers were most contacted in the immediate postpartum period and least contacted in the gestation period.

Finally, 9% of the health staff focused on promoting EBF until the sixth month of life, while the remaining 91% addressed the issue in a general way, that is, they promoted EBF with complementary feeding up to the second year and beyond.

### How EBFC is performed

55% of the participants indicated that BF training was provided in pairs to mothers and fathers during prenatal check-ups, individually to the mother in the immediate postpartum period (38%), and individually and in groups at hospital discharge (76%). During the discharge, the counseling was done when the mother went, with her partner or a relative (especially a woman), to the health institution for the newborn check-ups.

According to the health personnel interviewed, the main doubt that mothers have regarding breastfeeding is about the insufficient production of breast milk. This doubt appears from the beginning of the prenatal check-ups and persists until hospital discharge. Also, the main problems that mothers manifest are related to the physical alterations of the breasts and nipples.

Finally, it was found that 44% of the participants identified institutional barriers to providing BFC that included lack of time (50%); insufficient human resources (26.5%); limited material resources to support the counseling process, such as didactic devices, primers, brochures, etc. (14.7%); and lack of training and support (8.8%).

## Discussion

This research showed that only a small number of the staff reported that they were trained as BF counselors; in other words, very few counselors received the 40 hours of training indicated by the WHO to train health staff in knowledge and skills that would enable them to acquire BF counseling competencies.[17]

The WHO course on Infant and Young Child Feeding Counseling[17] seeks to develop primarily two sets of skills: on the one hand, listening and learning, and on the other, confidence building and support. However, the BFC training reported by staff members had a theoretical and practical component focused on the breastfeeding technique and its benefits; similarly, it barely referred to the practical component related to counseling skills. All this indicates that there is a lack of BFC training, and that emphasis is on BF knowledge acquisition instead.

It should be noted that the WHO course[17] is a world reference in the training of human talent in BFC. This course aims to develop skills related, firstly, to the facilitating attitudes proposed by the American psychologist Carl Rogers, quoted by Mereira,[20] who is considered one of the greatest exponents of the so-called humanistic psychology, and, secondly, to the characteristics that Patterson[21] states that counselors should have: *empathy*, which refers to how the client's world, in this case the mothers, is perceived and understood from their perspective; *unconditional positive acceptance,* which consists of absolute respect for the client's individuality;

and *congruence or authenticity*, which is described as the degree of correspondence between what the counselor experiences and what he or she communicates to the client.[22]

Furthermore, it is important to note that the follow-up to the participants of a counseling course is fundamental and mandatory, as implied in the WHO document.[17] Nevertheless, this study found that there was no follow-up of the counselors who claimed to be trained in BFC and that the supervision of the functions performed by these professionals is far from what is established by the WHO. Therefore, it is necessary to establish protocols that determine the expected achievements, the difficulties usually encountered, and the adjustments required in each case, so that EBFC is fully developed.[17]

The results of this study show that the counselors interviewed do not differentiate clearly an EBFC course from a BF training course since their response to the question on EBFC training was that the trainings given by the institutions permanently to health staff usually last less than 6 hours and focus on BF information. This is relevant when considering that short training courses on EBFC, in addition to not meeting the time frame for a counseling course, are focused on teaching basically the physiology of the mammary gland and the proper breastfeeding technique, and do not provide information on aspects related to the development of counseling skills as such. As mentioned above, said aspects are indispensable for the mother to gain confidence in her ability to breastfeed and to solve doubts related to the practice of breastfeeding, and thus be able to successfully carry out the practice of EBF up to the 6$^{th}$ month.

There may be a trend among health care staff and the health care institution to consider that people who know about BF and have contact with mothers over a long period of time are counselors. For this reason, it is necessary to understand the importance of BFC so that health personnel are trained as such and, at the same time, mothers receive this counseling as a form of care.

According to the findings, it could be said that the activities carried out by the health staff interviewed to promote EBF are not typical of EBFC,[22,23] but are more associated with specific teaching activities or information provided to the mother on breastfeeding techniques and its benefits. It was also possible to see that EBFC is not focused on promoting exclusive breastfeeding up to the sixth month of life at any of the three moments when the mother is contacted, despite the many known benefits of this practice.[24]

On the other hand, the counselor staff interviewed agrees that insufficient milk production is the main concern of mothers since they attend the prenatal check-ups until hospital discharge. This finding is consistent with what is reported in the literature, being this a factor that limits the initiation and maintenance of BF.[25,26] However, because of the way counseling is carried out in Bogotá, it is not possible to support the mother in this aspect, a situation that is also consistent with the findings of other studies.[27,28]

In the present study, the health staff reported teaching (but not counseling) BF to couples during prenatal check-ups, individually to the mother in the immediate postpartum period, and individually and as a group at hospital discharge. This type of contact with the mother is consistent with what Bueno & Teruya[29] recommend in their review article. Likewise, several studies claim that the interventions carried out during these three moments are more effective than those carried out only in one and that if several methodologies are developed to accompany the mother instead of using only one method, especially if this accompaniment is focused on the mother's needs rather than on educational activities carried out in a general way, the positive effect of counseling will be more evident.[6,10,30]

Although this study reports that counseling is done both individually and in groups during hospital discharge, the real contact occurs when mothers approach the health institution. This is evidence that home visits are not made and that the IAMIs do little or no monitoring of BF, even though mothers have the greatest need for support regarding the difficulties that arise with breastfeeding in the postpartum period.[26,31-33]

It is noteworthy that some of the counselors interviewed identified barriers to doing EBFC, the most frequent being those related to the health institution. These findings are consistent with those reported in other studies; for example, Renshaw & Henderson[27] found that staff shortages were the cause of poor care and negative attitudes toward mothers, while Hall & Hauck[34] found that elements such as absent staff, multiple contacts with different health professionals, and caregivers with inflexible attitudes make BF more difficult.

It should be noted that besides the fact that the counseling offered to mothers is based on information and explanation, the health staff recognizes that knowledge about BF and EBFC is not unified within the IAMIs. This is a barrier to overcome in these institutions, as it prevents mothers from having clear information, specific support, and consistent messages.[35-37]

## Conclusions

Breastfeeding counseling training focuses on providing information on how to breastfeed but not on developing counseling skills. In addition, there is no consensus among health care workers who serve as breastfeeding counselors about what EBFC means.

The health care staff interviewed saw themselves as EBF counselors, despite having minimal training in the subject, since they do so based on the time they have spent in contact with the mothers. Therefore, it is important to establish strategies for EBFC training and propose new ways of conceiving counseling in both BF and EBF and do the corresponding training.

## Conflicts of interest

None stated by the authors.

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# Formaldehyde in occupational environments: literature review and an occupational health surveillance proposal

*Formaldehído en ambientes laborales: revisión de la literatura y propuesta de vigilancia ocupacional*

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## Abstract

**Introduction:** Formaldehyde is a substance widely used in the industry; however, it is classified as mutagenic and carcinogenic to humans. In order to determine the risk of workers who are occupationally exposed to formaldehyde, it is necessary to monitor its environmental concentration levels and the biomarkers that allow identifying its potential health effects. Unfortunately, in Colombia there are not guidelines on occupational exposure to this substance.
**Objective:** To review recent studies on occupational exposure to formaldehyde to design a monitoring and surveillance strategy for Colombian workers exposed to this substance.
**Materials and methods:** A literature review was conducted in PubMed, MedLine, ScienceDirect and Embase using the following search strategy: articles on occupational exposure to formaldehyde published in English or Spanish between 2013 and 2017. The following search terms were used: "occupational exposure", "formaldehyde" "mutagenicity test" y "DNA adducts" and their Spanish equivalents.
**Results:** The initial search yielded 103 articles, of which only 36 met the inclusion criteria.
**Conclusions:** Proper management of the risk derived from occupational exposure to formaldehyde, as well as the appropriate medical follow-up of these workers, requires the implementation of a series of interdisciplinary actions that allow the creation of a comprehensive occupational health surveillance system for workers exposed to this substance.
**Keywords:** Occupational Exposure; Mutagenicity Tests; Biomarkers; Formaldehyde (MeSH).

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## Resumen

**Introducción.** El formaldehído es una sustancia ampliamente usada a nivel industrial; sin embargo, es considerada un agente mutagénico y carcinógeno para los humanos. Para determinar el grado de riesgo de los trabajadores ocupacionalmente expuestos (TOE) al formaldehído, debe hacerse un seguimiento de sus niveles de concentración ambiental y de los biomarcadores que permiten identificar su daño potencial para la salud. En Colombia, lamentablemente, no existen lineamientos respecto a la exposición ocupacional a esta sustancia.
**Objetivo.** Revisar estudios recientes sobre exposición ocupacional a formaldehído para diseñar una estrategia de seguimiento y vigilancia de los TOE a esta sustancia en Colombia.
**Materiales y métodos.** Se realizó una revisión de la literatura en PubMed, MedLine, ScienceDirect y Embase mediante la siguiente estrategia de búsqueda: artículos sobre exposición ocupacional a formaldehído publicados en inglés o español entre 2013 y 2017. Los términos de búsqueda fueron "occupational exposure", "formaldehyde" "mutagenicity test" y "DNA adducts" y sus equivalentes en español.
**Resultados.** La búsqueda inicial arrojó 103 registros, sin embargo solo 36 artículos cumplieron los criterios de inclusión establecidos.
**Conclusiones.** La gestión adecuada del riesgo derivado de la exposición ocupacional a formaldehido, así como el seguimiento médico apropiado de estos trabajadores, requiere la implementación de una serie de acciones interdisciplinarias que permitan la creación de un sistema de vigilancia ocupacional integral de los TOE a esta sustancia.
**Palabras clave:** Exposición ocupacional; Pruebas de mutagenicidad; Biomarcadores; Formaldehído (DeCS).

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## Introduction

In Colombia, the *Sistema de Gestión de Seguridad y Salud en el Trabajo* (Occupational Health and Safety Management System) considers formaldehyde (FA) as a priority substance [1] since it is included in the list of carcinogens of interest to the *Sistema de Vigilancia del Cáncer Ocupacional* (Occupational Cancer Surveillance System)[2] developed by the *Instituto Nacional de Cancerología* (National Cancer Institute.)[3]

Even though the Occupational Diseases List published by the Ministry of Labor[4,5] includes some of the pathologies associated with exposure to FA —such as acute bronchitis caused by chemical agents, pulmonary edema caused by chemical agents, inflammation of the upper respiratory tract caused by chemical agents, chronic diffuse emphysema, reactive airways dysfunction syndrome, pulmonary fibrosis, obliterative bronchiolitis and toxic effects—, diseases related to the carcinogenic potential of this substance have not been considered.

FA is a volatile organic compound with a characteristic and irritating odor, characterized by having a double bond with oxygen (H2C=O), which promotes its reactivity. FA is used dissolved in water at a maximum concentration of 40% and is produced on a large scale worldwide. An estimated 21 million tons per year[6] of this compound are used to manufacture a large number of industrial products such as urea and melamine phenolic resins, which have various applications in adhesives and binders; wood products such as cellulose pulp for making paper; plastic products; paints for coatings; and products for the textile industry.[7] In other areas, including the clinical field, it is used directly in aqueous solution as a disinfectant, tissue preservative, and biocide.

The main route of exposure to FA is inhalation[8] and, depending on its concentration, exposure to this compound can cause different symptoms. At concentrations of 0.1-5ppm, it can cause eye irritation, tearing, upper respiratory tract irritation and coughing; at concentrations of 5-30ppm, it can cause chest pain, airway irritation, respiratory distress, headache, asthmatic reactions and can aggravate pre-existing respiratory conditions;[9-11] and at concentrations of 50-100ppm, it can cause pneumonia, pulmonary edema and even death.[12,13] Permanent exposure to lower concentrations of FA can produce nasopharyngeal and squamous cell carcinoma in the tissues of the nose.[7]

The International Agency for Research on Cancer[14] classifies FA in the group of agents that are carcinogenic to humans (Group 1). Recent meta-analyses have reported a strong association between exposure to this substance and acute myeloid leukemia,[15] while other studies with limited evidence have established a link between FA and sinus cancer.[16-18]

Other consequences of FA exposure have been reported. For example, Lino *et al.*[19] found that this substance produces alterations in the physiological balance between oxidative and antioxidant enzymes in lung tissue, most likely favoring the oxidative pathway and generating lung inflammation. Schwensen *et al.*[20] explained that skin irritation occurs after having contact with this substance and that this, in turn, can produce contact dermatitis. Thrasher *et al.*[21] reported an association between recurrent exposure to this substance and immune system disorders since, in humans, FA conjugates with human serum albumin, forming a new antigenic determinant (F-HSA); this in turn causes the development of anti F-HSA antibodies. Finally, Thrasher *et al.*[22] described that exposure to FA produces genotoxic and cytotoxic effects such as increased chromosomal aberrations, sister chromatids exchange, and presence of micronuclei.

Since FA is a compound widely used at industrial level, multiple research works have been developed using genotoxicity tests to identify the risks that occupational exposure to this chemical poses to the health of workers, showing possible damage to DNA. The objective of this study is to review recent research on occupational exposure to FA to design a strategy for monitoring and surveillance of workers occupationally exposed to this substance.

## Materials and methods

A literature review was conducted in PubMed, MedLine, ScienceDirect, and Embase looking for human studies published between 2013 and 2017 in English or Spanish. The following descriptors were used: "occupational exposure", "formaldehyde", "mutagenicity test" and "DNA adducts", their Spanish equivalents and their combinations ("occupational exposure AND formaldehyde AND mutagenicity test OR mutagenicity test AND DNA adducts"). This search retrieved 103 articles whose titles and abstracts were analyzed.

Of the articles available in full text, those that met the following inclusion criteria were selected: assessed only exposure to FA, were conducted in occupational settings, and had quantitative results of airborne FA concentrations or genotoxicity tests that report the analytical technique used. In-vitro studies were excluded. Moreover, legal and technical sources were consulted to search publications that frame and regulate the monitoring of occupationally exposed workers (OEW) in Colombia, which should address the following issues: occupational exposure, medical monitoring, environmental concentration limits, FA and occupational cancer. Figure 1 shows the search flowchart.

## Results

The 36 articles that met the inclusion and exclusion criteria were included. Most of the papers were observational studies in which the concentration of FA was quantified, and genotoxicity tests were performed to establish the relationship between exposure to FA and the health consequences among OEW. Some of the health effects reported in the articles include acute responses such as airway and eye irritation, while chronic effects were analyzed by means of genotoxicity biomarkers,[23] which allow identifying and characterizing the damages that can be caused by this pollutant. Table 1 presents the results of the included articles that were considered most relevant to the objective of this study.

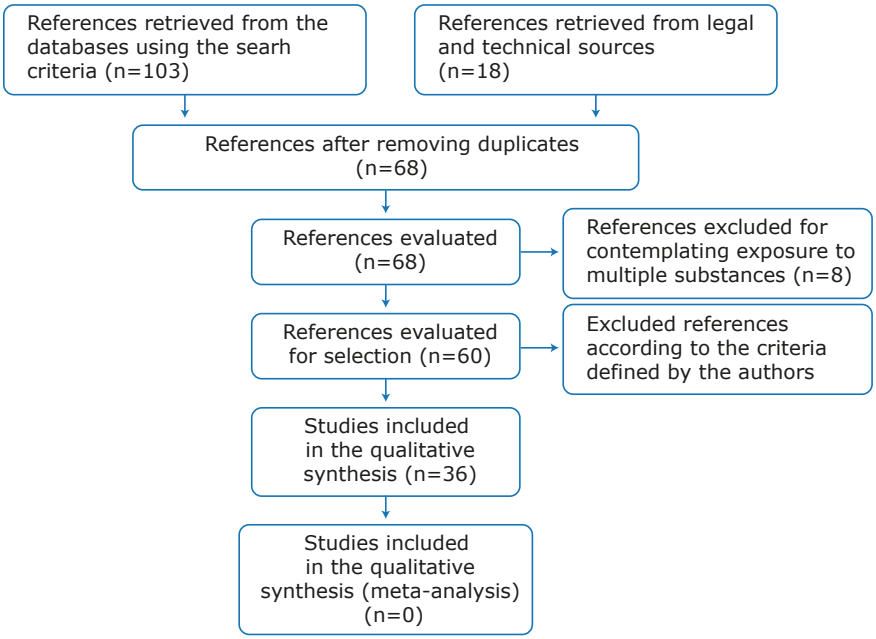



**Figure 1.** Search flowchart.
Source: Own elaboration.

**Table 1.** Formaldehyde concentration and genotoxicity test in occupationally exposed workers.

| Authors and reference number | Year | Country | Place of study | Work activity | Method used | Result | Study population (n) | Genotoxicity test (p) |
|---|---|---|---|---|---|---|---|---|
| Zendehdel *et al.*[24] | 2017 | Iran | 3 manufacturing workshops | Melamine tableware production | NIOSH 3500 (Personal Sampling Pump) | 0.086 mg/ $m^3$ | 49 exposed workers / 34 controls | Comet assay ($p<0.001$) |
| Ladeira *et al.*[25] | 2016 | Portugal | 6 hospital histopathology laboratories | Pathology laboratory work | NIOSH 2541 | 1.14ppm | 55 exposed workers/80 controls | MN frequency in peripheral blood lymphocytes ($p<0.05$)<br>MN assay in exfoliated buccal epithelial cells (p:0.391) |
| Peteffi *et al.*[26] | 2016 | Brazil | 7 sectors of a furniture plant | Furniture manufacturing and installation | OSHA 1007 (UME$^x$ 100 Passive Sampler) | 0.03-0.09 ppm in the plant 0.012 ppm in the control group | 46 exposed workers/45 controls | MN test ($p=0.08$)<br>Comet assay ($p=0.007$) |
| Peteffi *et al.*[27] | 2016 | Brazil | 2 beauty salons | Use of FA-free products | OSHA 1007 (UME$^x$ 100 Passive Sampler) | 0.04-0.02 ppm | 31 exposed workers/19 controls | MN test ($p=0.538$) Comet assay ($p=0.000$) |
| | | | 4 beauty salons | Use of products with Fa concentrations at 5.7%, 2.6%, 5.9% and 5.8% | | 0.07, 0.14, 0.16 and 0.14 ppm, respectively | | |

**Table 1.** Formaldehyde concentration and genotoxicity test in occupationally exposed workers. (continued)

| Authors and reference number | Year | Country | Place of study | Work activity | Method used | Result | Study population (n) | Genotoxicity test(p) |
|---|---|---|---|---|---|---|---|---|
| Attia *et al.*[28] | 2016 | Egypt | Cosmetics manufacturing plant | Cosmetic production | Not reported | Not reported | 40 exposed workers/ 20 controls | Estimation of p53 enzyme in plasma (p<0.05) |
| Saowakon *et al.*[12] | 2015 | Thailand | Suranaree University of Technology Anatomy Laboratory | Anatomical dissection | NIOSH 2016 (HPLC-UV) | 0.117-0.415 ppm | In the air of the laboratory | Not reported |
| | | | | | | 0.126-1.176 ppm | 36 students/ 4 professors | |
| Casas-Duarte[3] | 2015 | Colombia | Healthcare institutions | Laboratory work | NIOSH 2016 (HPLC-UV) | 2.32ppm | 38 laboratory assistants | Not applicable |
| | | | Universities | Dissection of bodies and blocks, anatomical specimens | | 5.03ppm | 10 professors and students | |
| Costa *et al.*[8] | 2015 | Portugal | 9 anatomical pathology laboratories in hospitals | Macroscopic examination, disposal of waste solutions and specimens | NIOSH 3500 (UV-Vis) | 0.08-1.30ppm | 84 exposed workers/87 controls | Chromosome aberration test 3.96±0.34 * (p<0.001) |
| | | | | | | | | Comet assay 11.67±0.72 * (p<0.001) |
| Fenech *et al.*[29] | 2015 | Austria | Pathological anatomy and wood and resin manufacturing laboratories | Laboratory work Wood and resin production | Systematic review | 0.11-2.56ppm | 21 publications evaluated | In 17 studies there was a significant increase in MN frequency (p:<0.0001) and a significant relationship between MN frequency and exposure to high levels of FA (p:<0.0001) |
| Souza & Devi[30] | 2014 | India | Departments of anatomy and forensic medicine from different universities | Laboratory work | Not reported | Not reported | 30 men exposed/30 controls | MN (p<0.001) |
| Watchalayann *et al.*[31] | 2014 | Thailand | Thammasat University Anatomy Laboratory | Anatomical dissection | NIOSH 2541 GC-FID | 0.441ppm | 36 samples of laboratory air | Not reported |
| | | | | | | 0.377ppm | 90 medical students and professors | |

**Table 1.** Formaldehyde concentration and genotoxicity test in occupationally exposed workers. (continued)

| Authors and reference number | Year | Country | Place of study | Work activity | Method used | Result | Study population (n) | Genotoxicity test(p) |
|---|---|---|---|---|---|---|---|---|
| Lin *et al.*[32] | 2013 | China | Plywood factory workshop | Plywood production | NIOSH 2016 (HPLC-UV) | 0.019-2.044 mg/m$^3$ | 178 exposed workers | DPC ($p<0.05$) ‡ MN ($p=0.01$) |
| Aydin *et al.*[33] | 2013 | Turkey | Companies that manufacture different products | Manufacturing of different products | NIOSH 3500 | 0.2ppm | 46 exposed workers/46 controls | No statistically significant difference in lymphocytes was found in the comet assay |
| Costa *et al.*[34] | 2013 | Portugal | 4 hospital histopathology laboratories | Laboratory work | NIOSH 3500 | 0.23-0.69ppm | 35 exposed workers/35 controls | MN ($p:<0.05$) |
| | | | | | | | | Sister chromatid exchanges ($p:<0.05$) |
| | | | | | | | | T-cell receptor (TCR) mutation assay ($p>0.06$) |
| Ladeira *et al.*[35] | 2013 | Portugal | 6 hospital histopathology laboratories | Laboratory work | NIOSH 2541 GC-FID | 0.16ppm | Environmental sampling | MN ($p<0.001$) |
| | | | | | PID † | 1.14ppm | 54 exposed workers/82 controls | |
| Bouraoui *et al.*[36] | 2013 | Tunisia | 6 hospital histopathology laboratories | Laboratory work | HPLC-UV | 0.2ppm, 1.8ppm and 3.4ppm | 31 exposed workers/21 controls | MN ($p:<0.05$) |

NIOSH: National Institute for Occupational Safety and Health; MN: micronucleus; OSHA: Occupational Safety and Health Administration; HPLC-UV: high-performance liquid chromatography-ultraviolet; UV-Vis: ultraviolet-visible spectroscopy; FA: formaldehyde; GC-FID: gas chromatography – flame ionization detector; PID: photoionization detector.* Mean±SD.
† Photoionization detector (11.7 eV lamp) with simultaneous video recording.
‡ Chromosome damage and DNA-protein cross-links in peripheral blood lymphocytes.
Source: Own elaboration.

The studies included in this review were carried out in Europe (38%), Asia (31%), South America (19%) and Africa (12%) in different working sectors, including the practice and teaching of health sciences, industrial manufacturing processes, and cosmetics production. The concern generated worldwide by occupational exposure to FA is evident in the increase in research on the subject in different work environments.

## Discussion

### Formaldehyde concentrations in working environments

According to the criteria of the United Nations' Globally Harmonized System of Classification and Labeling of Chemicals,[37] any solution containing a carcinogenic substance beyond a concentration of 0.1% should be considered carcinogenic; however, 5% of FA solutions are used for cadaver dissection. Saowakon *et al.*[12] reported concentrations of FA above permissible limits in both the air and the breathing zone of anatomy laboratory workers.

The concentration of FA can be quantified through standardized methods using different analytical techniques proposed by entities such as the Occupational Safety and Health Administration and the National Institute for Occupational Safety and Health. Table 2 depicts the methods used in the articles included in the review.

**Table 2.** Methods for quantifying formaldehyde in work environments.

| Agency | Method | Analytical technique | |
|---|---|---|---|
| NIOSH | 3500 | UV-Vis | UV-visible spectrophotometry |
| NIOSH | 2541 | GC-FID | Gas chromatography – flame ionization detector |
| OSHA | 1007 | HPLC | High-performance liquid chromatography |
| OSHA | 52 | GC-NPD | Gas chromatography - Nitrogen phosphorous detector |
| NIOSH | 2016 | HPLC-UV | High-performance liquid chromatography–UV detection |
| NIOSH | 3800 | FTIR | Fourier transform infrared spectroscopy |

NIOSH: National Institute for Occupational Safety and Health; OSHA: Occupational Safety and Health Administration. Source: Own elaboration based on Kennedy,[38] Occupational Safety and Health Administration[39] and Kennedy & Williams[40].

The highest concentrations of FA were found in studies conducted in China,[32] Colombia[3] and Tunisia,[36] while the lowest concentrations, with values below permissible exposure limits, were found in a research conducted at a wood manufacturing center in Brazil.[26] Studies by Lin *et al.*[32] and Ghasemkhani *et al.*[41] in China and Iran, respectively, found statistically significant differences in FA concentrations in the breathing zone of workers with the same job position depending on shift distribution and task performed.

The studies by Saowakon *et al.*[12] and Ladeira *et al.*[35], conducted in anatomical dissection laboratories, reported that the environmental concentration of FA in the breathing area of students and instructors was statistically different from the concentration found by fixed measurements in that area, the latter being higher.

In the articles included, the lack of engineering control systems, such as ventilation systems, extraction booths, localized extraction systems, among others, was identified. These systems would allow minimizing the concentration of FA in work environments.

Concerning medical surveillance, in 2015, Peteffi *et al.*[42] conducted a study on workers of the furniture manufacturing industry in Brazil who were exposed to different levels of FA. The authors found that the levels of formic acid in urine were significant only in workers exposed to high concentrations of this compound.

In a study conducted at the University of Erlangen-Nuremberg, Schmid *et al.*[43] compared the levels of formic acid in urine of 70 people not occupationally exposed to FA to the levels of 30 medical students attending anatomy classes during their practice with high exposure levels for a short period and of 8 pathology laboratory workers with long exposure periods. FA concentrations in the group of students were 0.32-3.48ppm and the levels of formic acid in urine fluctuated, so they were associated with the diet and not with the amount of FA in the air ($p=0.070$). In the group of workers, there was also no linear correlation between the levels of formic acid in urine and the concentrations of this pollutant in the air.

In 2010, Mautempo *et al.*[44] conducted a study on 31 workers, in whom they found significantly elevated levels ($p<0.0001$) of formic acid in urine compared to the control group. However, the results do not describe the environmental concentration of FA, so no relationship can be established between concentrations of formic acid in urine and exposure to the pollutant.

## Genotoxicity testing in workers occupationally exposed to formaldehyde

In two studies conducted in 2016 by Peteffi *et al.*[26] in a furniture factory and Peteffi *et al.*[27] in beauty salons, no significant differences were observed in the micronucleus test between OEW and the control group, while the comet assay showed significant differences, even though the workers were exposed to low concentrations of FA. These results are similar to those described by Zendehdel *et al.*,[24] who observed that DNA damage in peripheral blood lymphocytes can occur even in controlled work environments. For their part, Ladeira *et al.*[45] reported an increase in the frequency of micronuclei in exfoliated buccal cells and in peripheral blood lymphocytes in OEW and found significant differences compared to the control group.

Regarding the use of genotoxicity biomarkers, in a study carried out on workers in the cosmetics manufacturing industry, Attia *et al.*[28] proposed that malondialdehyde (MDA), a metabolite and reactive oxygen species resulting from lipid peroxidation, and the mutation of the p53 gene, a known indicator of carcinogenesis, could be considered biomarkers of genotoxicity, as they found statistically significant differences in these two biomarkers between the OEW and the control group.

In an investigation conducted on 84 workers from the pathological anatomy service of different hospitals in Portugal, who were exposed to FA at levels higher than those allowed, Costa *et al.*[8] found chromosomal aberrations and aneuploidies in the population studied through a structural chromosomal aberration test and a comet assay.

Furthermore, two systematic reviews were included, one by Fenech *et al.*,[29] who found significant differences in micronucleus frequency between workers exposed to high concentrations of FA and the control group in 17 of the 21 included studies, and another by Chiarella *et al.*,[46] who proposed protein adducts as a potential biomarker after reviewing 95 studies.

## Toxicological aspects of formaldehyde

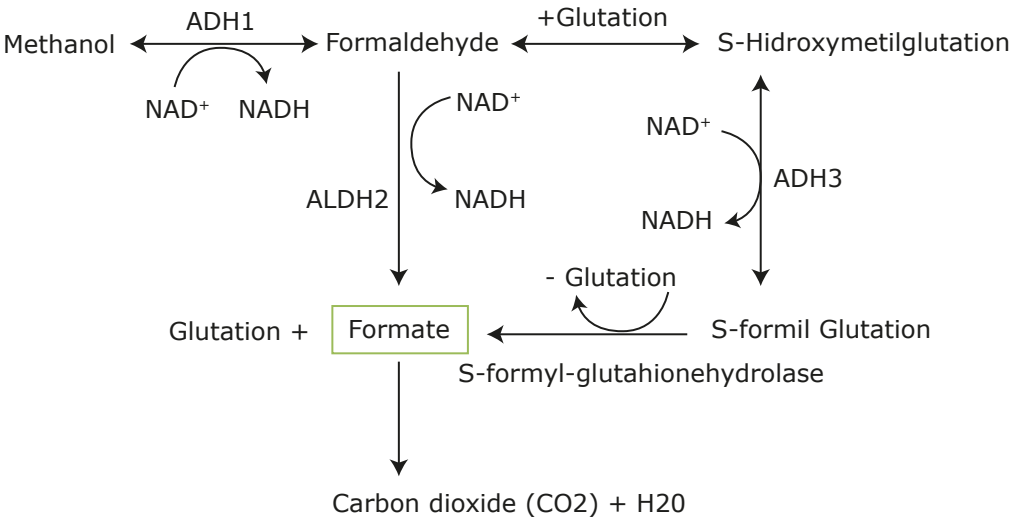
### *Toxicokinetics*

FA is produced endogenously in small quantities as part of the human body's metabolism. Its blood concentration reaches about 1.5-3 mg/L and is generated in processes such as methylamine deamination, methanol oxidation and histone demethylation by cytosolic alcohol dehydrogenase.[14]

When individuals are exposed to FA exogenously, this compound is absorbed by inhalation or ingestion. Therefore, the upper respiratory tract is its main route of entry into the human body and the nasal and nasopharyngeal mucosa are its target tissues; it has not been found significantly in other organs. Figure 2 shows the metabolic pathways that take place after entering the body.[47] FA can be converted to methanol by the alcohol dehydrogenase-1

(ADH1) enzyme or oxidized to formate. Mitochondrial oxidation is catalyzed by the formaldehyde or aldehyde dehydrogenase-2 (ALDH2) enzyme, while cytoplasmic oxidation is catalyzed by the alcohol dehydrogenase-3 (ADH3) enzyme to form S-formylglutathione and then formate.[46] Once formate is incorporated into the metabolic pathways, it can continue to oxidize towards carbon dioxide; another secondary metabolic pathway dependent on the tetrahydrofolate cofactor has also been reported.[46] Moreover, FA acts by creating reversible or irreversible adducts with macromolecules (RNA, RNA and proteins), which leads to mutations and proliferation of micronuclei in the cells.[14] MacAllister *et al.*[48] evaluated the excretion pathways of this pollutant in animal models and concluded that the main pathway is exhalation (40%), followed by urine (17%), and feces (4%).

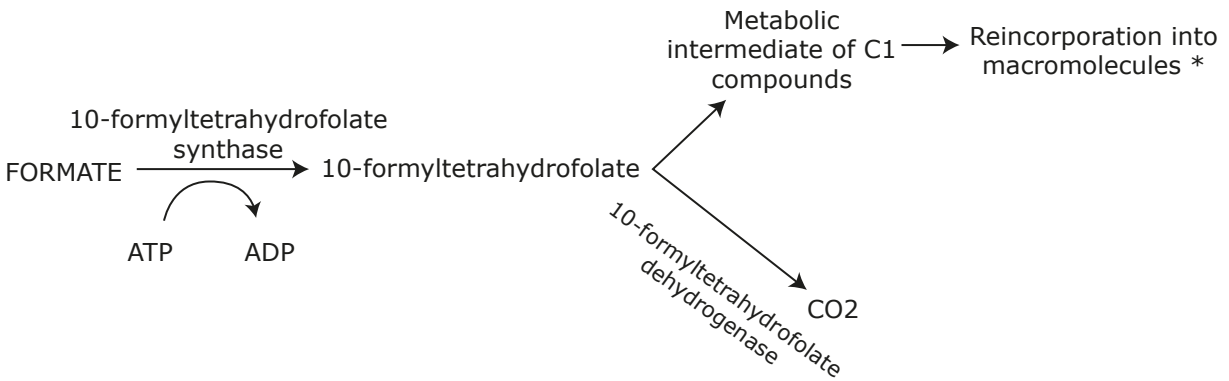
**1. Formaldehyde metabolism: via glutathione-dependent formaldehyde dehydrogenase and via aldehyde dehydrogenase**




FA can be converted to methanol via ADH1 or oxidized to formate. Mitochondrial oxidation is catalyzed by ALDH2 while cytoplasmic oxidation is catalyzed by ADH3 to form S-formyl-glutathione and then formate (46). Once formate is incorporated into the metabolic pathways, it can continue to oxidize to carbon dioxide.

ADH1: alcohol dehydrogenase 1; ADH3: alcohol dehydrogenase-3; ALDH2: alehyde dehydrogenase-2; FA: formaldehyde; GSH: glutation; NAD+: nicotinamide adenine dinucleotide; NADH: nicotinamide adenine dinucleotide+hydrogen

**2. Metabolism of formaldehyde via tetrahydrofolate (TH4)**




ATP: adenosine triphosphate; ADP: adenosine diphosphate

**Figure 2.** Formaldehyde metabolic pathways
Source: Own elaboration.

### *Toxicodynamics*

Although the exact mode of action that causes the irritant effect of FA is not yet well known, since this compound is an aldehyde, it is expected to react easily with the free amino acid groups to produce hydroxymethyl and a free radical (hydrogen proton). It has also been proposed that formaldehyde dehydrogenase becomes saturated when intracellular levels of FA are elevated, limiting natural protection mechanisms and making it easier for this xenobiotic to generate acute or chronic effects in the human body.[16,49]

### *Genotoxic effects*

Cytotoxicity caused by exposure to FA has been proven through nasal biopsies performed on OEW, in whom chronic inflammation, mild epithelial dysplasia, loss of respiratory cilia, hyperplasia, squamous metaplasia of the epithelium and cancer of the nasopharynx and sinuses were observed.[14,50] The toxic effects produced by FA metabolism in the human body that have been identified so far are gene mutation, chromosomal breakage, aneuploidy, epigenetic alterations, oxidative stress, cytotoxicity and induction of cell proliferation.[15]

In studies using cultures of human cells in vivo, Peteffi *et al.*[26] and Shaham *et al.*[51] showed that FA can produce genotoxicity, as it causes DNA damage and chromosome changes, often expressed as chromosome aberrations, DNA adducts, sister chromatid exchange and micronuclei. Additionally, it has been reported that this compound damages hematopoietic progenitor cells in vitro, which increases its possible relationship with hematological diseases such as acute myeloid leukemia.[15,16]

## Formaldehyde and formic acid as biomarkers of exposure

Although attempts have been made to determine the exogenous concentration of FA in blood, it cannot be used as a biomarker of exposure since only a very low inhaled fraction of FA enters the blood stream. Moreover, the half-life of FA in peripheral blood is 1 to 1.5 minutes, its high reactivity allows it to transform rapidly into other compounds, and the metabolic buffering capacity of the body's nasal cells keeps its levels in blood in the range of 2-3 mg/L.[52]

Formic acid can be a biomarker of exposure since it is a metabolite of FA excreted in urine; however, its use has been controversial because of its inter-individual variability and the influence of factors such as smoking, diet and nutritional status on the levels of this acid in urine. Also, formic acid can be produced from other substrates of metabolism, so it is not a specific biomarker for detecting exposure to FA. Therefore, Peteffi *et al.*[42] suggested that it could be a biomarker with interferences in its outcome, while Schmid *et al.*[43] concluded that the results of formic acid in urine do not allow assessing exposure to FA, even when the concentration of this pollutant in the working environment is above 50% of the permitted limit.

## Genotoxic effects and biomarkers of genotoxicity

Most studies included in the review agree on reporting two biomarkers of genotoxicity: the micronucleus assay on exfoliated cells from the buccal mucosa to visualize local damage, and the comet assay on peripheral blood lymphocytes to identify systemic damage.[53] Usually, two genotoxicity tests are done, although the results do not always coincide.

Fenech *et al.*[29] and Chiarella *et al.*[46] do not recommend the use of formic acid in urine or genotoxicity tests since they may be altered by exposure to other xenobiotics and, therefore, they may not be conclusive. However, the studies conducted by these authors were limited to animal models.

Souza & Devi[30] and Pira *et al.*[54] agree that the damage caused by FA is directly proportional to years of exposure and concentration in the work environment. This is consistent with Lin *et al.,*[32] who established a relationship between FA concentration and time of exposure, and genotoxic damage.

As for immunotoxicity, Jia *et al.,*[55] Aydin *et al.*[33] and Seow *et al.*[56] reported decreased immune cells and immunoglobulin production, as well as DNA damage. This was evaluated using a comet assay, which suggests that exposure to FA caused immunosuppression in the populations studied, which, in turn, may be associated with diseases of the myeloid system and may explain the mechanism of damage of FA cytotoxicity.

Although genotoxicity biomarkers are not specific for establishing exposure to FA, they provide information on the possible health effect of this pollutant on OEW, taking into account its mechanism of damage, which may facilitate preventive decision-making; therefore, evaluating their usefulness is suggested for individual surveillance. Formic acid in urine as a biomarker does not provide consistent information on exposure to FA, nor does it work to identify cases; on the contrary, it creates confusion and its results can cause the implementation of erroneous intervention and follow-up strategies.

## Occupational exposure limits

Although FA is found naturally in the air, there is an increase in its concentration in the most populated urban areas caused mainly by anthropogenic sources. In rural areas, airborne FA concentrations are generally <1 μg/m$^3$, while in urban environments levels are approximately 0.16ppm.[14] García-Reynoso *et al.*[57] reported that FA is the environmental pollutant with the highest concentration in Mexico City, increasing the probability of suffering from cancer; consequently, this result is associated with a decrease in life expectancy of the inhabitants of this city.

Regulatory agencies have established permissible limits for FA in work environments according to time of exposure to protect workers' health (Table 3). In 2012, the European Chemicals Agency Risk Assessment Committee concluded that the lowest adverse effects concentration of FA is 2ppm, causing histopathological lesions, polypoid adenomas, and cell proliferation.[58]

**Table 3.** Permissible limits for exposure to formaldehyde.

| Agency | Permissible limit | ppm | mg/m$^3$ |
|---|---|---|---|
| American Conference of Governmental Industrial Hygienists | TLV – TWA * | 0.1 | - |
| American Conference of Governmental Industrial Hygienists | TLV – STEL † | 0.3 | - |
| Occupational Safety and Health Administration | PEL - TWA | 0.75 | 0.93 |
| Occupational Safety and Health Administration | STEL | 2 | - |
| National Institute of Occupational Safety and Health | REL - TWA | 0.016 | - |
| National Institute of Occupational Safety and Health | CEILING ‡ | 0.1 | - |

TLV: threshold limit value; TWA: time weighted average; STEL: short term exposure limit; PEL: permissible exposure limit; REL: recommended exposure limit.
* Maximum concentration for 8 hours per day and 40 hours per week.
† Concentration that should not be reached when working for 15-minute periods, maximum 4 times per day, leaving a 1-hour rest period between exposures.
‡ Concentration to which workers should never be exposed during their work shift.
Source: Own elaboration based on the American Conference of Governmental Industrial Hygienists.[59]

The concentrations reported in most of the articles included in the review exceed the allowable limits proposed by the American Conference of Governmental Industrial Hygienists (TLV-TWA=0.1ppm),[59] indicating high exposure to FA in the populations studied.

The selection of the analytical technique to quantify FA depends on the level of sensitivity desired, the technology available, and the possible interferences present in the environment to be evaluated. The most used methods of analysis are NIOSH 3500[38] and NIOSH 2016,[40] which use the ultraviolet–visible spectrophotometry (UV-Vis) analytical technique. The studies by Peteffi *et al.*[26] and Peteffi *et al.*,[27] carried out in 2016 in Brazil, utilized passive monitoring systems because they are easier to use since they do not require a sampling pump.

### Control strategies

The studies included in the review showed the lack of control systems, such as extraction booths and ventilation systems, that reduce the concentration of FA in work environments.[41] In people who perform body dissection activities in anatomy laboratories, eye and nasal irritation and the sensation of fatigue seem to be constant symptoms.[31] Even though the effect of FA can be reduced by using personal protective equipment, students and professors of the health area rarely use it,[60] and the same thing happens among workers in other work environments.[30] As described by Saowakon *et al.*[12], only a small proportion of the population reported wearing goggles and, despite their use, they did not perceive the decrease in eye irritation; therefore, it is concluded that their use does not minimize the worker's exposure to FA. For their part, workers included in the Costa *et al.* study[8] reported not wearing goggles or respiratory protection, as these elements interfered with activities such as note taking, material handling, and communication.

Even though exposure to FA can be monitored, it is always recommended to consider the substitution of this compound by less hazardous substances for health, considering that it is classified as a carcinogenic substance for humans. For example, Rocha-Ferreira *et al.*[61] studied a solution of ethanol and glycerol for the preservation of corpses, achieving results that can be replicated.

Preference should be given to the establishment of closed processes in which the worker has no contact with this pollutant and perform engineering controls that minimize its presence in the work environment. Furthermore, these measures should be included when technology and production systems are updated, applying control strategies according to their hierarchy: first at the source, then in the environment, and finally in the worker.

## Conclusions

According to the Colombian regulations,[1,62,63] employers must periodically evaluate the levels of exposure of workers to chemicals considered a priority. In other words, potentially carcinogenic agents should be monitored to determine the risk they pose to OEW, the effectiveness of the control systems in place, and perform relevant medical follow-up. However, care guidelines for occupational exposure to FA have not yet been established.

Strategies implemented as part of the surveillance system often include workplace environmental measurements, spirometry, and formic acid test in urine, although the latter is not a reliable biomarker of FA exposure. Therefore, based on the articles included in this review, we propose a sequence of actions to carry out the epidemiological surveillance of OEW and present biomonitoring alternatives for this population (Figure 3).

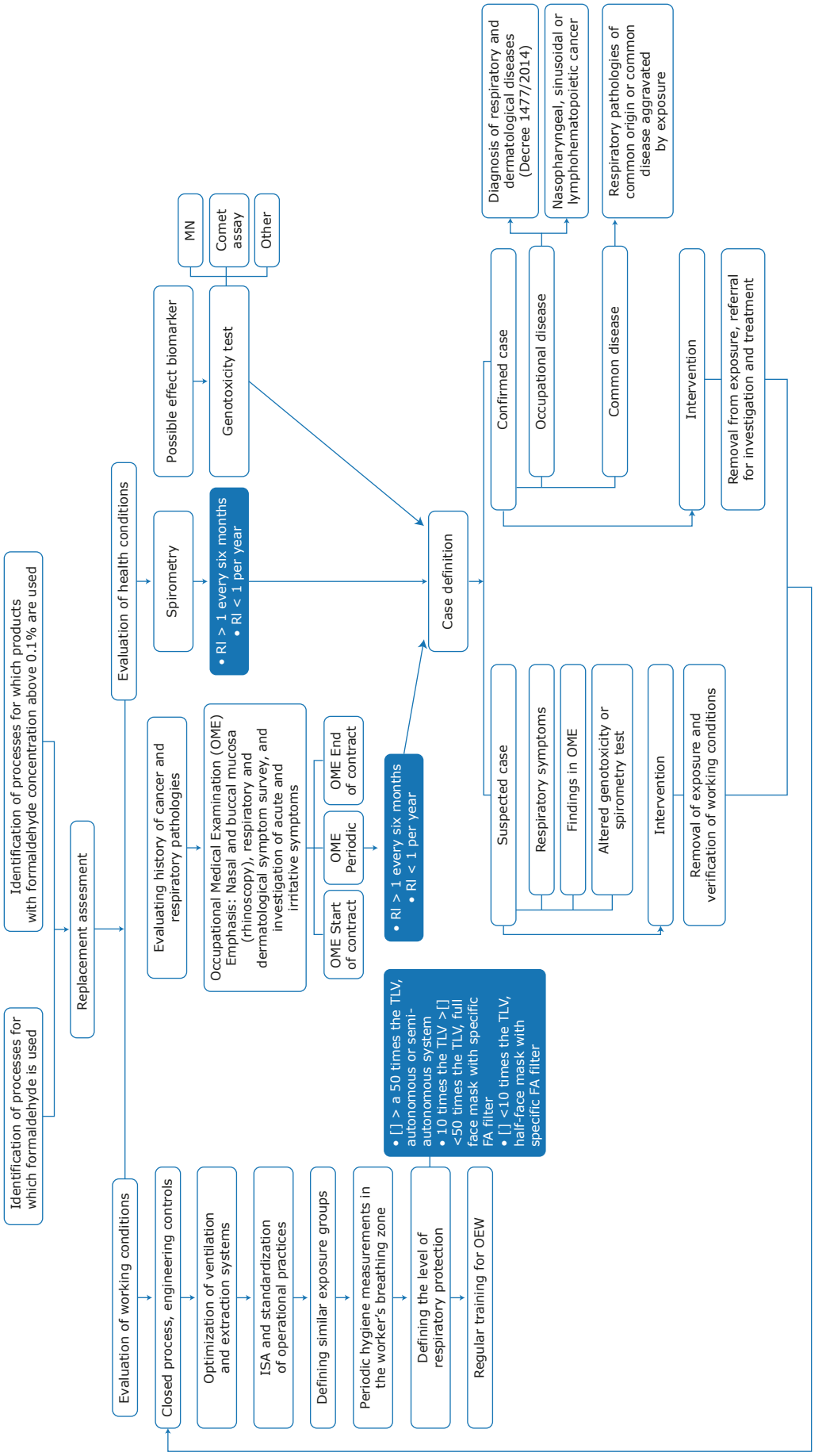



**Figure 3.** Flowchart for epidemiological surveillance of workers occupationally exposed to formaldehyde.
FA: formaldehyde; JSA: job safety analysis; OEW: occupationally exposed workers; OME: occupational medical examination; TLV: threshold limit value; RI: risk index; MN: macronuclei.
Source: Own elaboration.

Additionally, acute symptoms and chronic injuries should be monitored, and the use of respiratory protection should be implemented whenever workers are exposed to FA. This seeks to reduce the damages caused by this pollutant since harmful effects could occur even if exposure is at low concentrations.[14,24,26]

Occupational environmental measurements should be made in the breathing area of the OEW; no fixed environmental measurements should be made, as the results are statistically different. FA in blood and formic acid in urine are not reliable biomarkers of exposure to this compound, since they are not very sensitive and specific, and their results can be affected by different factors. Genotoxicity markers are a better option for identifying the mechanism of FA damage and for medical follow-up of OEW.

The proper management of the risk derived from occupational exposure to FA, as well as the appropriate medical follow-up of these workers, requires the implementation of a series of interdisciplinary actions that allow the creation of a comprehensive occupational surveillance system of OEW to this substance, taking into account that it is currently the most used preservative to manufacture multiple products.

## Conflicts of interest

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# Torque estimation based on surface electromyography: potential tool for knee rehabilitation

*Estimación de par basada en electromiografía de superficie: potencial herramienta para la rehabilitación de rodilla*

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## Abstract

**Introduction:** Multiple signal processing studies have reported the application of surface electromyography (sEMG) signals in robotics and motor rehabilitation processes.
**Objective:** To conduct a literature review on the use of sEMG signals as an alternative method for knee torque estimation in order to objectively measure the progress of patients at different stages of knee injury rehabilitation.
**Materials and methods:** A literature review of studies published between 1986 and 2018, without geographical limits, was carried out in the Engineering Village, IEEE Xplore, ScienceDirect, Web of Science, Scopus, and PubMed databases by combining 8 search terms.
**Results:** After completing the initial search, 355 records were retrieved. Duplicated publications were eliminated, and 308 articles were analyzed to determine if they met the inclusion criteria. Finally, 18 studies describing, in a comparative way, how to estimate torque based on sEMG signals were included.
**Conclusion:** The use of sEMG signals to calculate joint torque is an alternative method that allows therapists to obtain quantitative parameters and assess the progress of patients undergoing knee rehabilitation processes.
**Keywords:** Knee Joint; Electromyography; Torque; Muscle Contraction (MeSH).

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## Resumen

**Introducción.** Múltiples estudios de procesamiento de señales han reportado la aplicación de las señales de electromiografía de superficie (sEMG) en robótica y en procesos de rehabilitación motora.
**Objetivo.** Realizar una revisión de la literatura sobre el uso de señales de sEMG como alternativa para la estimación del par de rodilla con el fin de medir objetivamente el progreso de los pacientes en las diferentes etapas de rehabilitación de lesiones de rodilla.
**Materiales y métodos.** Se realizó una revisión de la literatura publicada entre 1986 y 2018, sin límites geográficos, en las bases de datos Engineering Village, IEEE Xplore, ScienceDirect, Web of Science, Scopus y PubMed mediante la combinación de 8 términos de búsqueda.
**Resultados.** Al finalizar la búsqueda inicial se obtuvieron 355 registros. Luego de realizar la remoción de duplicados esta cifra descendió a 308, los cuales fueron analizados para determinar si cumplían con los criterios de inclusión. Finalmente se incluyeron 18 estudios que describen de forma comparativa cómo estimar el par a partir de señales de sEMG.
**Conclusión.** El uso de señales de sEMG para calcular el par en una articulación es una herramienta alternativa que permite al terapeuta acceder a parámetros cuantitativos y, de esta forma, valorar el progreso de los pacientes durante el proceso de rehabilitación de rodilla.
**Palabras clave:** Articulación de la rodilla; Electromiografía; Contracción muscular (DeCS).

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## Introduction

The knee is one of the most complex joint structures in the human body. It is composed of the tibiofemoral and patellofemoral joints[1-4] and its formation involves both bone components (femur, tibia, and patella) and soft tissue components (synovial membrane, joint capsule, bursae, retinaculum, meniscus, and ligaments).[1,4-6]

The movements of the knee occur in the tibiofemoral joint and are mainly flexion and extension, but there may also be internal and external rotation to a lesser extent.[2,6,7] The range of motion for knee flexion is 130° to 140°; however, these values may increase or decrease depending on the position of the hip joint during knee movement.[2,8]

Currently, there are different diagnostic tests and specific exploratory maneuvers to assess the anatomic and functional characteristics of the knee joint complex. These tools are based on tests and clinical signs, and require the expertise of the physical therapist for a correct execution and interpretation of the results, and for a proper assessment of the integrity of the cartilage, muscles, menisci, ligament stability, etc.[9]

The functioning of the knee can be affected by pathologies of traumatic, degenerative, genetic, neurological, or autoimmune origin,[10] the first two being the most common types. Depending on the type of injury, different intervention protocols should be implemented, using different techniques aimed at proprioceptive re-education to encourage the execution of reflex activities and activate and strengthen muscle groups to stabilize the joint and improve its muscle elasticity and joint thickness. These techniques are also useful for gait training and re-education of the sporting gesture.

Rehabilitation processes are based on protocols and clinical practice guidelines with therapeutic objectives that seek to potentiate joint motion through anisometric contractions that modify the length of the muscle.[11-13] Also, to determine the progress of the interventions, multiple devices are available to measure variables such as angular position, angular velocities, force and torque in different joints of the body.[14-17] However, these equipment are expensive and rehabilitation centers cannot afford them and must perform therapies in the traditional manner. Therefore, it is common that physical therapists do not have access to quantitative data that help them determine patients' progress during the different phases of rehabilitation.

Specifically, joint torque measurement is used to objectively determine patient progress as rehabilitation progresses[15-17] and is used in therapeutic interventions for anterior cruciate ligament injuries,[11,17] postoperative meniscectomy rehabilitations,[16] lumbar injuries,[15] among others. To this end, devices such as the Contrex[18] and Human Norm[19] systems are available on the market to monitor torque and allow the visualization of graphs that evidence the progress of this variable but, as mentioned above, they can be expensive and, in the Colombian case, they cost at least 10 times more than surface electromyography (sEMG) signal processing equipment.[20,21]

Isokinetic dynamometers are instruments that allow obtaining information on torque during knee flexion-extension movement and, this way, establish its angle and maximum peak, as well as muscle power, muscle balance, etc.; these results allow quantifying objectively the recovery of the patient.[16,22-27] It should be noted that, despite its usefulness, the periodic collection of these data is limited due to high technology costs and, therefore, institutions prefer to use isometric dynamometers that have a lower cost but only allow measurements in static positions. This considerably limits the collection of relevant information for the implementation of rehabilitation processes.

On the other hand, sEMG signals are used as an alternative to estimate joint movements and the amount of force needed to perform a motor task,[28] as well as to determine the state of the musculoskeletal or neuromuscular system,[29-31] as they provide valuable information on the timing and relative intensity of muscle activity.[32,33] These signals are measured with surface electrodes placed on the skin above the muscle group of interest.[28,29,34] Currently, there are several low-cost sEMG sensors, which represents an advantage over other devices such as isokinetic dynamometers.

Given this scenario, the objective of the present work was to conduct a literature review on the use of sEMG signals as an alternative to calculate knee joint torque to objectively measure patients' progress during the different stages of rehabilitation of injuries in this joint.

## Materials and methods

A literature review was conducted based on the Cochrane Collaboration handbook.[35] The search was performed on the Engineering Village, IEEE Xplore, ScienceDirect, Web of Science, Scopus and PubMed databases using the following search strategy: years of publication: 1986 to 2018; type of publications: article and conference proceedings; language: English and Spanish; search equation: ("torque measurement" OR "torque estimation" OR "estimation of torque") AND (EMG OR sEMG OR electromyography OR electromyographic) AND Knee.

This review was based on the algorithms that have been developed to estimate knee joint torque through sEMG signals. It also considered how these algorithms can be used as an alternative to quantify the progress of patients during rehabilitation. To determine the search equation, MeSH terms that met the description required by the authors were established.

Publications in which sEMG signals were used to calculate knee joint torque were included. State-of-the-art reviews and references where torque was not measured using sEMG signals or which estimated torque in joints other than the knee were excluded. For information analysis, the current commercial value of isometric and isokinetic dynamometers in Colombia was considered.

355 records were retrieved, of which 47 were eliminated because they were duplicated. Exclusion and inclusion criteria were applied to the remaining 308 records, which led to eliminate 290 of them. Therefore, 18 publications were finally included (Figure 1).

## Results

A total of 18 publications that describe, in a comparative way, how to estimate knee joint torque from sEMG signals were retrieved; the most relevant aspects are presented in Table 1. All the articles found were published in English and were original research works published in indexed journals and in memoirs of events.

Table 2 classifies the records included according to the year of publication. It shows that most articles were published in 2017, with 27.78%.

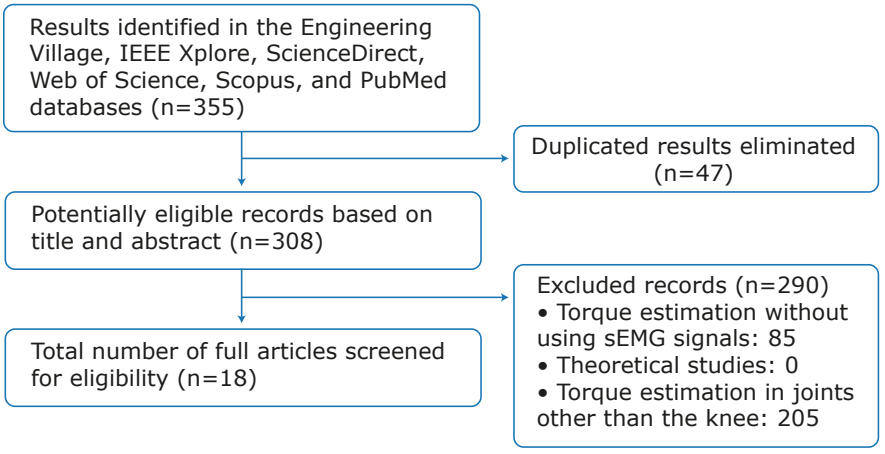


**Figure 1.** Bibliographic search flowchart.
Source: Own elaboration.

**Table 1.** Torque estimation algorithms based on surface electromyography signals.

| Author/Year | Torque estimation strategy | Surface electromyography signal processing | Muscles used | Type of contraction | Number of people studied |
|---|---|---|---|---|---|
| Hahn [36] 2007 | Neural networks | Full wave rectification and 5Hz low-pass filter | Vastus lateralis and biceps femoris | Isokinetic, eccentric, and concentric | 20 |
| Anwar *et al.*[37] 2017 | Neural networks, fuzzy logic | Quadratic mean | Rectus femoris and vastus medialis | Isokinetic | 1 |
| Anwar & Al-Jumaily[38] 2017 | Support vector machine | Mean frequency, median frequency, total transformed spectral power, and wavelet | Rectus femoris, vastus medialis, vastus lateralis, biceps femoris, semitendinosus, semimembranosus | Isometric | 5 |
| Nurhanim *et al.*[39] 2017 | Particle swarm optimization | Quadratic mean | Vastus lateralis | Isokinetic | 1 |
| Peng *et al.*[40] 2015 | Neural networks | Full wave rectification and 2Hz low-pass filter | Rectus femoris, vastus lateralis, vastus medialis, biceps femoris, and semitendinosus | Eccentric and concentric | 1 |
| Menegaldo *et al.*[41] 2014 | Hill's muscle model | Rectification and band-pass filter | Rectus femoris, vastus medialis, and vastus lateralis | Isometric | 1 |
| Tsutsui *et al.*[42] 2005 | Neural networks | Rectification and moving average | Rectus femoris and biceps femoris | Isometric | 1 |
| Simon *et al.* [43] 1995 | Polynomial model | Rectification and low-pass filter | Rectus femoris, vastus lateralis, vastus medialis, semitendinosus, and biceps femoris | Isokinetic | 5 |
| Heine *et al.*[44] 2018 | Hill's muscle model | Rectification and 6Hz low-pass filter | Vastus medialis, vastus lateralis, vastus medialis, and rectus femoris | Isokinetic | 1 |
| Ardestani *et al.*[45] 2014 | Wavelet neural networks | Quadratic mean and 1Hz low-pass filter | Semimembranosus, biceps femoris, vastus intermedius, vastus lateralis, and rectus femoris | Gait | 4 |
| Anwar & Anam[46] 2016 | Neural networks and machine learning | Mean frequency, median frequency, average power, total power, power spectral density, spectral momentum, and power spectral ratio | Rectus femoris, vastus medialis, vastus lateralis, biceps femoris, semitendinosus, semimembranosus | Isometric | 5 |

**Table 1.** Torque estimation algorithms based on surface electromyography signals. (continued)

| Author/Year | Torque estimation strategy | Surface electromyography signal processing | Muscles used | Type of contraction | Number of people studied |
|---|---|---|---|---|---|
| Peng *et al.*[47] 2015 | Musculoskeletal model and optimization with genetic algorithms | 2Hz low-pass filter | Quadriceps, hamstrings, and gastrocnemius | Eccentric and concentric | 1 |
| Bai *et al.*[48] 2013 | Continuous wavelet transform | Mean frequency | Quadriceps and hamstrings | Eccentric and concentric | 10 |
| Simon *et al.*[49] 1994 | Pattern comparison | Rectification and low-pass filter | Rectus femoris, vastus lateralis, vastus medialis, biceps femoris, and semitendinosus | Isokinetic | 5 |
| Amarantini & Martin[50] 2004 | Optimization | Full wave rectification | Rectus femoris, vastus medialis, biceps femoris, and gastrocnemius | Site walks | 9 |
| Anwar & Al-Dmour[51] 2017 | Adaptive neural networks and fuzzy logic | - | Quadriceps | Isokinetic | 1 |
| Liu *et al.*[52] 2017 | Hill's muscle model | Full wave rectification, low-pass filter | Rectus femoris, vastus lateralis and semitendinosus | Eccentric and concentric | 1 |
| Shabani & Mahjoob [53] 2016 | Hill's muscle model | Full wave rectification, 200Hz low pass filter | Rectus femoris, vastus medialis, vastus lateralis, semimembranosus, semitendinosus, and biceps femoris | Eccentric and concentric | 1 |

Source: Own elaboration.

**Table 2.** Number of works included per year.

| Year | 1994 | 1995 | 2004 | 2005 | 2007 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Articles | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 5 | 1 |

Source: Own elaboration.

The Journal of Biomechanics was the source from which the largest number of publications was retrieved (2 references). The remaining journals and conferences only contributed one article each (Table 3).

**Table 3.** Sources of the publications included.

| Name of journal or conference | Number of articles | References |
|---|---|---|
| Journal of Biomechanics | 2 | 36,50 |
| Procedia Computer Science | 1 | 37 |
| 2016 International Conference on Systems in Medicine and Biology (ICSMB) | 1 | 38 |
| 2016 2nd IEEE International Symposium on Robotics and Manufacturing Automation (ROMA) | 1 | 39 |
| 2015 International Joint Conference on Neural Networks (IJCNN) | 1 | 40 |
| Biomedical engineering online | 1 | 41 |
| Optomechatronic Sensors and Instrumentation | 1 | 42 |
| Proceedings of 17th International Conference of the Engineering in Medicine and Biology Society | 1 | 43 |
| Medical Engineering & Physics | 1 | 44 |
| Expert Systems with Applications | 1 | 45 |
| 2016 6th IEEE International Conference on Biomedical Robotics and Biomechatronics (BioRob) | 1 | 46 |
| 2015 IEEE International Conference on Robotics and Biomimetics (ROBIO) | 1 | 47 |
| 2013 IEEE 13th International Conference on Rehabilitation Robotics (ICORR) | 1 | 48 |
| Proceedings of 16th Annual International Conference of the IEEE Engineering in Medicine and Biology Society | 1 | 49 |
| 2017 IEEE Symposium Series on Computational Intelligence (SSCI) | 1 | 51 |
| 2017 IEEE International Conference on Cyborg and Bionic Systems (CBS) | 1 | 52 |
| 2016 4th International Conference on Robotics and Mechatronics (ICROM) | 1 | 53 |

Source: Own elaboration.

Of the 18 papers included, 14 used algorithms to calculate knee joint torque during the execution of motor tasks involving movement[36,38-41,43,45,47-53] and 4 used them for motor tasks without joint movement.[37,42,44,46]

Each algorithm has different characteristics, such as the type of sEMG signal processing, the muscles used, the strategy implemented for the development of the algorithm, and the number of people studied. Some of the strategies used are neural networks, fuzzy logic, Hill's muscle model, support vector machines, particle swarm optimization, polynomial models, wavelet neural networks, and wavelet transform. Similarly, the algorithms differ in the types of contractions (concentric, eccentric, isokinetic, or isometric) used during sEMG signal detection.

Moreover, 13 of the articles reviewed used black-box techniques to estimate knee joint torque, while 5 did so using white-box models, specifically Hill's muscle models. Of the 13 investigations that opted for black-box models, 7 used neural networks; 3, regression and optimization-based models; 1, continuous wavelet transform; 1, vector support machines; and 1, pattern matching.

With this in mind, the authors of the present research describe below a work developed using neuronal networks, one using a regression model (black-box model), and another using a musculoskeletal model (white-box model).

First, Han[36] estimated the knee joint torque of 20 individuals using a three-layer feed-forward artificial neural network in two stages. In the first stage, they were asked to perform the maximum voluntary contraction; in the second stage, they were asked to perform exercises at 30°/s and 60°/s within the whole range of motion of the knee, exercising eccentric and concentric contraction. In both stages, the measurements of the sEMG signals and joint torque were recorded. It should be noted that in the neural network model, the second layer contained a variable number of "hidden" units (5, 10, 15, 20, 25, 30) that represented the portion of the network learning process in which most of the processing solution occurred. Also, age, sex, height, body mass, the envelopes of the sEMG signals of the agonist (vastus lateralis) and antagonist (biceps femoris) muscles, which were obtained from full wave rectification using a 5 Hz low-pass filter, the joint angle and joint speed were considered as predictive variables of net torque. The study concluded that artificial neural network models achieved a more accurate torque estimate (R=96) compared to stepwise regression models (R=0.76), that the accuracy of the model increased considerably when the number of "hidden" units increased from 5 to 10, that accuracy improved progressively as more hidden units were added, and that, according to the results obtained, it is possible to say that the performance of the model could be the best if 15 or more "hidden" units were used, achieving 100% convergence and 88% to 90% accuracy.

On the other hand, Simon *et al.*[43] analyzed in 5 test subjects the relationship between the sEMG signals of the rectus femoris, vastus lateralis, vastus medialis, semitendinosus and biceps femoris muscles, as well as knee joint torque during flexion and extension. In this work, the authors designed a regression model as a function of angular position and velocity, the previous values of the torque and the rectified and smoothed sEMG signals. Based on this, they determined the coefficients using the least squares method from the information of 3 of the test subjects; the information of the 2 remaining subjects was used to validate the model. The authors obtained acceptable results in the validation subjects, where the R^2 values were 0.98 and 0.96 for extension, and 0.92 and 0.73 for flexion.

Finally, Peng *et al.*[47] designed a model that consists of two main modules. Firstly, a muscle-tendon model calculates muscle force through the dynamics of muscle contraction; secondly, the values of these forces are entered into a musculoskeletal model to estimate joint torque. This model requires knowing details related to the muscles, such as length, force-length relationship, force-velocity relationship, among others; to validate it, the researchers used the mean squared error and the correlation coefficient, obtaining 3.65Nm in the first one and 0.96 points in the second one when they delayed the signal in 100ms. The results were considered logical due to the nature of the sEMG signal, which occurs 10-100ms before joint movement. It should be noted that this type of model allows us to know the individual contribution of each of the muscles studied, which can optimize patients' rehabilitation plans.

The algorithms of knee joint torque estimation found in this research have been developed by means of diverse techniques and their main objective is to estimate torque using the electrophysiological signals of the muscles of this joint. Unlike other algorithms that do not use muscle signals, they allow physical therapists to obtain additional and relevant information, such as muscle activation during rehabilitation processes.

## Discussion

### The processing of sEMG signals allows measuring knee joint torque during the execution of movements

According to the literature reviewed, there are multiple algorithms that allow estimating knee torque using sEMG signals from the muscles associated with the flexion and extension of this joint. 23% of the algorithms found are used for measurements under static conditions[37,42,44,46] and the remaining 77% for measurements during the execution of movements.[36,38,39-41,43,45,47-53] To develop these algorithms, techniques such as the Hill's muscle model,[29,41,44] particle swarm optimization,[39] polynomial models,[49] wavelet neural networks and wavelet transform are used.[45] Of these, only the Hill's muscle model is white-box because it is based on biomechanical models; the others are classified as black-box models since they do not pretend to know the structure of the study muscles.

Although there are methods based on biomechanical analyses and physical laws of motion dynamics to calculate the torque exerted by a subject during knee flexion and extension movements,[54] algorithms based on electrophysiological signals, especially sEMG signals from the muscles of interest, are an effective alternative for measuring the torque exerted by this joint during movement and in different static positions.[50] The latter method provides physical therapists with quantitative information to support the rehabilitation process of the subject since it allows assessing the activation and contraction of the muscles associated with the joint to be rehabilitated, in this case, the knee.[9,28]

Likewise, sEMG signals make it possible to objectively determine progress in terms of strengthening the muscles that provide stability to the knee joint. In practice, this is usually done by means of manual or external resistance elements, such as dumbbells, obtaining inaccurate measurements.

In this sense, estimating knee joint torque by means of sEMG signals has advantages as the measurement can be carried out with low-cost commercial devices, such as the MyoWare Muscle Sensor from Sparkfun Electronics. Similarly, these types of signals provide information related to the activation of the muscles involved in the joint of interest (knee) during exercises that require movement and resemble the muscles necessary for the development of activities of daily living. Finally, the algorithms for estimating joint torque based on black-box models[40,42,45,46] and using sEMG signals as input allow obtaining algorithms that behave appropriately for a specific subject without the need to know muscle parameters, which are required by Hill-type muscle models.

The sEMG signals have some limitations for the estimation of joint torque, such as the fact that the algorithms that focus on regressions and optimizations[39,43,50] seek to adjust the parameters of the models according to the experimental data obtained in a single person and, therefore, cannot be applied to any population. The same happens with algorithms based on neural networks: Anwar & Al-Jumaily[38] did not validate it with data other than training data; Han[36] trained a neural network to estimate joint torque in 20 people, but the training and the validation were done with information from a single patient, which can lead to an over-trained neural network; and Anwar & Al-Dmour[51] trained a neuronal network with the data of a person for isokinetic exercises, with which acceptable results of torque estimation at low speeds were observed, however, the results for exercises at high speeds were not satisfactory and the information collected cannot be generalized.

On the other hand, Peng *et al.*[40] & Bai *et al.*[48] conducted studies in which they sought to provide an approximate measure of torque in the assessed joints by detecting user intent through sEMG signals. This approximate torque is used as input to rehabilitation systems for active-assisted exercises: however, it is not a precise torque. Finally, other studies were found[41,44,47,52,53] in which algorithms based on the Hill's muscle model use information related to the muscles of interest, such as the length of the tendons, which varies according to the angle at which the joint is located. Nevertheless, this model requires the calibration of these parameters for each subject and the measurement of the maximum voluntary contraction in each session, which makes it a subject-dependent model.

It should be mentioned that, to measure knee joint torque and torque of any joint in general, the electrodes must be properly placed on the muscles of interest since the sEMG signal varies depending on that location. In addition, there are other variables that affect signal, such as crosstalk, skin impedance, sweating, and ambient and skin temperature.[18]

Most of the methods found require other signals besides sEMG signals to measure knee joint torque, such as kinematic signals[36,37] and force signals.[43] This implies that it is necessary to use additional elements to carry out the measurements.

## Estimating knee torque using sEMG signals allows physical therapists to assess the condition of the muscles that provide stability to the joint and measure progress during rehabilitation

For decades, sEMGs have contributed to the diagnosis of various pathologies in the field of rehabilitation.[19] According to the reviewed literature, the intensity of the sEMG signal is highly correlated with the intensity of muscle force, which allows estimating the intention of movement and joint torque.[35-39] Moreover, some studies show that dynamic and static measurements, in different positions of the joint, allow determining the value of the maximum torque that the subject is able to exert.[11,15,23,20]

Technological advances to capture and extract information from sEMG signals make it possible to measure torque periodically. This provides the therapist with relevant information about the condition of the muscle and allows determining the progress of the subject during rehabilitation. In addition, the information obtained allows performing a quantitative evaluation of the patient's condition and, based on this, determining the adequate resistance that may be required to perform different motor tasks during the rehabilitation process of injuries to structures such as the anterior cruciate ligament[11,17] and the menisci,[16] as well as for gait training.[25]

Consistent with the above, sEMG signals could be used not only as an interface between humans and robotic rehabilitation systems, as is the case with exoskeletons,[36,40,41] but also as a strategy for patient assessment and joint torque measurement.

Physical therapists in Colombia do not usually have tools that allow them to obtain quantitative data to determine the patient's progress during the rehabilitation process.[19,21] For this reason, the measurement of joint torque by means of sEMG signals would be of great help and would allow them to guide the intervention plan in accordance with clinical observations. However, it is necessary to determine the times and moments in which sEMG is used to quantitatively determine the state of the muscles that provide stability to the joint since muscle fatigue reduces the efficiency of the contractions and the movements performed,[54] which could yield erroneous data on the progress of patients.

## Exercises based on anisometric contractions and torque measurement during a sequence of joint movement allow determining patients' progress

Anisometric contractions are useful during therapeutic interventions because they allow increasing muscle force, power, and resistance by means of muscle fiber recruitment. This in turn optimizes joint stability and mobility and allows for a wide range of torque during a movement sequence, which can be estimated using algorithms that take sEMG signals as inputs.

During knee rehabilitation and training processes in athletes, it is important to determine the activity of the muscle during the execution of motor tasks to optimize the performance of the muscle based on the calculation of resistance and its influence in accessory muscles.[19] According to this, sEMG signals are a tool that, in addition to estimating joint torque, allows monitoring the electrical activity of the muscles.

In this scenario, it is proposed that measuring joint torque by means of sEMG signals is of great help for physical therapists during the diagnostic phase since they allow defining the therapeutic objectives based on quantitative data, determining the capacity of muscle fiber recruitment during the execution of the movement, establishing the appropriate resistance for the execution of motor tasks, and determining the progress of the patients during the rehabilitation process.[50]

## Conclusions

The present literature review led to find an important number of publications that document the calculation of knee joint torque from sEMG signals during the execution of anisometric exercises. However, no publications were identified in which the torque calculated from sEMG signals was used in rehabilitation processes as such, so it is necessary to carry out research on this topic, which promises interesting applications in physical therapy.

Results regarding the measurement of knee joint torque from sEMG signals are an application of the biomedical signal processing theory and, therefore, an alternative route to traditional work in biomechanics and rehabilitation, which usually involves the application of mechanical laws.

In practice, measuring joint torque dynamically using sEMG signals represents an easily accessible and low-cost alternative to the use of isokinetic dynamometers for the patient's rehabilitation process. This alternative is also an option that expands the possibilities of monitoring and assessment.

Another advantage of measuring knee joint torque using sEMG signals is that they are always available for processing and, therefore, the physical therapist permanently has data on muscle activation, which are not provided by other joint torque measurement technologies. However, sEMG signals also have limitations because they require professionals to have basic knowledge of the capture technique to obtain good-quality results.

## Conflicts of interest

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# *Cnidoscolus aconitifolius*: therapeutic use and phytochemical properties. Literature review

## *Cnidoscolus aconitifolius: usos terapéuticos y propiedades fitoquímicas. Revisión de la literatura*

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## *Abstract*

**Introduction:** Medicinal plants have been traditionally used to cure or alleviate infectious and non-infectious diseases. They are widely accepted due to their low cost and low toxicity indexes. These plants are frequently used in cases involving skin irritation, superficial wounds, insect bites, and snake bites.
**Objective:** To compile available evidence on the main therapeutic uses and phytochemical components of *Cnidoscolus aconitifolius* (popularly known as chaya), a plant that grows in tropical regions of Mexico and Central America.
**Materials and methods:** A literature review of studies on *C. aconitifolius* published until 2017 was conducted in the BIREME, PubMed/Medline, Elsevier and SciELO databases. Descriptors *"Cnidoscolus"* and *"aconitifolius"* were used for the literature search, and no language restrictions were applied.
**Results:** 82 articles were retrieved after completing the initial search. Once the studies were filtered by title (descriptors in the title) and duplicates were removed, 18 articles were reviewed. Based on the information found, it was possible to confirm that this plant has multiple health benefits.
**Conclusions:** The traditional therapeutic use of *Cnidoscolus aconitifolius* is backed by scientific evidence. Therefore, further research aimed at identifying new phytochemical properties of this plant should be conducted to establish alternative therapies for treating different conditions.
**Keywords:** Plants, Medicinal; Phytochemicals; Therapeutic Uses (MeSH).

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## *Resumen*

**Introducción.** El uso tradicional de plantas medicinales para tratar diferentes enfermedades, ya sean infecciosas o no, es ampliamente aceptado debido a su bajo costo y sus bajos índices de toxicidad. Estas plantas son frecuentemente usadas en casos que involucran irritaciones de la piel, heridas superficiales, picaduras de insectos y mordeduras de víboras.
**Objetivo.** Recopilar la información disponible sobre los principales usos terapéuticos y los componentes fitoquímicos de *Cnidoscolus aconitifolius*, una planta conocida popularmente como chaya y que crece en regiones tropicales de México y Centroamérica.
**Materiales y métodos.** Se realizó una revisión de la literatura sobre *C. aconitifolius* publicada hasta 2017 en las bases de datos BIREME, PubMed/Medline, Elsevier y SciELO. Para la búsqueda se emplearon los descriptores *"Cnidoscolus"* y *"aconitifolius"*, y no se aplicaron filtros de idioma.
**Resultados.** Se identificaron 82 artículos luego de completar la búsqueda inicial. Después de filtrar los estudios por título (presencia de descriptores de búsqueda en el título) y remover duplicados, se incluyeron 18 artículos en la revisión. De acuerdo a la información encontrada, fue posible confirmar que esta planta ofrece diversos beneficios para la salud.
**Conclusiones.** El uso terapéutico tradicional de la chaya está sustentado por evidencia científica, por lo que se sugiere realizar más investigaciones centradas en la identificación de nuevas propiedades fitoquímicas de esta planta y, así, establecer alternativas terapéuticas para distintas afecciones.
**Palabras clave:** Plantas medicinales; Fitoquímicos; Usos terapéuticos (DeCS).

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## Introduction

About 80% of people living in developing countries practice traditional medicine as an alternative therapy for their health care. Specifically, the use of medicinal plants in therapy (defined as any plant species that can be used for therapeutic purposes due to its composition or whose active ingredients can serve as precursors for the synthesis of new drugs), also known as phytotherapy, is quite widespread worldwide. It is worth noting that around 67% of the species used in these types of therapies come from least developed and developing countries.[1-6]

Traditional medicine is based on folk knowledge, which determines its efficacy through observable benefits. This type of medication may pose challenges; for example, in popular phytotherapy, it is very difficult to control the dose and quality of the product, which can lead to risks and damage to health. This problem is mainly explained by the fact that many traditional remedies are made from wild plants whose chemical components can vary due to genetic or environmental reasons.[7,8] It should be noted that ethnobotany has no scientific validation.[9-10]

The traditional use of medicinal plants to treat both infectious and non-infectious diseases has been widely accepted since ancient times due to their low cost, accessibility, and low toxicity rates compared to synthetic products.[11-13] Humans commonly resort to this therapeutic option in the presence of skin irritations, wounds, insect bites, and snake bites.[14,15]

Currently, there is an exponential increase in the use of phytotherapy to maintain an adequate state of general health.[16] In this regard, the World Health Organization (WHO) states that more than two thirds of the world's population use or have used at least one medicinal plant to treat some condition.[4]

Chronic non-communicable diseases are a new challenge in the fight to improve global health and are a public health concern despite the progress made by the pharmaceutical industry. Moreover, it should be noted that some populations do not have easy access to medicines and medicinal plants are their first, or even only, treatment option.

In this context, a relevant example of the use of phytotherapy is chaya (*Cnidoscolus aconitifolius*), a plant of the genus *Cnidoscolus* that belongs to the family *Euphorbiacea*, which has been attributed different benefits for the treatment and control of certain pathologies. The family *Euphorbiacea* comprises 50 species, of which 20 are considered endemic to Mexico and are distributed mainly in tropical and subtropical zones, Mesoamerica being the area where they are most produced and where their domestication is most frequent.[17-19]

Hypoglycemic,[20] antioxidant,[21] analgesic and anti-inflammatory effects[22-24] are the main benefits attributed to chaya. It is commonly used to treat rheumatism, gastrointestinal disorders[25] and inflammatory diseases,[26,27] and it has also been reported that it has an important nutritional contribution as poultry feed, especially in Africa.[28] In recent years, to measure its efficacy and safety, various investigations have analyzed the components of this plant, the leaves being the most studied part.[29,30]

The objective of this research was to review the available literature on the main medical uses and phytochemical components of *C. aconitifolius* to answer the question: Is there sufficient scientific evidence on the therapeutic properties of chaya to treat human pathologies?

## Materials and methods

A literature review on *C. aconitifolius* was conducted in the BIREME, PubMed/Medline, Elsevier and SciELO databases with the descriptors "*Cnidoscolus*" and "*aconitifolius*". The search was limited to articles published until 2017; no articles were excluded because of language restrictions or methodological reasons.

### Data search

The first step was to make a general query without restrictions, and then a new search was made using the title as a filter. The strategies presented in Table 1 were applied.

**Table 1.** Databases analyzed and search strategies used.

| Database | Search strategy (syntax) | Search limits | No. of articles |
|---|---|---|---|
| Elsevier | TITLE(*Cnidoscolus aconitifolius*) | Title | 3 |
| SciELO | (ti:(*cnidoscolus*)) AND (ti:(*aconitifolius*)) | Titulo | 1 |
| BIREME | (ti:(*Cnidoscolus aconitifolius*)) | Titulo | 15 |
| PubMed/ Medline | *Cnidoscolus*[Title] AND *aconitifolius*[Title] | Title | 14 |

Source: Own elaboration.

### Selection of articles

In the first search without restriction, 82 articles were retrieved. During the subsequent search, after filtering the publications by title, 33 were obtained, of which 15 were excluded because they were repeated. Finally, 18 articles were included in the research. The algorithm for selecting the articles of interest is shown in Figure 1.

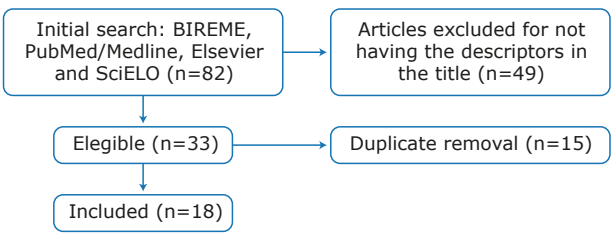


**Figure 1.** Flow chart used for selection of the articles of interest. Source: Own elaboration.

### Data collection

The selected articles were reviewed to synthesize, analyze, and facilitate the understanding of the results. The relevant data of each study were summarized in two groups: main phytochemical constituents of *C. aconitifolius* and medicinal properties of *C. aconitifolius*.

### Captured photographs

During the study, some photographs of *C. aconitifolius* were taken (Figure 2) to complement the study with visual

material. The pictures were taken using a Sony DSC-H400/VC E33 digital camera on January 21, 2018, in the community of Santo Tomás Tamazulapam (district of Miahuatlán de Porfirio Díaz, state of Oaxaca, Mexico), which is located in the following coordinates: latitude: 16.2705 and longitude: -96.5874 16° 16′ 14″ North, 96° 35′ 15″ West.


**Figure 2.** Photographs of *Cnidoscolus aconitifolius*. A) flower buds and plant flowers; B) lamina, primary and secondary veins, and petiole; C) stem; D) canopy.
Source: Documents obtained during the study.

## Results

Thirty-three research articles were included and classified according to the year of publication as shown in Figure 3. The largest number of articles about *C. aconitifolius* were published in 2010 and 2016 (8 each year).

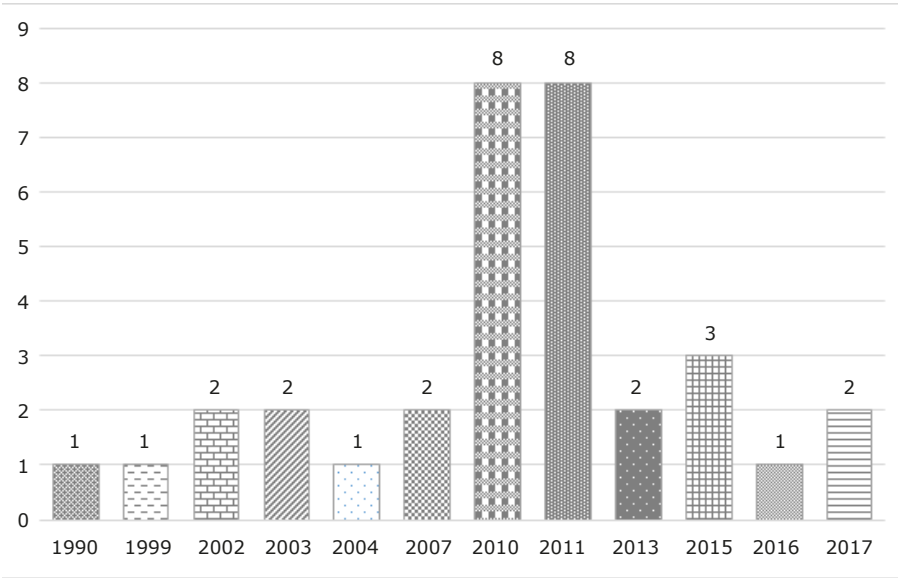


**Figure 3.** Number of publications on *Cnidoscolus aconitifolius*. The arrow indicates the year of publication of the first study found on this plant.
Source: Own elaboration.

By refining the articles and eliminating duplicates, a final sample of 18 articles was obtained with which the final analysis of the data was carried out. The publications were organized according to the main phytochemical constituents (Table 2) and the medicinal properties of *C. aconitifolius* (Table 3).

**Table 2.** Main phytochemical constituents of *Cnidoscolus aconitifolius.*

| Authors Year | Type of study | Part of the plant studied | Phytochemical constituents |
|---|---|---|---|
| Donkoh *et al.*[28] 1990 | Phytochemical study of the dry leaf | Leaves | High dietary protein potential for animals and toxic hydrocyanic glycosides that are degraded by cooking. |
| Sarmiento-Franco *et al.*[29] 2003 | Phytochemical study | Leaves | Raw fiber (140 g/kg), protein (305 g/kg), calcium (15.3 g/kg) and seven amino acids: alanine, arginine, aspartic acid, glutamic acid, leucine, isoleucine, and phenylalanine. |
| Escalante-Erosa *et al.*[30] 2004 | Epicuticular wax study | Tall leaves | Three triterpenoids: amirenone, β-amyrin acetate, and α-amyrin acetate. |
| Numa *et al.*[31] 2015 | Phytochemical study | Leaves | Flavonoids (hispidulin sulfate, eucalyptin and epigallocatechin di-O-gallate), sesquiterpene (triptofordin D1), xanthones (moreolic acid), polyanxanthone c, cadensin g, arvixanthone d and lignan (tiegusanin f). |
| Oyagbemi *et al.*[32] 2011 | Phytochemical screening | Leaves | Flavonoids, alkaloids, saponins, tannins, magnesium, manganese, iron, potassium, phosphate, and zinc. |
| Adaramoye *et al.*[33] 2011 | Clinical study on protection from liver damage | Leaves | Tannins, alkaloids, saponins, anthraquinones, flavonoids, cardiac glycosides, and phlobatannins. |
| Jaramillo-Jaramillo *et al.*[34] 2015 | Phytochemical study | Leaves of adult flowering plants | Fatty acids, triterpenes, and sugars. |
| Jiménez-Aguilar *et al.*[35] 2015 | Phytochemical study | Dry leaves | Calcium, magnesium, potassium, phosphorus, sulfur, iron, sodium, vitamin C (more abundant than in other green plants), as well as phenolic compounds at high levels, and flavonoids at medium levels. |
| Morales-Alvarado *et al.*[36] 2016 | Phytochemical study | Dehydrated leaves | Cyanogenic glycosides precursors of hydrocyanic acid, although it was proved to be easily eliminated by heat treatment. |
| Awoyinka *et al.*[37] 2007 | Phytochemical study | Dry leaves | Alkaloids, tannins, phlobatannins, saponins, and cardiac glycosides. |

Source: Own elaboration.

**Table 3.** Medical properties of *Cnidoscolus aconitifolius.*

| Authors Year | Medicinal potential of the plant described | Animal model | Study element | Main efficacy results |
|---|---|---|---|---|
| Azeez *et al.*[19] 2010. | Antioxidant effect | 25 male Wistar rats weighing from 100 to 250 grams | Leaves | *C. aconitifolius* improved the hematological parameters of alloxan-induced diabetes. |
| Saba *et al.*[22] 2010 | Hepatoprotective and antioxidant effect | 30 male Wistar rats weighing from 220 to 250 grams | Leaves | *C. aconitifolius* showed a significant restoration of hematological parameters and a decrease in blood ureic nitrogen and creatinine levels. |
| Oyagbemi *et al.*[23] 2010 | Hepatoprotective effect against paracetamol damage | 25 healthy male Wistar rats weighing from 220 to 250 grams | Leaf extract obtained from ethanol | *C. aconitifolius* had a hepatoprotective effect against paracetamol. |
| Onasanwo *et al.*[24] 2011 | Analgesic and anti-inflammatory effect | 30 Sprague-Dawley rats/mice weighing from 140 to 160 grams. | Leaves | *C. aconitifolius* demonstrated significant anti-inflammatory and analgesic effects. |
| Adaramoye *et al.*[33] 2011 | Stimulation of insulin secretion | 6-week old male Wistar rats weighing from 170 to 180 grams | Leaves | *C. aconitifolius* showed hepatoprotective and antioxidant effects, as well as protection against ethanol-induced poisoning. |
| Jaramillo-Jaramillo*et al.*[34] 2015 | Antioxidant effect | Male Wistar rats | Leaves | *C. aconitifolius* had an antioxidant effect but not a hypoglycemic effect. |

**Table 3.** Medical properties of *Cnidoscolus aconitifolius. (continued)*

| Authors Year | Medicinal potential of the plant described | Animal model | Study element | Main efficacy results |
|---|---|---|---|---|
| Sarmiento-Franco *et al.*[38] 2002 | Fattening effect on corn-fed chickens | Two-week old Hubbard chickens and day-old Ross chickens | Leaf flour | *C. aconitifolius* improved fattening of chickens on low-protein diets. |
| Oladeinde *et al.*[39] 2007 | Hypoglycemic effect | 4-8-week-old male mice weighing 25 grams | Leaves | *C. aconitifolius* stimulated dormant β cells to secrete insulin. |
| Adaramoye & Aluko[40] 2011 | Nephro-protective effect of methanol extract against chronic ethanol exposure. | 42 male Wistar rats weighing from 170 to 180 grams | Leaf extract obtained from ethanol | *C. aconitifolius* had a nephroprotective effect against chronic ethanol exposure and reduced glucose, protein, gamma-glutamyltransferase, and creatinine clearance levels. |
| Achi *et al.*[41] 2017 | Hypoglycemic, anticholesterolemic and antihypertriglyceridemic effect. | Albino and healthy male rats weighing 120 to 130 grams | Leaves | *C. aconitifolius* reduced blood glucose levels, increased weight and serum insulin level, and had a hypoglycemic, antihypercholesterolemic, insulin modulating and antihypertriglyceridemic action. |

Source: Own elaboration.

## Discussion

According to the available evidence, there are several investigations on *C. aconitifolius*[19,22-24,28-41] that confirm that its use as a medicinal plant has some benefits in the treatment of several diseases or injuries[42,43]. Therefore, further studies on the phytochemical properties and possible therapeutic uses of this plant should be conducted to identify new therapeutic alternatives for the treatment of different conditions[24,37], which will undoubtedly improve the quality of life of communities where traditional medicine is the main form of medical therapy.

Aguilar *et al.*[44] state that *C. aconitifolius*, besides having medicinal properties, is used as a vegetable and as fodder, which coincides with what is reported by Ross-Ibarra & Molina-Cruz.[45] Furthermore, according to Parra-Tabla *et al.,*[46] this plant can be consumed at any time as long as it has not lost more than 50% of its leaves, which depends on the type of climate in which it develops.

Some studies[22,23,33,40] describe the benefits of *C. aconitifolius* to treat hepatotoxicity and hematotoxicity since the plant components help reduce toxicity. Likewise, other works[39,41] have shown that chaya plays a key role in reducing high glucose levels in animal models.

It is worth mentioning that the results also show that *C. aconitifolius* has antioxidant[19,34,35] and antimicrobial[37,47] properties due to its secondary metabolites (flavonoids, tannins, saponins,[30-32] etc.).[48,49] Similarly, it was found that this plant contains phenolic components, which are the most abundant group of non-energy substances in foods of plant origin.[50]

Other species in the genus *Cnidoscolus* also show health benefits.[42,43] For example, Poot-López *et al.*[51] reported the diuretic and hypoglycemic effects of *Cnidoscolus chayamansa*. During this review, we also found that Donkoh *et al.*[52] suggested the inclusion of chaya in the food industry as a potential ingredient for poultry diet. In the study by Saba *et al.*[22] on the effects of *C. aconitifolius* leaf extract in rats with liver damage induced by carbon tetrachloride, it was found that the compounds of the plant restore the levels of hematological parameters, blood ureic nitrogen, and creatinine. Finally, Oyagbemi *et al.,*[23] in an analysis of the anti-diabetic properties of ethanolic extract of chaya made in male Wistar rats with alloxan-induced diabetes mellitus, showed that *C. aconitifolius* extract significantly reduces blood glucose and plasma cholesterol levels.

## Conclusions

*C. aconitifolius* is a plant species that has a significant protein content and is rich in flavonoids, tannins, and saponins. These characteristics grant it hypoglycemic, hepatoprotective, nephroprotective, anti-inflammatory and antioxidant properties.

The safety and efficacy of the traditional therapeutic use of chaya is supported by scientific evidence. Therefore, further research should be carried out focusing on the identification of new phytochemical properties of this plant and, thus, establish therapeutic alternatives for different conditions.

## Conflicts of interest

None stated by the authors.

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# Neurotoxical activity of *Micrurus* snake venom and methods for its analysis. A literature review

*Actividad neurotóxica del veneno de serpientes del género Micrurus y métodos para su análisis. Revisión de la literatura*

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## Abstract

**Introduction:** Snakes of the genus *Micrurus* have fossorial habits, passive temperament and scarce production of powerful venom with neurotoxic characteristics that block the synaptic transmission at the neuromuscular junction.
**Objective:** To present an overview of the neurotoxicity of the *Micrurus* snake venom, and its functional characterization by *ex vivo* analysis methods.
**Materials and methods:** A literature review was conducted in MedLine and ScienceDirect using specific terms and their combinations. Search strategy: type of studies: articles on the neurotoxicity of *Micrurus* snake venom and techniques to determine its neurotoxic activity by *in vitro, in vivo* and *ex vivo* models; publication period: articles published until June 2018; publication language: English and Spanish.
**Results:** Out of 88 studies identified in the initial search, 28 were excluded because they did not meet the inclusion criteria (based on reading their titles and abstracts). 8 additional articles (books and reports) were included, since, according to the authors' opinion, they complemented the information reported by the selected studies. The studies included in the review (n=68) were original research papers (n=44), review articles (n=16), and book chapters, reports, guides and online consultations (n=8).
**Conclusions:** Studies performed using *ex vivo* muscle and nerve preparations to evaluate the effect of neurotoxins provide a good model for the characterization of the pre-synaptic and post-synaptic effect of the venom produced by snakes of the genus *Micrurus.*
**Keywords:** *Elapidae; Micrurus;* Phospholipases A2; Neuromuscular Junction (MeSH).

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## Resumen

**Introducción.** Las serpientes del género *Micrurus* son animales de hábitos fosoriales, de temperamento pasivo y escasa producción de un potente veneno con características neurotóxicas que bloquean la transmisión sináptica en la placa neuromuscular.
**Objetivo.** Presentar un panorama general de la neurotoxicidad del veneno de las serpientes *Micrurus* y su caracterización funcional mediante métodos de análisis *ex vivo.*
**Materiales y métodos.** Se realizó una revisión de la literatura en MedLine y ScienceDirect usando términos específicos y sus combinaciones. Estrategia de búsqueda: tipo de estudios: artículos sobre la neurotoxicidad del veneno de serpientes *Micrurus* y técnicas para determinar su actividad neurotóxica mediante modelos *in vitro, in vivo* y *ex vivo;* periodo de publicación: sin límite inicial a junio de 2018; idiomas: inglés y español.
**Resultados.** De los 88 estudios identificados en la búsqueda inicial, se excluyeron 28 por no cumplir los criterios de inclusión (basándose en la lectura de títulos y resúmenes); además, se incluyeron 8 documentos adicionales (libros e informes), que, a criterio de los autores, complementaban la información reportada por las referencias seleccionadas. Los estudios incluidos en la revisión (n=68) correspondieron a las siguientes tipologías: investigaciones originales (n=44), artículos de revisión (n=16) y capítulos de libros, informes, guías y consultas en internet (n=8).
**Conclusiones.** Los estudios que describen el uso de preparaciones *ex vivo* de músculo y nervio para evaluar el efecto de neurotoxinas ofrecen un buen modelo para la caracterización del efecto presináptico y postsináptico del veneno producido por las serpientes *Micrurus*.
**Palabras clave:** *Elapidae; Micrurus*; Fosfolipasas A2; Unión neuromuscular (DeCS).

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## Introduction

Ophidian accidents are events caused by the bite of a snake and are of public health interest worldwide. Specifically, in Central and South America, about 300 000 bites of these animals are reported each year, of which 12 000 generate sequelae and 4 000 lead to death.[1] In Colombia, according to the *Instituto Nacional de Salud* (National Health Institute), 4 978 cases of snakebites were reported in 2017, of which 66 were caused by snakes of the genus *Micrurus*,[2] the most diverse and representative of the family *Elapidae*.[3-6]

Snakes of the genus *Micrurus*, also known as coral snakes, are docile animals that do not attack humans unless provoked. These reptiles have coloration patterns that serve as a defense mechanism and repel their predators. They also possess a powerful venom with a neurotoxic effect that they only use to defend themselves[7] and proteroglyph dentition, that is, their venom inoculating fang is located at the front end of the upper jaw. In this type of dentition, the groove through which the venom passes in the fang is not completely closed and, for this reason, the snake must hold onto their prey for a few seconds to ensure the entry of the venom.[8]

These species have a venom gland situated on each side of the head, which is made up of a main gland, a primary duct, and an accessory mucous gland. Moreover, the main gland is surrounded by branches of the pterygoid muscles and external jaw adductors.[8-11]

Since the production of venom in snakes is a slow process, they store it mainly in intracellular form in seromucous cells or in the central lumen of the venom gland (to a lesser extent).[8,12] In addition, the production of toxins in this gland is stimulated by biochemical and morphological changes in the secretory epithelial cells; this production process is carried out asynchronously after the extraction or inoculation of the venom, so its concentration is altered.

The amount and composition of the venom produced by snakes depends on epigenetic variations between individuals, the species, the site of origin, the ontogenetic stages, the phylogenetic changes and the feeding habits of each individual, as well as on the environmental conditions where they develop and live.[10,12-16] Costa-Cardoso *et al.*[10] state that the venom of coral snakes contains 25% total solids, 70-90% proteins and polypeptides and 10-30% low molecular weight substances such as amines, carbohydrates, amino acids, ions and inorganic compounds. Lomont *et al.*[15] identified 22 protein families in the venom of *Micrurus* snakes using analytical techniques; the most abundant and representative are three-finger toxins (3FTx) and phospholipases A2 (PLA2), which contribute to the neurotoxic effect of these substances.

The proportion of PLA2 and 3FTx toxins in coral snake venoms is a key element for identifying the main neurotoxic effects of the venoms of all species of the genus *Micrurus*.[6,9,15-17] Different researches on this subject have established that neurotoxins act through two mechanisms: on the one hand, presynaptic neurotoxins block the release of acetylcholine from the presynaptic neuron and, on the other, the postsynaptic neurotoxins competitively bind to the nicotinic receptor at the neuromuscular junction.[10,18,19] Both situations lead to respiratory failure and death of the patient, if adequate treatment with antivenom is not provided timely.

The presence of these presynaptic and post-synaptic neurotoxins makes *Micrurus* venom lethal at low doses,[20-22] making the study of the effects of this venom on the neuromuscular transmission of electrical impulses highly relevant. To this end, *ex vivo* preparations of striated muscle tissue and nerve are used.[23,24]

Based on the abovementioned, two types of tests are used to evaluate the neurotoxic and myotoxic effects of snake venom: *ex vivo* assessment of neurotoxicity and *ex vivo* assessment of myotoxicity. The neurotoxicity assessment of these venoms should be performed in both muscle and nerve preparations due to the responses of the models, as explained below.[25-27]

### *Ex vivo* techniques for the assessment of neurotoxicity

The neurotoxic activity of the venom produced by *Micrurus* species is determined by applying a stimulus through the electrodes that are in contact with the biventer cervicis muscle of 4- to 8-day-old male chicks, or with the diaphragm and the phrenic nerve of male mice with body weight between 25g and 35g, which results in muscle contraction under normal conditions.[24] To perform this analysis, electrical impulses (0.1Hz for 0.2ms) are applied using a low-frequency stimulator and muscle contractions are recorded with a force displacement transducer that is coupled to recording equipment located in the muscle tissue of an isolated organ perfusion system. After a stabilization period of 20 minutes, a single concentration (0.1, 0.5, 1, 5 or 10 µg/mL) of the venom under study is added to the organ bath. To confirm the complete block of muscle contractions,[8,10] and to establish the concentration of the venom that caused such an effect,[27] it is necessary to apply new electrical stimuli and verify the records using a dose-response curve.

### *Ex vivo* techniques for the assessment of myotoxicity

Using muscle preparations similar to the biventer cervix muscle of male chicks, it is also possible to evaluate the ability of the venom to induce muscle damage.[26]

To achieve a selective stimulation of the muscle by suppressing neuromuscular activity, the preparations are placed in an organ bath in 10µM d-tubocurarine and the muscle is directly stimulated with electrical impulses of 0.1Hz at a maximum voltage of 0.2ms. The poison is then added to the preparation and left in contact until contraction is blocked or after 3 hours, after which time the tissues are immersed in 10% formaldehyde for histological examination to confirm myotoxicity.[19,23,25,27]

### Electrophysiological alterations

*Micrurus* snake venom, or some of its specific toxins, can alter the transmission of the normal electrical pulse in the neuromuscular junction. This is reflected, on the one hand, in a decrease or blockage of the response to direct electrical stimulation on the muscle and, on the other, in fluctuations in resting membrane potential, such as changes in amplitude, form and frequency, and Wedensky inhibition in some cases; these effects are caused by both prolonged and short exposures to the venom or one of its toxins.[24,28]

Similarly, by evaluating muscle contractility after applying electrical stimulation in the presence of acetylcholine

(ACh) and the venom under study, it is possible to determine if there are effects on the post-synaptic response to ACh. When there are no alterations in muscle contractility, the effect is considered presynaptic.[24,25]

Myotoxicity can be evaluated in an observational way and without the need for a pathological study, assessing the response of the striated muscle when exposed to the venom and the blocking action of the toxins on muscle contracture in the presence of a direct electrical impulse and high concentrations of $K^+$ in the organ bath.[26,27]

Since there is new information on *Micrurus* snake venoms and considering the large number of this genus species in Colombia, it is necessary to encourage research that characterizes these substances biochemically and biologically and promotes the development of more specific and useful antivenins to treat snakebite accidents.

In this context, the objective of this review was to present an overview of the neurotoxicity of *Micrurus* snake venom and its functional characterization using *ex vivo* analysis methods.

## Materials and methods

A literature review was conducted in the MedLine and Science Direct databases using the following search strategy: type of studies: research articles, reviews and specialized book chapters addressing neurotoxicity of *Micrurus* snake venom and techniques to determine their neurotoxic activity by means of *in vitro*, *in vivo* and *ex vivo models;* publication period: no initial limit until June 2018; languages: English and Spanish; search terms: "*Micrurus*", "*Elapidae*", "actividad neuromuscular", "neurotoxicidad", "miotoxicidad", "veneno de *Micrurus*", "fosfolipasas A2" and "Toxinas de tres dedos", which were combined with the "AND" and "OR" connectors to establish the search equations.

The review started with the search of the basic concepts of venom, mechanisms of neurotoxicity, myotoxicity and characterization, and determination *in vitro.* References that made a functional characterization of the venom using *ex vivo* preparations of the biventer cervicis muscle of chicks or the phrenic nerve of mice were included, and those that did not meet the search criteria were excluded.

A total of 151 publications were retrieved, of which 63 were eliminated because they were duplicated; the remaining 88 were reviewed for title, abstract and methodology, and 28 were excluded because they were not relevant to the topic of interest or did not meet the selection criteria. The study also included 8 additional records (books and reports) identified through other sources and which, in the authors' opinion, complemented the information reported by the selected references; finally, 68 publications were included in the review (Figure 1).

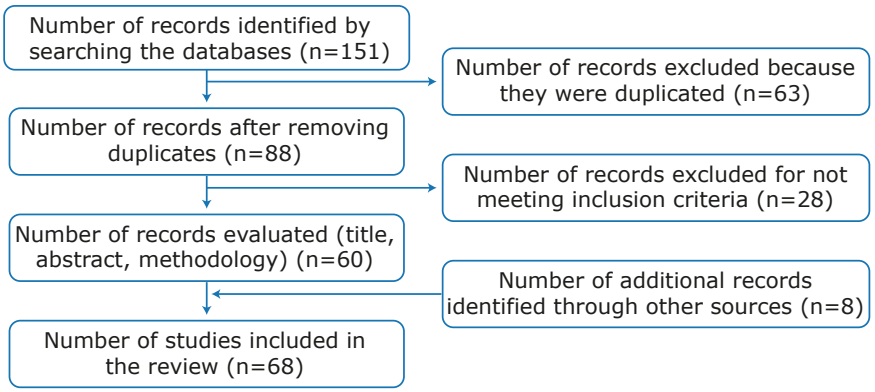


**Figure 1.** Review flowchart.
Source: Own elaboration.

## Results

Most of the studies (n=28) included in the review were published between 2010 and 2018, with a significant increase in the number of publications since 2000 (Figure 1). Except for 3 works developed in Colombia by regulatory bodies, all the literature found was published in English.

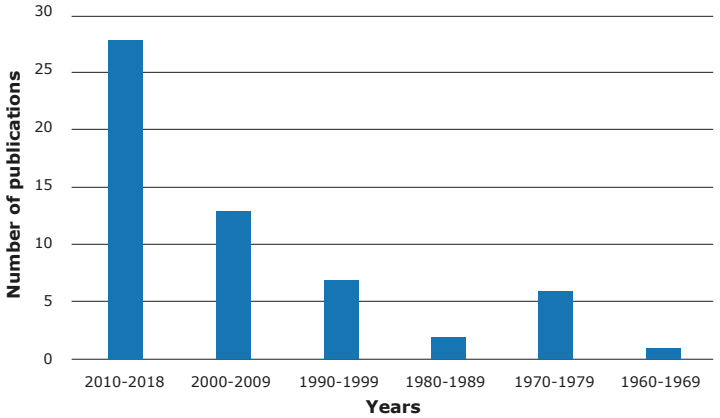


**Figure 2.** Number of publications on neurotoxicity of *Micrurus* snake venom and methods for its analysis.
Source: Own elaboration.

Of the 68 documents included, 16 were review articles, 5 were book chapters, 2 were guidelines and reports, and 1 was an Internet search; the remaining 44 publications were original articles and 18 of them used venoms of snakes of the genus *Micrurus* as samples (Table 1). Of the articles that specifically studied coral snake venom, only 6 were on Colombian species, including *Micrurus dumerilii*, *Micrurus mipartitus*, *Micrurus dissoleucus*, *Micrurus lemniscatus*, *Micrurus spixii and Micrurus surinamensis*, that is, only about 16% of the snake venoms of the genus *Micrurus* found in the country have been studied. Out of these species, only the proteome of the venom of *M. dumerilii* and *M. mipartitus* have been characterized[16,21,29] since they are the main varieties involved in snakebites.

One of the studies found[19] assessed the neurotoxic activity of the venom of *M. mipartitus* and *M. dissoleucus* by means of isolated muscle preparations and established the functional characterization of each one. Another study[20] described the multiple enzymatic activities of the venom of *M. lemniscatus*, *M. spixii* and *M. surinamensis* and evaluated the toxicity of each venom on different prey animals.

The study developed by Rey-Suarez *et al.*[29] showed that the venom proteome of the species *M. mipartitus* found in Colombia has a higher proportion of 3FTx, which is a different phenotype from that of the venom of *M. dumerilii*, a species that has higher levels of PLA2.[16,21] Moreover, the study by Renjifo *et al.*[19] found that the venom of *M. mipartitus* species has post-synaptic activity associated with the inhibition of muscle contraction caused by the presence of ACh, which is related to the large amount of 3FTx.

The use of *ex vivo* models for the assessment of snake venom neurotoxicity began with studies on elapid species, especially in the Old World, as evidenced in 7 of the articles included in the review.[24,26,28,30-33] Table 1 contains the studies found that were conducted on snakes of the genus *Micrurus*, as well as the articles that assessed neurotoxic activity of elapid venoms.

**Table 1.** Articles that assess neurotoxic activity included in the review.

| Authors | Type | Title | Year | Snakes of the genus *Micrurus* | Venom from species found in Colombia |
|---|---|---|---|---|---|
| Chang *et al.*[30] | Original research | The presynaptic neuromuscular blocking action of Taipoxin. A comparison with Beta-Bungarotoxin and Crotoxin | 1977 | No | No |
| Su *et al.*[24] | Original research | The presynaptic neuromuscular blocking effect and phospholipase A2 activity of textilotoxin, a potent toxin isolated from the venom of the Australian brown snake, *Pseudonaja textilis.* | 1983 | No | No |
| Su & Chang[31] | Original research | Presynaptic effects of snake venom toxins which have phospholipase A2 activity (beta-bungarotoxin, taipoxin, crotoxin) | 1984 | No | No |
| Rowan *et al.*[28] | Original research | On the blockade of acetylcholine release at mouse motor nerve terminals by beta-bungarotoxin and crotoxin | 1990 | No | No |
| da Silva *et al.*[34] | Original research | Comparative chromatography of Brazilian coral snake *(Micrurus)* venoms | 1991 | Yes | No |
| Harvey *et al.*[26] | Original research | Screening of snake venoms for neurotoxic and myotoxic effects using simple *in vitro* preparations from rodents and chicks | 1994 | No | No |
| Wilson *et al.*[32] | Original research | Induction of giant miniature end-plate potentials during blockade of neuromuscular transmission by textilotoxin | 1995 | No | No |
| Da Silva & Aird[20] | Original research | Prey specificity, comparative lethality, and compositional differences of coral snake venoms | 2001 | Yes | Yes |
| Hodgson & Wickramaratna[23] | Review | *In vitro* neuromuscular activity of snake venom | 2002 | No | No |
| Hodgson *et al.*[33] | Original research* | The neuromuscular activity of paradoxin: a presynaptic neurotoxin from the venom of the inland taipan *(Oxyuranus microlepidotus)* | 2007 | No | No |
| Olamendi-Portugal *et al.*[17] | Original research | Proteomic analysis of the venom from the fish-eating coral snake *Micrurus* surinamensis: novel toxins, their function and phylogeny | 2008 | Yes | No |
| Moreira *et al.*[35] | Original research | Frontoxins, three-finger toxins from *Micrurus* frontalis venom, decrease miniature endplate potential amplitude at frog neuromuscular junction | 2010 | Yes | No |
| Fernández *et al.*[36] | Original research | Venomic and Antivenomic Analyses of the Central American Coral Snake, *Micrurus nigrocinctus (Elapidae)* | 2011 | Yes | No |

**Table 1.** Articles that assess neurotoxic activity included in the review. (continued)

| Authors | Type | Title | Year | Snakes of the genus *Micrurus* | Venom from species found in Colombia |
|---|---|---|---|---|---|
| Rey-Suárez *et al.*[29] | Original research | Proteomic and biological characterization of the venom of the redtail coral snake, *Micrurus mipartitus (Elapidae),* from Colombia and Costa Rica | 2011 | Yes | Yes |
| Corrêa-Netto *et al.*[37] | Original research | Snake venomics and venom gland transcriptomic analysis of Brazilian coral snakes, *Micrurus altirostris* and *M. corallinus.* | 2011 | Yes | No |
| Ciscotto *et al.*[38] | Original research | Venomic analysis and evaluation of antivenom cross-reactivity of South American *Micrurus* species | 2011 | Yes | No |
| Renjifo *et al.*[19] | Original research | Neuromuscular activity of the venoms of the Colombian coral snakes *Micrurus dissoleucus* and *Micrurus mipartitus:* an evolutionary perspective | 2012 | Yes | Yes |
| Vergara *et al.*[39] | Original research | Eastern coral snake *Micrurus fulvius* venom toxicity in mice is mainly determined by neurotoxic phospholipases A2 | 2014 | Yes | No |
| Bérnard-Valle *et al.*[40] | Original research | Biochemical characterization of the venom of the coral snake Micrurus tener and comparative biological activities in the mouse and a reptile model | 2014 | Yes | No |
| Fernández *et al.*[41] | Original research | Snake venomics of *Micrurus* alleni and *Micrurus mosquitensis* from the Caribbean region of Costa Rica reveals two divergent compositional patterns in New World elapids | 2015 | Yes | No |
| Rey-Suárez *et al.*[21] | Original research | Integrative characterization of the venom of the coral snake *Micrurus dumerilii (Elapidae)* from Colombia: Proteome, toxicity, and cross-neutralization by antivenom | 2016 | Yes | Yes |
| Henao-Duque & Núñez-Rangel[14] | Original research | Maintenance of red-tail coral snake *(Micrurus mipartitus)* in captivity and evaluation of individual venom variability | 2016 | Yes | Yes |
| Casais-E-Silva *et al.*[42] | Original research | Lemnitoxin, the major component of *Micrurus lemniscatus* coral snake venom, is a myotoxic and pro-inflammatory phospholipase A2. | 2016 | Yes | No |
| Lomonte *et al.*[43] | Original research | Venom of the Coral Snake *Micrurus clarki:* Proteomic Profile, Toxicity, Immunological Cross-Neutralization, and Characterization of a Three-Finger Toxin | 2016 | Yes | No |
| Sanz *et al.*[22] | Original research | Venomic analysis of the poorly studied desert coral snake, *Micrurus tschudii tschudii,* supports the 3FTx/PLA2 dichotomy across *Micrurus* venoms | 2016 | Yes | No |
| Rey-Suárez *et al.*[16] | Original research | Primary structures and partial toxicological characterization of two phospholipases A2 from *Micrurus mipartitus* and *Micrurus dumerilii* coral snake venoms | 2017 | Yes | Yes |

Source: Own elaboration.

## Discussion

Although the number of publications on snake venoms of the genus *Micrurus* has increased worldwide since 2007, studies in Colombia are still scarce. This increase in research may be explained by the development of proteomic techniques that allow analyzing the protein composition of venoms; thus, techniques such as reversed-phase high-performance liquid chromatography, electrophoresis and mass spectrometry have been used to identify the proteins present in venoms and determine their relative abundance and sequencing.[32,44-46] However, it should be noted that this type of study may have limitations in terms of accessibility, cost and operation of some of the equipment used.

The neurotoxicity of coral snake venom is associated with PLA2 and 3FTX, which lead to flaccid paralysis of the respiratory muscles. For this reason, the development of neurotoxicity models that allow verifying the influence of full venom and these toxins on the synaptic transmission at the neuromuscular junction can be key for its functional characterization, as it has been evidenced in studies developed with elapid venoms of the genus *Bungarus*,[28,30,31,47] *Oxyuranus*,[24,30,31,34,48] *Pseudonaja*,[23,33] and *Notechis*.[49]

The following are the findings on *Micrurus* snake venom, its neurotoxicity, and its effects on the neuromuscular junction.

## Mechanism of action of PLA2 and 3FTx

The venom of snakes from the genus *Micrurus* has neurotoxic components. Lomonte *et al.*[15] identified the following families of proteins in its proteome: 3FTx (α-neurotoxins), PLA2 (β-neurotoxins), metalloproteases, L-amino-acid oxidases, Kunitz-type serine protease, C-type lectin-like proteins, acetylcholinesterase and hyaluronidases, being the first two the ones with more involvement. The proportion of PLA2 and 3FTx toxins in these venoms is a key element for identifying their main neurotoxic and myotoxic effects.[15,16,18]

Table 2 presents some of the neurotoxins identified in snakes of the family *Elapidae*. It also includes the characteristics of the snake venom of the genus *Crotalus durissus* due to its neurotoxic and myotoxic behavior.[22]

**Table 2.** Neurotoxins identified in snake venom.

| Species | Toxin | Type | Reference |
|---|---|---|---|
| *Notechis scutaus* | Notexin | β-neurotoxins | 49 |
| *Oxyuranus scutellatus* | Taipoxin | β-neurotoxins | 30,31,48 |
| *Oxyuranus microlepidotus* | Paradoxin | β-neurotoxins | 34,50 |
| *Crotalus durissus terrificus* | Crotoxin | β-neurotoxins | 28,30,31,51,52 |
| *Pseudonaja textiles* | Textilotoxin | β-neurotoxins | 23,33 |
| *Bungarus multicinctus* | β-bungarotoxin | β-neurotoxins | 28,31 |
| *Micrurus frontalis* | Frontoxin | α-neurotoxins- 3FTX | 35 |
| *Micrurus lemniscatus* | Lemnitoxin | β-neurotoxins | 42 |
| *Micrurus dumerilli* | MdumPLA2 | β-neurotoxins | 16 |
| *Micrurus mipartitus* | MmipPLA2 | β-neurotoxins | 16 |

Source: Elaborated based on Hodgson & Wickramaratna.[23]

Recent studies in proteomics have demonstrated the predominance of PLA2 and 3FTx toxins in the venom phenotype in species of the genus *Micrurus* and have shown that their proportions vary widely across the American continent.[14,16,21,22,41-43] Similarly, Lomonte *et al.*[15] made a projection of the behavior of these two toxins, finding that PLA2 is more abundant in the southern cone and that 3FTx predominates in Central and North America. However, it is worth mentioning that this projection should be corroborated by a detailed analysis of each of the venoms since the evolutionary and ecological processes of each species are factors that determine the greater proportion of one of these 2 toxins.

### PLA2 toxins

PLA2 is a superfamily of enzymes composed of 16 groups that are classified according to their type into: secreted PLA2 (sPLA2), cytosolic PLA2 (cPLA2), calcium-independent PLA2 (iPLA2), platelet activating factor (PAF), lipoprotein-associated PLA2 (LpPLA2s), adipose PLA2 (AdPLA2s) and lysosomal PLA2 (LPLA2s). The first two are especially important because they are involved in the inflammatory and degenerative response of the central nervous system.[53] sPLA2 are present in different classes of venoms and are classified in four main subtypes, and types 1 and 2 are found in snake venoms, mainly in elapids, vipers and crotalids; these enzymes are single-chain polypeptides and have a molecular mass of 13-15 kDa, with approximately 7 disulfide bonds. Finally, cPLA2 has a molecular mass of 40-100 kDa and depends on calcium for functioning.[53]

Even though the exact neurotoxic route of PLA2 is not known, at least three mechanisms of action by which these enzymes exert their presynaptic toxic activity have been described: 1) the neurotoxin induces phospholipid hydrolysis of the presynaptic membrane and prevents it from interacting with the acetylcholine vesicles, 2) the damage described in the cell membranes favors the excessive influence of $Ca^{++}$ inside the cells, which causes an exaggerated release of the acetylcholine neurotransmitter, as well as the alteration of its recycling process and its subsequent depletion, and 3) its enzymatic activity is left aside, so the protein complexes that favor the coupling of the vesicle and the presynaptic membrane are blocked.[16,23,47,54-56]

### 3FTx toxins

3FTx are non-enzymatic polypeptide structures made up of between 60 and 74 amino acid residues that are among the main components of elapid venoms.[57] Its structure has 3 loops of β-sheets that extend from a small globular hydrophobic core that is linked by 4 preserved disulfide bonds; this structure resembles that of a hand with 3 fingers, which is why they are known as three-finger toxins.[57,58]

Neurotoxicity (main effect of coral snake venom), cytotoxicity and cardiotoxicity are some of the pharmacological effects identified in 3FTx. However, it should be noted that its biological activity varies depending on the affinity it has with the receptors[59-61] (Table 3).

**Table 3.** Three-finger toxins found in elapid venoms.

| 3FTx type | | Mechanism of action | Example |
|---|---|---|---|
| Neurotoxins | α | α1 and/or α7 nAChR antagonists. | α-bungarotoxins |
| | κ | They recognize different subtypes of neuronal α3β4 nAChR | κ-bungarotoxins |
| | MT | They selectively bind to mAChR. | *Dendroaspis angusticeps* MT1 |
| Cardiotoxins | | They form ionic pores in lipid membranes. | Cardiotoxin V4II from *Naja mossambica* |
| β-cardiotoxins and others alike | | They bind to β1 and β2 adrenergic receptors. | CTX9, CTX14, CTX15, CTX21 and CTX23 from *Ophiophagus Hannah* |
| Non-conventional | | Weak neurotoxins with nanomolar affinity to AChR α1 (reversible binding) and α7 (poorly reversible binding) | Candoxin |
| Acetylcholinesterase inhibitors | | They bind to acetylcholinesterase | Fasciculins |
| L-type $Ca^{2+}$ channel blockers | | They block L-type $Ca^{2+}$ channel in skeletal and heart muscles | Calciseptine |
| Platelet aggregation inhibitors | | They interfere with the interaction between fibrinogen and the glycoprotein IIB-IIIa receptor ($\alpha_{IIB}\beta3$). | Dendroaspins |

nAChR: nicotinic acetylcholine receptor; mAChR: muscarinic acetylcholine receptors; MT: muscarinic toxin; CTX: cardiotoxin
Source: Elaboration based on Utkin[59], Kini & Doley[60] and Nirthanan *et al.*[61]

Depending on the amino acid sequence, 3FTx neurotoxins can be classified into two types: short-chain neurotoxins (type I) and long-chain neurotoxins (type II), both with a molecular mass varying between 6 and 9 kDa.[58,61] Short-chain α-neurotoxins are the main responsible for the neurotoxic effect of elapid venoms due to their high- affinity binding for nicotinic acetylcholine receptor (nAChR) and the inhibitory control they exert on this receptor without affecting the release of neurotransmitters from the presynaptic terminal.[59,62,63]

### Functional characterization of the neurotoxic activity of venoms of the *Elapidae* family and the *Micrurus* genus in particular

Recent studies on the classical biochemistry of elapid venom composition in Colombia have made major progress in the description of the ontogenetic characteristics and phylogenetic trees of these species.[16,19,21] In this regard, multiple research works assess the peripheral neurotoxic and myotoxic activity of the venom of *M. dissoleucus, M. mipartitus*,[19] *M. lemniscatus*, *Micrurus frontalis* and *M. surinamensis,*[13] or the PLA2 of the species *Micrurus nigrocinctus.*[64]

Specifically, for Australian elapids (*Pseudechis* spp.), Hart *et al.*[65] indicated that binding of neurotoxins to nAChR is more effective in preparation from chick muscle than in human and rat skeletal muscles. This difference is explained because the synaptic junctions are almost absent in birds, even though neuromuscular junctions in avian tissues are almost the same size as in rats; this makes nAChR more susceptible to post-synaptic neurotoxins and more sensitive to the neurotoxic action of elapid venoms.[65]

Although the neurotoxic activity of *Micrurus* snake venom has not been sufficiently studied, several methodologies have been used as complementary techniques besides organ baths, e.g. cell culture models, that can contribute to the understanding of the actions of the full venom and its main components (PLA2 and 3FTx). For example, hippocampal tissue has been used to prove viability and conservation of cellular function (integrity of mitochondria and intracellular calcium variability) after the administration of different doses of venom from these species,[66] to establish toxin binding to transmembrane receptors,[67] and determine electroencephalographic and neuropathological changes in behavioral studies of animal models.[68]

## Conclusions

Advances in venomics, the global study of venom through omic techniques, allow for a better understanding of the protein constituents of snake venoms. In the specific case of the genus *Micrurus*, such advances are of vital importance due to the small amount of venom produced by these species and the limitations of having them in captivity. Furthermore, the identification of proteins with neurotoxic properties such as α-neurotoxins and β-neurotoxins, main components of *Micrurus* venom, and the understanding of their mechanism of action in *ex vivo* muscle tissue preparations, are fundamental tools for the development of toxinology and allows understanding the mechanism of action of these components and the great protein variability of each species and each individual.

Establishing the characteristics of snake venom proteomes has potential benefits for basic research on these substances, such as the identification of new molecules in the venom. This also contributes to a better understanding of the evolution and biological effects that these venoms can have. Likewise, this characterization is useful for the clinical diagnosis of snakebites and for the development of new research tools and drugs with clinical potential as specific antivenoms.

Studies with *ex vivo* muscle and nerve preparations to assess the effect of neurotoxins are a good model to characterize the pre-synaptic and post-synaptic effect of *Micrurus* snake venom. Moreover, these preparations serve as a support for muscle tissue histopathology to determine myotoxicity resulting from exposure to poison.

## Conflicts of interest

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# *Candida auris osteomielitis:* Case report

*Osteomielitis por Candida auris: reporte de caso*

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## *Abstract*

**Introduction:** *Candida auris* is an opportunistic yeast associated with multiple infections, which was first reported in 2009 in Tokyo, Japan. Provided that it has great antifungal resistance to azoles and amphotericin B, its treatment options are limited, and therefore an empiric therapy using echinocandins such as micafungin should be considered.
**Case presentation:** A rare case of a 48-year-old male patient with osteomyelitis caused by *C. auris* was reported in the city of Popayán, Colombia. The patient had a history of femoral head fracture, paraplegia due to firearm-related injury and neurogenic bladder, and reported having experienced abundant purulent foul-smelling secretions through trochanteric right ulcer for 15 days. MRI images revealed myositis and bone intensity alterations, which allowed diagnosing him with osteomyelitis.
Due to repeated isolations of *C. haemulonii* in several bone samples, antifungal management was initiated. However, since no improvement in the patient's condition was observed, a culture was sent to the Colombian National Institute of Health to identify the pathogen considering the repeated isolations of *C. haemulonii* and its apparent resistance to antifungals. *C. auris* was finally confirmed as the pathogen.
**Conclusion:** Osteomyelitis by *C. auris* is a rare entity, which must be considered when treating patients with predisposing risk factors such as long hospital stays, bearing in mind that this is an inpatient-associated opportunistic infection.
**Keywords:** Osteomyelitis; *Candida auris;* Drug Resistance, Fungal (MeSH).

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## *Resumen*

**Introducción.** *Candida auris* es una levadura oportunista asociada a múltiples infecciones que, en 2009, fue descrita por primera vez en Tokio, Japón. Dado que tiene una gran resistencia antifúngica a los azoles y a la anfotericina B, su manejo es limitado, por lo que se debe considerar iniciar un tratamiento empírico con equinocandinas como la micafungina.
**Presentación de caso.** Caso inusual de osteomielitis por *C. auris* en un hombre de 48 años de Popayán, Colombia, con antecedentes de fractura de cabeza de fémur, paraplejia por herida con arma de fuego y vejiga neurogénica. El paciente tenía cuadro clínico de 15 días de evolución consistente en salida abundante de líquido purulento fétido en úlcera derecha por presión trocantérica. Mediante resonancia magnética se identificaron miositis y alteraciones de intensidad ósea, por lo que fue diagnosticado con osteomielitis.
Debido a la identificación de aislamientos repetidos de *Candida haemulonii* en varias muestras óseas, se inició manejo antifúngico; sin embargo, ya que no se observó ninguna mejora en la condición del paciente, el cultivo fue enviado al Instituto Nacional de Salud para confirmar la identificación del patógeno debido a aislamientos repetidos de *C. haemulonii* y su aparente resistencia a los antifúngicos. Finalmente, el patógeno identificado fue *C. auris.*
**Conclusión.** La osteomielitis por *C. auris* es una entidad inusual cuyo diagnóstico debe ser considerado en pacientes con factores de riesgo predisponente, como aquellos con larga estancia hospitalaria, ya que esta es una infección oportunista asociada a pacientes hospitalizados.
**Palabras clave:** Osteomielitis; *Candida auris;* Farmacorresistencia fúngica (DeCS).

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## Introduction

*Candida auris* is an opportunistic yeast associated with multiple infections. It was first described in Tokyo, Japan, in 2009, after being isolated from external ear discharge of a 70-year-old patient.[1] Two years later, 3 cases of *C. auris* associated with fungemia were described in South Korea; their isolates were erroneously reported as *C. haemulonii and Rhodotorula glutinis,*[2] making evident how difficult it can be to identify this fungus.

After its discovery, *C. auris* has been recorded around the world and more cases are reported every day. In America, the first case was reported in March 2012 in the intensive care unit (ICU) of a tertiary care hospital in Maracaibo, Venezuela.[3,4] In Colombia, the first reports were made in Santa Marta, Bogotá D.C., and Valledupar in 2013; then, between 2015 and 2016, isolations were reported in Barranquilla, and in 2016, an outbreak occurred in a pediatric ICU in Cartagena.[4] In 2017, 77 cases of *C. auris* were reported in the U.S., and the pathogen was found in mattresses, beds, windows, chairs, infusion pumps, and countertops, indicating environmental contamination.[5]

*C. auris* osteomyelitis is a highly drug-resistant and difficult-to-treat pathology, and available literature on this subject is scarce.[6] For this reason, to provide adequate treatment, it is necessary to use correct identification methods that allow making a precise and timely diagnosis.

The following is a rare case of *C. auris* osteomyelitis in a man in whom it was possible to isolate this microorganism in a tissue sample by means of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS), which was analyzed at the *Instituto Nacional de Salud* (National Institute of Health - INS) of Colombia.

## Case presentation

The following is the case of a 48-year-old man, truck laborer, who attended a secondary healthcare center on March 27, 2017, after experiencing abundant purulent foul-smelling secretions through trochanteric right ulcer for 15 days. The patient had a history of right femoral head fracture and gunshot wound in 2012, which caused him paraplegia due to T12 spinal cord injury and neurogenic bladder that had been treated with intermittent catheterization.

Upon physical examination, the patient was found in acceptable general conditions, alert and oriented to person, place, time, and situation; his vital signs were: blood pressure: 100/60 mmHg, heart rate: 100 bpm, respiratory rate: 22 brpm, temperature: 35.9°C, and oxygen saturation: 99%. The subject had a stage 2 ulcer of 8cm in diameter superinfected with purulent secretion in the right trochanteric region and a stage 1 ulcer of 3cm in diameter in the left gluteus; in addition, both lower limbs presented decreased muscle tone and muscle trophism.

Given the findings, the patient was hospitalized with a diagnosis of sepsis of cutaneous and/or urinary origin secondary to pressure ulcers. Treatment with broad-spectrum antibiotics (meropenem and vancomycin) and management by general surgery (lavage and surgical debridement of the ulcers) and enterostomal therapy were indicated. After two weeks of hospitalization, the right trochanteric ulcer evolved to stage 4 and developed necrotic edges and foul-smelling soft tissues with some seropurulent secretion inside and devitalized patches. The right femoral trochanter was exposed, finding a soft and porous bone, as well as exposure of osteosynthesis material suggestive of osteomyelitis. Blood and ulcer secretion cultures were performed, yielding negative results for pathogenic microorganisms.

A week after the trochanteric ulcer evolved to stage 4, a nuclear magnetic resonance (NMR) of the right thigh was performed, showing alterations in bone density and post-surgical changes in both the neck and the diaphysis of the femur. Similarly, severe myositis was observed in the gluteus and hamstring muscles, which later extended through the anterior and lateral thigh to the greater trochanter, findings that suggested a diagnosis of osteomyelitis.

Four days after the NMR, the patient's clinical condition worsened due to bleeding in the surgical wound of the right femur; a blood culture was then performed, isolating multidrug-resistant *Pseudomona aeruginosa*, for which trochanteric ulcer lavage and curettage surgery was performed. In the inguinal region, lesions compatible with cutaneous candidiasis were found; they were managed with topical treatment.

One month after the patient's condition deteriorated, another culture was taken from a new sample of right femur bone, isolating *C. haemulonii* sensitive to amphotericin B, itraconazole, fluocytosine, voriconazole, and fluconazole; in the case of the latter, the sensitivity of the fungus depended on the dose used and the minimum inhibitory concentration (MIC) was 16. The identification of this pathogen allowed diagnosing chronic osteomyelitis, for which treatment with itraconazole was initiated (200 mg every 12 hours for 2 days and then 200 mg every 24 hours until completing 4 to 6 weeks). A week after starting this treatment, the patient had an allergic drug reaction, so itraconazole was switched to fluconazole (400 mg every 12 hours). A plastic surgery was performed to cover the skin with flaps to repair the defect caused by the ulcer because there were no signs of local infection or systemic inflammatory response. The patient continued with antifungal treatment with fluconazole and received intravenous steroid due to persistent rash.

Since the patient's condition did not improve, the culture was sent to the INS to confirm the pathogen due to repeated isolations of *C. haemulonii* and its apparent resistance to antifungal agents. Finally, it was possible to establish the presence of *C. auris* by means of the MALDI-TOF MS technique, which analyzes the proteomic profile through the creation of a specific mass spectrum of each genus and species, allowing the precise identification of the yeast and, thus, determining antifungal susceptibility.

## Discussion

*C. auris* is an emerging and opportunistic yeast with worldwide presence and responsible for a large number of clinical manifestations, ranging from simple fungal colonization to deep infections and candidemia.[7,8] Moreover, it has great potential for transmission of infections and is often multi-resistant to antifungal drugs.[9,10] When treatment fails, fungemia can occur, which is accompanied by high mortality rates.[11]

Since it was first described, *C. auris* has spread around the world and health authorities have been on the alert.

In this regard, Chowdhary *et al.*[12] reported that isolates of this pathogen had already been reported in South Korea, India, Pakistan, Israel, Kenya, South Africa, Spain, UK, Germany, Norway, USA, Venezuela, and Colombia by 2017. Then, by 2018, several studies reported cases in China, Saudi Arabia, Canada, Switzerland, United Arab Emirates, Malaysia, Oman, and Brazil.[13-16] In Colombia, the INS issued a global emergency alert in 2016 for invasive infections caused by *C. auris* and established guidelines for its timely and proper identification.[17]

Multiple *C. auris* outbreaks and related studies suggest that transmission occurs in hospital settings, as it has been isolated in patient rooms and ICUs, and indicate that colonization can occur in different parts of the body such as the nares, groin, armpits, and rectum.[12,13] In addition, according to Sears & Schwartz,[9] clinically speaking, it is an agent that causes fungemia, ventriculitis, otomastoiditis, complicated intra-abdominal infections, pericarditis, complicated pleural effusions, and vulvovaginitis.

The risk factors associated to infection by this pathogen are similar to those of other types of *Candida spp:* immunosuppression, significant medical comorbidities (diabetes mellitus or chronic kidney disease), malignancies with or without chemotherapy, central venous or urinary catheter, recent invasive surgery, parenteral nutrition, continuous exposure to broad-spectrum antibiotics, prolonged hospital stay, ICU stay, stays in a nursing home, low birth weight, and early neonatal sepsis.[9,10,12,18-20]

On the other hand, some studies have shown that factors such as history of prolonged hospitalizations, underlying respiratory conditions, vascular surgeries, previous exposure to antifungal drugs and low APACHE II scores increase the probability of developing *C. auris* fungemia with respect to other types of *Candida* spp.[9,20] Furthermore, according to Chowdhary *et al.*,[12] this yeast has virulence factors such as proteinases and phospholipases and forms biofilms that facilitate its adherence in the environment and to hospital equipment such as catheters.

The group of fungi that causes the greatest number of osteoarticular infections is *Candida*, comprising at least 15 different species, of which *C. albicans* is the most common. Also, as immunosuppression and antifungal exposure increases, the incidence of infections caused by *Candida no albicans* also increases.

*C. auris i*s phylogenetically related to *C. haemulonii* and *C. ruelliae*[9] and is usually mistaken for various species, as in the present case.[21] This is also reported in the study by Kathuria *et al.*,[22] where the fungus remained unnoticed in microbiology laboratories because 90% of isolates characterized by commercial identification systems mistakenly labeled it as *C. haemulonii.*

Fluconazole to treat *C. auris* has shown high minimum inhibitory concentration (MIC), which in many cases reaches >64 mg/L, and, therefore, has a high rate of treatment failure.[13,14] Other drugs to which *C. auris* is resistant are azoles such as itraconazole, voriconazole and isavuconazole, and there is also variability in the susceptibility of isolates to amphotericin B.[14] Given this great resistance, initiating empirical treatment with echinocandins, such as micafungin, should be considered since they have yielded the best results, even though cases with reduced susceptibility have been reported.[13]

A genetic study in India found genes related to anti-fungal resistance (*ERG3, ERG11, FKS1, FKS2 and FKS3)* and important ABC and MSF carrier genes in multidrug resistance (MDR) pumps. This could explain why *C. auris*[23] is multi-resistant and the possible reasons why groups of antibiotics such as azoles, including fluconazole, fail, as happened in the case presented here.

Although the literature reports high resistance to antifungal drugs, [14,16,22] in the reported case, treatment with azole was effective: itraconazole had low MIC (<0.125), while fluconazole had dose-dependent susceptibility.

## Conclusion

*C. auris* osteomyelitis is a rare entity whose diagnosis should be considered in patients with predisposing risk factors, such as long hospital stays, since this is a resistant and opportunistic infection associated with hospitalized patients.

## Ethical considerations

The present work is a retrospective case report in which no interventions on the subject were performed by the researchers. Therefore, this is a minimal risk research, approved by the Research Ethics Committee of the Clínica La Estancia by means of Minutes No. GCI-42 of March 12, 2018.

## Conflicts of interest

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# Endocarditis caused by *Leuconostoc lactis* in an infant. Case report

*Endocarditis por Leuconostoc lactis en un lactante. Reporte de caso*

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## Abstract

**Introduction:** Infections caused by *Leuconostoc lactis* are rare and are associated with multiple risk factors. According to the literature reviewed, there are no reported cases of endocarditis caused by this microorganism in the pediatric population.
**Case presentation:** An infant with short bowel syndrome was taken by his parents to the emergency department due to malnutrition. During his prolonged hospital stay, he presented multiple infections, so he required central venous catheter, prolonged enteral tube feeding and parenteral nutrition. In one of his nosocomial infection episodes, peripheral blood cultures were taken, and an echocardiogram was performed, achieving the diagnosis of endocarditis by *L. lactis,* which was treated with linezolid. After 21 days of treatment, the infectious process was controlled; however, in order to improve his condition and due to another bacteremia episode, he remained hospitalized. Finally, after 113 days, the patient was discharged, and comprehensive outpatient care was ordered.
**Conclusion:** Although rare in the pediatric population, endocarditis by *L. lactis* should be suspected in patients with multiple risk factors and polymicrobial infections. Timely and specific treatment, as in the reported case, can help avoid future complications.
**Keywords:** Infant; Endocarditis; *Leuconostoc* (MeSH).

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## Resumen

**Introducción.** Las infecciones por *Leuconostoc lactis* son raras y se asocian a múltiples factores de riesgo; además, de acuerdo con lo revisado en la literatura relevante, no hay reportes de endocarditis causada por este microorganismo en población pediátrica.
**Presentación del caso.** Lactante con síndrome de intestino corto que fue llevado por sus padres al servicio de urgencias por desnutrición. Durante su estancia hospitalaria prolongada, el paciente presentó múltiples infecciones, por lo que requirió catéter venoso central (CVC), alimentación enteral prolongada y nutrición parenteral. En uno de los episodios infecciosos intrahospitalarios se tomaron hemocultivos periféricos y se realizó un ecocardiograma, lo que permitió diagnosticarlo con endocarditis por *L. lactis* y por lo cual se decidió iniciar manejo con linezolid. Luego de 21 días de tratamiento, la infección fue controlada, pero con el fin de mejorar su estado nutricional y debido a un nuevo episodio de bacteremia, se decidió prolongar su estancia hospitalaria. Finalmente, después de 113 días de hospitalización, fue dado de alta para continuar manejo integral ambulatorio.
**Conclusión.** A pesar de ser una entidad poco frecuente en pediatría, la endocarditis por *L. lactis* debe sospecharse en pacientes con múltiples factores de riesgo y con infecciones polimicrobianas. Un tratamiento oportuno y específico como el usado en el presente caso puede evitar complicaciones futuras.
**Palabras clave:** Lactante; Endocarditis; *Leuconostoc* (DeCS).

Sarmiento-Ortiz EA, Oliveros-Andrade OA, Rojas-Hernández JP. [Endocarditis por *Leuconostoc Lactis* en un lactante: reporte de caso]. Rev. Fac. Med. 2020;68(3):467-70. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n3.77425.

## Introduction

*Leuconostoc* is a genus of gram-positive bacteria with cocci morphology from the *Leuconostocaceae* family. It is catalase-negative, produces lactic acid, and is characterized by its intrinsic and chromosomal resistance to vancomycin.[1,2,3] This type of bacteria, which can be found in green vegetables and are used in wine, cheese, and sugar production, is not part of the microbiota of human beings.[1] However, in some cases, their presence is associated with the use of central venous catheters (CVC), the implementation of parenteral and enteral nutrition, gastrointestinal pathologies such as short bowel syndrome, and immunodeficiencies;[4-8] they have also been identified as part of polymicrobial infections.[1]

Infections caused by these microorganisms are rare in humans. Still, the most common species involved in human infections are *L. mesenteroides*, *Leuconostoc pseudomesenteroides*, *Leuconostoc citreum* and *Leuconostoc lactis.*[1] It is worth mentioning that *L. lactis* bacteremia has been associated with high mortality in immunodeficient patients.[9] Both systemic[9-11] and localized *Leuconostoc* infections have been reported in the literature,[12-24] including adult patients with endocarditis associated or not with intravenous drug administration.[23-28]

The present report describes the case of an infant treated at the Fundación Clínica Infantil Club Noel in the city of Cali (Colombia), who developed infectious endocarditis due to *L. lactis* while being treated in the pediatric intensive care unit (PICU).

## Case presentation

The following is the case of a premature infant (born at 32 weeks of gestation) with a chronological age of 10 months, who presented neurodevelopmental delay, short bowel syndrome and bilateral hydronephrosis. The patient, who had a complete vaccination schedule for his age, had undergone an ileostomy for ileus stenosis correction at three days of birth, which he was still carrying.

The child was taken to the emergency department due to hyporexia. His physical examination on admission showed that he was hemodynamically stable and without clinical respiratory deterioration; however, he looked emaciated, pale, hypotonic and with bilateral enophthalmos. The anthropometric index for weight/height was -5.73 standard deviations (σ), for weight/age was -5.19 σ, and for height/age was -2.23 σ. Based on these results, the patient was diagnosed with acute malnutrition and malabsorption syndrome. He was admitted to the hospital and feeding with extensively hydrolyzed milk formula plus trace elements by nasogastric tube was initiated.

48 hours after admission, the patient presented septic shock and was transferred to the PICU, where empirical antibiotic treatment was started with vancomycin (60 mg/kg/day) plus cefepime (150 mg/kg/day). On the second day at the PICU, a CVC was placed to administer parenteral nutrition. In turn, peripheral blood cultures were taken, two of which were positive for *Klebsiella pneumoniae* with extended-spectrum beta-lactamase resistance pattern, so vancomycin and cefepime were replaced with meropenem (180 mg/kg/day), which was administered for 10 days.

Despite the antibiotic regime provided during his stay in the PICU, the patient persisted with fever >38°C. For this reason, the CVC was removed, and a peripheral blood culture was performed, which showed *Candida parasilopsis.* Based on that microbiological isolate, imaging studies were performed (echocardiogram and transfontanellar and total abdominal ultrasound scans), which ruled out fungal growths in the brain, abdomen, heart, and eyeball; the latter was assessed by the ophthalmology service. Considering the isolate obtained, management with intravenous fluconazole was administered (impregnation dose: 12 mg/kg/day, maintenance dose 6mg/kg/day) for 14 days; however, on the second day, the patient presented fever, tachycardia, hypotension and signs of breathing difficulty, so life support was provided. The patient underwent further testing in which two peripheral blood cultures were identified as positive for *Klebsiella pneumoniae* with a low-level penicillinase resistance pattern. Given these findings, cefazolin antibiotherapy (100 mg/kg/day) for 7 days was indicated. At the end of the treatment, two new blood cultures were taken, obtaining negative results for *C. parasilopsis*.

After 34 days in the PICU, the patient was transferred to the floor to continue comprehensive treatment. However, 11 days after being there, he presented a fever and tachycardia, so 2 peripheral blood cultures were requested, which isolated *L. lactis.* An echocardiogram was performed and showed vegetations in the right atrium, findings that allowed diagnosing infectious endocarditis and ruling out other organic foci of septic emboli. Considering the patient's condition, treatment with linezolid at 30 mg/kg/day for 21 days was indicated.

*Acinetobacter baumannii* was also isolated in the last 2 peripheral blood cultures; therefore, according to the antibiogram, therapy with ampicillin plus sulbactam (200 mg/kg/day) for 10 days was indicated. It should be noted that *A. baumannii* infection yielded negative results before *L. lactis*.

After the resolution of the bacteremia by *L. lactis* and *A. baumannii*, a new bacteremia by *Escherichia coli* with extended-spectrum beta-lactamase resistance pattern was documented, so treatment with meropenem (120 mg/kg/day) for 10 days was indicated.

After the removal of the CVC, the patient was treated using peripheral catheters. Also, during his hospital stay, the patient presented multiple infections, thus he underwent several tests to rule out immunodeficiency. The child also received intravenous immunoglobulin infusion since he underwent a flow cytometry that yielded normal results for T and B cells. Hypogammaglobulinemia M (35 mg/dL, normal range for age: 43-247 mg/dL) and hypogammaglobulinemia G (459 mg/dL, normal range for age: 486-1797 mg/dL) were also detected.

During his hospital stay, the patient received oral feeding, enteral feeding by nasogastric tube, mixed feeding (by nasogastric tube and parenteral nutrition) and parenteral nutrition for 3, 16 days, 84 and 10 days, respectively. After the patient was clinically stable and the blood cultures were negative, surgical closure of the ileostomy was indicated. Finally, after 113 days of hospitalization, when the control echocardiogram was normal and the child reached nutritional recovery, he was discharged from the hospital to continue comprehensive outpatient treatment.

The patient was readmitted to the hospital due to sepsis secondary to community-acquired pneumonia and acute diarrheal disease four months after discharge and was hospitalized for 48 days; once these pathologies solved, he was discharged from the hospital. It was not possible to continue with the outpatient follow-up.

## Discussion

This article presents the case of an infant admitted to the emergency department due to acute malnutrition secondary to malabsorption of nutrients caused by short bowel syndrome. The patient developed immunodeficiency due to such malnutrition, which played an important role in the development of multiple infections. Factors such as CVC use, parenteral nutrition, continuous enteral feeding, short bowel syndrome and immunodeficiencies, which have been associated with *Leuconostoc* infections,[4-8] were observed in the present case.

It has been established that in patients with short bowel syndrome who require continuous enteral and parenteral nutrition, *L. lactis* may enter the gastrointestinal tract through contaminated enteral formulas.[1] However, in the present study, it could not be established whether the formulas used were contaminated by such bacteria. In this type of patients, it has also been identified that *L. lactis* can reach the bloodstream through CVC or enteral feeding tubes; in the case of the tubes, the bacteria can enter through possible mucosal lesions in the gastrointestinal tract.[1]

Only two cases of endocarditis due to *Leuconostoc* were found in the literature, and none of them occurred in pediatric patients. Firstly, Valencia *et al.*[25] presented the case of an immunocompetent adult with endocarditis, history of intravenous drug use, aortic valve involvement and septic emboli in retina, spleen and brain; the patient was treated for *Leuconostoc* with ceftriaxone (2 grams per day) and daptomycin (600 milligrams per day) for 6 weeks until negative blood cultures were obtained. Secondly, Starr[26] reported the case of an immunocompetent adult patient with endocarditis and aortic valve involvement who received treatment for *Leuconostoc* with penicillin (6 million units every 6 hours) for 6 weeks, and gentamicin (80 milligrams every 8 hours) for 2 weeks; even though the infection was controlled, the patient required aortic valve replacement.

Penicillin, alone or combined with aminoglycosides, is the first choice to treat *Leuconostoc* infections;[1,28] however, in immunodeficient patients with invasive infections, as in the present case, the indication should be daptomycin or linezolid.[28]

## Conclusions

*L. lactis* infections, including endocarditis, are rare and should be suspected in patients with polymicrobial infections, short bowel syndrome, and continuous enteral and parenteral nutrition. Also, proper diagnosis and timely and specific treatment, as used in the present case, can help avoid future complications.

## Ethical considerations

This case report was approved by the Ethics Committee of the Fundación Clínica Infantil Club Noel in Cali, Colombia, according to an unnumbered meeting minutes from January 30, 2019. Similarly, informed consent was obtained from the patient's mother.

## Conflicts of interest

None stated by the authors.

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Articles shall only be received at our OJS (Open Journal System) website (http://goo.gl/rsVzGU). Submission must include: article, metadata and complementary files (assignment of copyright https://goo.gl/EfWPdX and authorship responsibility https://goo.gl/6zztk4)

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1. Provide a title in the language in which the article is written
2. Provide a title in a second language (English or Spanish depending on which language is written the article)
3. Provide a short title no longer than 40 characters (including blank spaces)
4. All authors' full names and last names must be stated; their institutional affiliation must be identified with superscript Arabic numerals.
5. Institutional affiliation for each author must be presented without specifying positions, only institutions and sections/departments within them shall be included.
6. Provide the ORCID number for each author.
7. Complete contact details of the main author or the corresponding author must be provided (name, institutional address, telephone, city, country, email).
8. Word count: please state the total number of words that make up the article without taking into account words included in titles, abstracts, acknowledgments, tables, figures, and the list of references. The number of words

must not exceed the maximum allowed for each the type of article (see Section F)
9. Number of figures and tables: please state the total number of tables and figures included in the article. The maximum numbers of tables and figures allowed is 6.

**II. Abstract (in Spanish)**

1. It must not exceed 200 words.
2. References must not be included.
3. In case of experimental studies, protocol (clinical trial) registry number must be included in the last line of the abstract, example: https://www.ncbi.nlm.nih.gov/pubmed/29791437
4. Original research articles, review articles and short communications must have an abstract made up the following sections: "introduction", "objective", "materials and methods", "results" and "conclusions".
5. For case reports, abstracts shall be presented in accordance with the CARE checklist of information to include when writing a case report (http://www.care-statement.org/resources/checklist), item 3, Abstract.
6. Keywords (in Spanish): Include 3 to 6 exact descriptors from DeCS Bireme (http://decs.bvs.br/).

**III. Abstract**

1. It must not exceed 200 words.
2. References must not be included.
3. In case of experimental studies, protocol (clinical trial) registry number must be included in the last line of the abstract, example: https://www.ncbi.nlm.nih.gov/pubmed/29791437
4. Original research articles, review articles and short communications must have an abstract made up the following sections: "introduction", "objective", "materials and methods", "results" and "conclusions".
5. For case reports, abstracts shall be presented in accordance with the CARE checklist of information to include when writing a case report (http://www.care-statement.org/resources/checklist), item 3, Abstract.
6. Keywords: Include 3 to 6 exact MeSH descriptors (http://www.nlm.nih.gov/mesh/).

**IV. Introduction**

The summarized rationale of the study must be included in this section. Furthermore, at the end of this section, the purpose of the study must be clearly stated. Only the references required to support the ideas depicted here are to be included.

**V. Materials and methods**

The type of study and the methodology used (sample identification, selection criteria, statistical methods, etc.) shall be described here. If the procedures performed during the study involved humans or animals, authors must explicitly state that they followed the ethical principles for medical research on humans of the Declaration of Helsinki (2013) and any other applicable national regulations, said documents must be duly referenced. Additionally, it must be clearly expressed that the study was approved by the ethics committee of the institution or institutions where it was carried out, and the corresponding letter of approval from the ethics committee must be enclosed.

In case of experimental studies, registration of clinical trials in a public trials registry at or before the time of first patient enrollment as a condition of consideration for publication is mandatory. An example of a public trial registry can be found at https://clinicaltrials.gov. The clinical trial registration number must be included in the last line of the abstract.

**VI. Results**

The results obtained in the study must be presented in a logical and coherent way. Data can be shown in tables or figures, but not simultaneously in both. Avoid repeating the data presented in tables and figures within the body of the article, and do not combine the presentation of results with your discussion, as the latter has its own section.

**VII. Discussion**

In this section, results obtained in the study must be addressed without making a general review of the subject. Authors must only discuss the new and most relevant aspects presented by the study and the conclusions proposed from them. Limitations of the research and the agreement or disagreement of findings reported in the article with other studies on the subject, duly referenced, must be reported.

**VIII. Conclusions**

Conclusions must be related to the objectives of the study described in the "introduction" section. Do not draw conclusions that are not supported by the findings of your study or that are supported by a work that has not yet been finalized. If appropriate, create new hypotheses but present them as such. Propose your recommendations.

**IX. Conflict of interests**

Please state, based on the funding sources of the study or any other reason, whether the authors have a conflict of interest or not. Authors must complete and sign the Conflict of Interest Disclosure Form of the ICJME (http://www.icmje.org/about-icmje/faqs/conflict-of-interest-disclosure-forms) and attach it to the submission (step 4).

**X. Funding**

Please state if the study was funded by external sources and if they influenced its completion.

**XI. Acknowledgment**

Express your gratitude only to people and institutions that have contributed substantially to your work. Authors are responsible for acknowledging the people or institutions that could be recognized as contributors to the results of the work and its conclusions by the readers.

**XII. Tables, figures and references**

1. Tables

A maximum of 6 tables and/or figures is allowed. Tables shall be editable, have a title, be listed in order of appearance, be mentioned within the body of the article and be included immediately after the paragraph in which they are first mentioned. If abbreviations are used, they must be clarified in table footers. If a table already published is partially or totally reproduced, the corresponding reference must be added and a letter of permission for its reproduction must be attached. If a table is created by the authors, the legend "Source: own elaboration." must be included.

2. Figures

A maximum of 6 tables and/or figures is allowed. Figures must be editable and have a minimum 72 dpi resolution. Figures include any type of illustration other than tables (graphics, x-rays, photographs, etc.) and must be listed in order of appearance. Every figure shall be mentioned within the body of the article and included immediately after the paragraph in which it is first mentioned. If abbreviations are used, they must be clarified in figure footers. Titles and legends must not be included in the figure but below it. If a figure already published is partially or totally reproduced, the corresponding reference must be added and a letter of permission for its reproduction must be attached. If a table is created by the authors, the legend "Source: own elaboration." must be included.

Please refrain from including any description in figures footers, such explanations shall only be included in the main text of the article.

**XIII. References**

Both in-text and end references must conform strictly to the Vancouver style adopted by the ICJME in its recommendations. References must be introduced in order of appearance and identified by Arabic numerals in parentheses, without superscripts, at the end of the sentence or paragraph where they are alluded to. For a complete guide on the Vancouver system, please go to https://goo.gl/XdCdmS or https://goo.gl/8DJ5Er.

## E. Type of articles accepted – Specific structure

In addition to the general structure described above, each type of article must meet the following requirements:

**I. Editorial**

An editorial is a paper written by the editor, by a member of the Editorial Board or by a guest researcher on orientations in the subject domains of the journal.

The maximum number of words allowed for Editorials, excluding abstracts, tables and figures, and references, is 1000.

**II. Original research**

Original research articles are papers that present in detail the original results of both research projects already finished and biomedical researches. It is an unpublished text that provides new information on specific aspects, as well as relevant contributions to scientific knowledge.

Original research articles shall have a structured abstract and must comply with the general structure for writing articles required by the Revista de la Facultad de Medicina (see Section D).

If the procedures performed during the study involved humans or animals, authors must explicitly state that they followed the ethical principles for medical research on humans of the Declaration of Helsinki (2013) and any other applicable national regulations, said documents must be duly referenced. Additionally, it must be clearly expressed that the study was approved by the ethics committee of the institution or institutions where it was carried out, and the corresponding letter of approval from the ethics committee must be enclosed.

In case of experimental studies, registration of clinical trials in a public trials registry at or before the time of first patient enrollment as a condition of consideration for publication is mandatory. An example of a public trial registry can be found at https://clinicaltrials.gov. The clinical trial registration number must be included in the last line of the abstract, for example: https://www.ncbi.nlm.nih.gov/pubmed/29791437

Articles reporting results of clinical trials in "Materials and methods" must include a data sharing statement that complies with the provision of the ICMJE recommendations, Section II, Subsection L, paragraph ii (Data Sharing).

The maximum number of words allowed for Original Research articles, excluding abstracts, tables and figures, and references, is 3500.

**III. Short communication**

It's a brief article reporting final, partial or preliminary original results of a technologic or scientific research that usually requires a rapid dissemination.

Short communications shall have a structured abstract (in English and Spanish) and must comply with the general structure for writing articles required by the Revista de la Facultad de Medicina (see Section D).

If the procedures performed during the study involved humans or animals, authors must explicitly state that they followed the ethical principles for medical research on humans of the Declaration of Helsinki (2013) and any other applicable national regulations, said documents must be duly referenced. Additionally, it must be clearly expressed that the study was approved by the ethics committee of the institution or institutions where it was carried out, and the corresponding letter of approval from the ethics committee must be enclosed.

The maximum number of words allowed for Short communications, excluding abstracts, tables and figures, and references, is 1500.

**IV. Systematic Review**

Review articles are the result of a research where the results of published or unpublished researches on a field of science or technology are analyzed, systematized and integrated in order to report development trends and the progresses that have been made in the field the review addresses. This type of paper is characterized by a careful literature systematic review

of at least 50 references.

- Only systematic reviews are to be submitted. Narrative or literature reviews will not be accepted anymore, unless the editor asks authors to submit this type of article to start the publication process
- Systematic reviews shall have a structured abstract and must comply with the general structure for writing articles required by the Revista de la Facultad de Medicina (see Section D).
- At least 50 references shall be included.
- Systematic reviews must strictly comply with all the items established in the PRISMA checklist: http://prisma-statement.org/PRISMAStatement/Checklist
- Systematic reviews must comply with the following structure: Introduction, Materials and methods, Results (where the PRISMA based studies selection flowchart (https://goo.gl/hD7PWq) should be included), Discussion and Conclusions, this in line with the structure established in the PRISMA checklist: http://prisma-statement.org/PRISMAStatement/Checklist

The maximum number of words allowed for Systematic reviews, excluding abstracts, tables and figures, and references, is 4000.

**V. Reflection paper**

When writing reflection papers authors shall present the results of a research from their analytical, interpretative or critical perspective on a specific topic and using original sources. Essays and reflection papers s on topics related to medicine and health areas are to be included in this section.

Reflection papers must have the following structure: "Introduction", "other sections of the article", "conclusions".

The maximum number of words allowed for Reflection papers, excluding abstracts, tables and figures, and references, is 3500.

**VI. Case report**

A case report is an article where the results of a study on a particular situation are presented in order to make known the technical and methodological experiences considered in a specific case. It includes a brief review of the literature related to the condition being reported.

Case reports submitted to the Journal must follow all the items of the CARE checklist for writing case reports (http://www.care-statement.org/resources/checklist).

When submitting a case report, the informed consent signed by the patient(s), or legal representative(s), whose data and/or experience was used for writing the report must be uploaded as a supplementary file in step 4 of the submission process.

The maximum number of words allowed for Case reports, excluding abstracts, tables and figures, and references, is 2000.

**VII. Letter to the editor**

A document presenting critical, analytical or interpretative stances on documents published in the Journal that, in the opinion of the Editorial Board, constitute an important contribution to the subject discussion by the scientific community of reference.

The maximum number of words allowed for Letters to the editor, excluding abstracts, tables and figures, and references, is 1000.

## F. Assignment of rights, responsibility of authorship and translation commitment letter

All submissions must be accompanied by the assignment of rights, responsibility of authorship and translation commitment letter forms, duly completed and signed by all authors. The forms are available in https://goo.gl/EfWPdX, https://goo.gl/6zztk4 and https://goo.gl/4rhxxh, respectively. These forms can be loaded during step 4 of the submission.

## G. Similarity and plagiarism report

Once received, articles will be analyzed, using the TurnItin Software, to generate a similarity and plagiarism report. If the article exceeds 15% of similarity, and if said similarity is not derived from a thesis (be aware this report does not take into account references and less than 7 words matches), it will be sent back to the authors for modification or rejected as appropriate.

## H. Ethics and transparency

The Revista de la Facultad de Medicina accepts and adheres to the "Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals" issued by the International Committee of Medical Journal Editors (ICMJE) (www.icmje.org) and to the guidelines established by the Equator (Enhancing the QUAlity and Transparency Of health Research) Network (http://www.equator-network.org/) and the Committee on Publication Ethics (COPE) (http://publicationethics.org/) in order to guarantee the quality of scientific publications, their transparency, integrity and respect for the ethical principles that govern biomedical research. In consequence, the works sent to the Journal must be adjusted to these guidelines.

When procedures have been carried out on humans or animals, the ethical principles for medical research on humans of the Declaration of Helsinki 2013 (https://goo.gl/C5BPi3) and any other applicable national regulations must be explicitly stated and duly referenced. Additionally, the study must be approved by the ethics committee of the institution or institutions where it was carried out, and the respective letter of approval issued by the ethics committee must be enclosed.

If personal images or data are used during the study, the identity and the privacy of the people involved must be protected by editing the images included in the article and using terms and conventions to refer to their data or names.

The articles (or important parts of them) sent to the Revista de la Facultad de Medicina must be unpublished documents that do not correspond to translations or adaptations of other sources already published. By submitting the article together with the assignment of rights (https://goo.gl/EfWPdX) and authorship responsibility (https://goo.gl/6zztk4) forms duly completed, the authors state that:

1. They grant an exclusive license to publish and reproduce their work to the Revista de la Facultad de Medicina in

case the article is accepted.
2. They assume full responsibility for the content of the document, as well as legal and moral responsibility to ensure that matters relating to the accuracy or integrity of any part of the article are properly investigated and resolved.
3. The document has not been previously published under any modality, has not been submitted to another journal and that it will not be sent to other journals while waiting for acceptance or rejection.
4. They accept that the Journal reserves the right to make modifications to the original text during the proofreading and layout processes and to only accept the changes suggested by the authors that the journal team considers pertinent.

## Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. The article (or most of it) has not been published, is not in the process for publication in another journal and will not be sent to other journals while waiting for acceptance or rejection.
2. The text is typed and double-spaced on letter-sized sheets, with margins of 2.5x2.5x2.5x2.5, and 12-point Verdana font. Unless the paper is an Editorial or Letter to the Editor, its writing style does not use any first person (plural or singular) form of conjugation.
3. The maximum limit of words allowed by the journal has been preserved, excluding the abstracts, tables, figures and references: 4 000 for "Systematic Reviews"; 3 500 for "Literature reviews", "Original Research" and "Reflection articles"; 2 000 for "Case Reports", and 1 000 for "Letter to the Editor" and "Editorial".
4. An abstract in Spanish and one in English, of maximum 200 words each, have been included. Three to six keywords were added, both in Spanish and English, taken from the DeCS and MeSH descriptors, respectively.
5. All the indications for the submission of articles, as established in the "Guidelines for authors", have been met. In case of breaching 4 or more items, the article will be rejected.
6. The article is organized according to the structure required for each type of article, as established in the "Guidelines for authors".
7. The references strictly follow the Vancouver style, as required by the journal, and were chosen as recommended in the "Guidelines for authors", including DOI where applicable. For further examples, please visit https://goo.gl/XdCdmS.
8. References include all material published in widely circulated journals, books, official information available online and other types of information that can be cited according to the Vancouver system. Abstracts of papers presented at congresses or symposia can only be referenced when they are published in widely circulated journals.
9. If this study involved humans or experimental animals, the "Materials and methods" section explicitly states that the applicable international ethical standards were met and that the study was approved by the ethics committee of the institution or institutions where it was made. The respective letter of approval issued by the ethics committee is enclosed.
10. The tables and figures are editable, respect the maximum allowed (6) and were made considering the amount of data they contain and the parameters established in the "Guidelines for authors".
11. If tables or figures already published are reproduced, written authorization of their authors or copyright owners is attached, as appropriate.
12. Photographs, figures (x-rays, etc.) and data respect the anonymity and privacy of the people involved.
13. Metadata (author contact details, title, abstract, keywords, references, etc.) are duly entered in step 2 of the submission.
14. The assignment of rights (https://goo.gl/EfWPdX), authorship responsibility (https://goo.gl/6zztk4) and translation commitment letter (https://goo.gl/4rhxxh) forms were completed and signed by all the authors to be loaded in step 4.

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La Revista de la Facultad de Medicina (RFCM) se adhiere a las "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals del International Committee of Medical Journal Editors (ICJME) (http://www.icmje.org/icmje-recommendations.pdf).

## A. Envío de artículos a la Revista de la Facultad de Medicina

Solo se recibirán artículos a través del portal OJS (Open Journal System) en el link http://goo.gl/rsVzGU, donde se deberá realizar el envío completo: artículo, ingreso de todos sus metadatos y archivos complementarios (cesión de derechos https://goo.gl/EfWPdX y responsabilidad de autoría https://goo.gl/6zztk4)

## B. Idiomas de recepción e idioma de publicación

A partir del 10 de enero de 2018 y de acuerdo con en el editorial del V65N2 (https://goo.gl/HaZ37B), se empezará un proceso de transición de publicación en inglés, por lo cual se recibirán artículos en inglés, español y portugués siempre que se cumplan las siguientes condiciones:

### I. Envío en inglés

Deberá ir acompañado de una carta firmada por traductor oficial o personal especializado (certificado este último con nivel C2 en inglés) en la que afirme que ha escrito o ha revisado el artículo y que el mismo cumple con las reglas de redacción de dicho idioma. Todo envío será revisado de forma y de concluirse que no cumple con los requisitos mínimos de idioma, será rechazado.

### II. Envíos en español y portugués

Los autores adjuntarán firmado el oficio de compromiso de publicación en inglés (https://goo.gl/4rhxxh) en el que, siempre que el artículo apruebe el proceso editorial de publicación, se comprometen a traducirlo al inglés con uno de los traductores oficiales de la revista, cuyos datos les serán suministrados. Este proceso estará a cargo de la Revista y los detalles se informarán cuando documento llegue a esta etapa del proceso. Una vez los autores realicen el pago al traductor seleccionado (quienes manejarán una misma tarifa), este último informará a la revista para proceder al envío final del artículo con corrección de estilo para realizar su traducción al inglés, versión que revisarán y aprobarán los autores y la revista. La tarifa actual de la traducción es de 120 pesos colombianos por palabra original traducida (aproximadamente 0.06 usd por palabra), no se contará la lista de referencias para estos efectos. Se tendrán en cuenta excepciones para quienes demuestren dificultades para el pago de este servicio, por ejemplo autores que residan en países como Venezuela o Cuba debido a la compleja tasa cambiaria.

## C. Autoría

Quienes figuren como autores de los artículos enviados deberán cumplir en su totalidad con los criterios de autoría establecidos en Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals del International Committee of Medical Journal Editors (ICJME), sección II, subsecciones A y B, http://www.icmje.org/icmje-recommendations.pdf.

## D. Presentación del artículo - Secciones generales

De acuerdo a las recomendaciones de ICJME los artículos deben cumplir con la siguiente estructura general (según el tipo de artículo se requerirá una estructura específica, al respecto ver la sección F de estas indicaciones):

### I. Página de portada

1. Título en el idioma en que se presente el artículo (Español, Inglés, Portugués)
2. Título en segundo idioma (inglés o español según idioma de presentación del artículo)
3. Título corto que no exceda 40 caracteres contando espacios (inglés y español).
4. Nombres completos de autores con filiación identificada por número arábigo en superíndice
5. Filiación completa de cada autor sin especificar cargos, solo instituciones y secciones dentro de las mismas
6. Identificación ORCID de cada autor. Esta información también debe incluirse en los metadatos del envío (paso 2 del envío en el portal OJS).
7. Correspondencia completa del autor principal (nombre, dirección institucional, teléfono, ciudad, país, correo electrónico).
8. Recuento de palabras: indique el número total de palabras en el texto sin tener en cuenta las palabras de títulos, resúmenes, agradecimientos, tablas y figuras, ni listado de referencias. El número de palabras no debe exceder el máximo permitido según tipo de artículo (ver Sección E)
9. Número de figuras y tablas: indique el número total de tablas y figuras en el artículo. No debe exceder el máximo permitido: 6.

### II. Resumen

1. No debe superar las 200 palabras.

2. No debe incluir referencias.
3. En caso de estudios experimentales, incluir el registro del protocolo (ensayo clínico) en la última línea del resumen, ejemplo: https://www.ncbi.nlm.nih.gov/pubmed/29791437
4. Para Investigación original, Artículo de revisión, y Comunicación breve debe estructurarse en "Introducción", "objetivo", "materiales y métodos", "resultados", "conclusiones".
5. Para reportes de caso debe estructurarse de acuerdo con los lista de comprobación CARE para presentación de reportes de caso (http://www.care-statement.org/resources/checklist), ítem 3 Resumen.
6. Palabras clave: Incluir 3 a 6 descriptores exactos que se encuentren DeCS Bireme (http://decs.bvs.br/).

**III. Abstract**

1. No debe superar las 200 palabras.
2. No debe incluir referencias.
3. En caso de estudios experimentales, incluir el registro del protocolo (ensayo clínico) en la última línea del resumen, ejemplo: https://www.ncbi.nlm.nih.gov/pubmed/29791437
4. Para Investigación original, Artículo de revisión, y Comunicación breve debe estructurarse en "Introduction", "objective", "materials and methods", "results", "conclusion".
5. Para reportes de caso debe estructurarse de acuerdo con los lista de comprobación CARE para presentación de reportes de caso (http://www.care-statement.org/resources/checklist), ítem 3 Resumen.
6. Keywords: Incluir 3 a 6 descriptores exactos que se encuentren en MeSH (http://www.nlm.nih.gov/mesh/).

**IV. Introducción**

Sintetice la racionalidad del estudio y, al final de esta sección, indique el objetivo del mismo. Cite solo las referencias estrictamente necesarias.

**V. Materiales y métodos**

Describa el tipo de estudio y la metodología empleada en la realización del artículo (identificación de la muestra, criterios de selección, métodos estadísticos, etc.). Si se realizaron procedimientos en seres humanos o animales debe expresarse de forma explícita que se respetaron los principios éticos para las investigaciones médicas en seres humanos de la Declaración de Helsinki (2013) y cualquier otra normativa nacional que aplique, debidamente referenciadas, y que el estudio fue aprobado por el comité de ética de la institución o instituciones donde fue realizado, acompañando el envío con la respectiva carta de aprobación por parte del comité de ética. En caso de estudios experimentales se requiere que el protocolo del estudio (ensayo clínico) haya sido registrado previamente en una base de datos de registro de protocolos, se sugiere consultar https://clinicaltrials.gov, Incluir el registro en la última línea del resumen.

**VI. Resultados**

Presente de forma lógica y coherente los resultados obtenidos. Los datos se pueden mostrar en tablas o figuras, pero no de forma simultánea en ambas. Evite repetir en el texto los datos presentados en tablas y figuras y no combine la presentación de los resultados con su discusión, pues esta última tiene su propia sección.

**VII. Discusión**

Aborde los resultados obtenidos en el estudio sin realizar una revisión del tema en general. Discuta únicamente sobre los aspectos nuevos e importantes que aporta su trabajo y las conclusiones propuestas a partir de los mismos. Indique las limitaciones de la investigación y las concordancias o discordancias de sus hallazgos con los obtenidos en otros estudios sobre el tema, debidamente referenciados.

**VIII. Conclusiones**

Deben estar relacionadas con los objetivos del estudio que fueron descritos en "introducción". No formule conclusiones que no estén respaldadas por los hallazgos del estudio o que se apoyen en otros trabajos aún sin finalizar. Si lo considera pertinente, plantee nuevas hipótesis pero califíquelas como tales. Cuando sea apropiado, proponga sus recomendaciones.

**IX. Conflicto de intereses**

Indique si a partir de la financiación del estudio o por otro motivo los autores presentaron o no conflicto de intereses en la realización del artículo. Debe diligenciarse el formato de divulgación de conflicto de intereses del ICJME (http://www.icmje.org/about-icmje/faqs/conflict-of-interest-disclosure-forms) y adjuntarse como archivo complementario (paso 4 del envío).

**X. Financiación**

Señale si el estudio contó con financiación externa y si esta influenció su realización.

**XI. Agradecimientos**

Agradezca solo a personas e instituciones que hayan contribuido sustancialmente a su trabajo. Los autores son responsables por la mención de personas o instituciones a quienes los lectores podrían atribuir un apoyo a los resultados del trabajo y sus conclusiones.

**XII. Tablas, figuras y referencias**

1. Tablas

Deben ser editables. Se permitirá un máximo de 6 tablas y/o figuras. Deberán tener título, enumerarse en orden de aparición, mencionarse en el texto e incluirse inmediatamente después del párrafo en que son nombradas. Si se utilizan abreviaturas han de ser aclaradas en forma de pie de tabla. Si una tabla ya publicada es reproducida parcial o totalmente indíquelo referenciándolo y adjuntando en el envío carta de permiso para la reproducción de la misma. Si una tabla es creación de los autores indíquelo con la leyenda Fuente: elaboración propia.

2. Figuras

Deben ser editables y tener una resolución mínima de 30 dpi. Denomine como figura cualquier tipo de ilustración que no sea tabla (gráficos, radiografías, fotografías, etc.) y enumérelas en orden de aparición. Toda figura deberá mencionarse en el texto e incluirse inmediatamente después del párrafo en que es nombrada. Si se utilizan abreviaturas, las mismas tienen que ser aclaradas en forma de pie de figura. Los títulos y leyendas no deben aparecer en la figura, sino abajo de la misma. Si una figura ya publicada es reproducida parcial o totalmente indíquelo referenciándolo y adjuntando en el envío carta de permiso para la reproducción de la misma. Si una figura es creación de los autores indíquelo con la leyenda Fuente: elaboración propia.

No incluir descripciones en los pies de figura, estas explicaciones deben incluirse en el cuerpo del documento.

**XII. Referencias**

La citación de referencias, tanto in texto como en el listado final, debe ajustarse estrictamente al formato Vancouver aprobado por el ICJME en sus recomendaciones . La enumeración debe realizarse en orden de aparición y debe identificarse mediante números arábigos entre paréntesis, sin superíndice, ubicados al final de la frase o párrafo en donde se les alude. Para una guía sobre el sistema Vancouver ir a https://goo.gl/XdCdmS o https://goo.gl/8DJ5Er.

## E. Tipos de artículo, estructura y máximo de palabras

Además de la estructura general antes descrita, cada tipo de artículo debe cumplir con los siguientes requisitos:

**I. Editorial**

Documento escrito por el editor, un miembro del Comité Editorial o un investigador invitado sobre orientaciones en las áreas de especialidad de la revista.

Máximo permitido de palabras 1000, sin contar títulos, resúmenes, tablas y figuras y referencias.

**I. Investigación original**

Artículo que presenta, de manera detallada, los resultados originales de proyectos de investigación ya terminados, así como de investigaciones biomédicas. Es un trabajo inédito que aporta nueva información sobre aspectos específicos y contribuye de manera relevante al conocimiento científico.

Debe incluir resumen estructurado y cumplir con la estructura general requerida por la revista (ver Sección D).

Si se realizan estudios en o con datos de seres humanos o animales deben haberse tenido en cuenta los principios éticos de investigación de la Declaración de Helsinki y la normativa nacional que aplique (debidamente referenciadas), indicar que fue aprobado por comité de ética institucional y acompañar el envío con la carta de aprobación por parte de dicho comité.

En caso de estudios experimentales se requiere que el protocolo del estudio haya sido registrado previamente en una base de datos de registro de protocolos, se sugiere consultar https://clinicaltrials.gov, Incluir el registro en la última línea del resumen, ejemplo: https://www.ncbi.nlm.nih.gov/pubmed/29791437.

Si la investigación reporta resultados de ensayos clínicos debe incluirse (en materiales y métodos) una declaración sobre la divulgación de datos que cumpla con lo establecido por en las recomendaciones del ICMJE, Sección III, Subsección L, literal ii (Data Sharing).

Máximo permitido de palabras 3500, sin contar títulos, resúmenes, tablas y figuras y referencias

**III. Comunicación breve**

Documento breve que presenta resultados originales finales, preliminares o parciales de una investigación científica o tecnológica que, por lo general, requiere de una pronta difusión.

Debe incluir resumen estructurado y cumplir con la estructura general requerida por la revista (ver Sección D).

Si se realizan estudios en o con datos de seres humanos o animales deben haberse tenido en cuenta los principios éticos de investigación de la Declaración de Helsinki y la normativa nacional que aplique (debidamente referenciadas), indicar que fue aprobado por comité de ética institucional y acompañar el envío con la carta de aprobación por parte de dicho comité.

Máximo permitido de palabras 1500, sin contar títulos, resúmenes, tablas y figuras y referencias

**IV. Artículo de revisión sistemática**:

Documento resultado de una investigación donde se analizan, sistematizan e integran los resultados de investigaciones publicadas o en prensa sobre un tema específico con el fin de dar cuenta de los avances y tendencias de desarrollo en este campo. Se caracteriza por presentar una cuidadosa revisión sistemática de la literatura médica de por lo menos 50 referencias.

- Solo se aceptarán revisiones sistemáticas. Las revisiones narrativas no serán aceptadas, a menos que exista invitación previa por parte del Editor para su presentación a proceso de publicación
- La revisión sistemática debe incluir resumen estructurado y cumplir con la estructura general requerida por la revista (ver Sección D)
- Mínimo de referencias a incluir: 50
- Debe cumplir estrictamente con todos los ítems de la lista de comprobación PRISMA: http://prisma-statement.org/PRISMAStatement/Checklist
- Debe estructurarse en Introducción, Materiales y métodos, Resultados (donde debe incluirse el flujograma formato PRISMA https://goo.gl/hD7PWq), Discusión y conclusiones, esto en línea con la estructura de la lista de comprobación PRISMA: http://prisma-statement.org/PRISMAStatement/Checklist
- Máximo permitido de palabras: 4000, sin contar títulos, resúmenes, tablas y figuras y referencias

**V. Artículo de reflexión**

Documento que presenta los resultados de una investigación, desde una perspectiva analítica, interpretativa o crítica del autor, sobre un tema específico en el que se recurre a fuentes

originales. En esta sección también se incluyen aquellos ensayos y artículos de reflexión sobre temáticas relacionadas con la medicina y el área de la salud.

Deberá estructurarse en "Introducción", "texto del artículo", "conclusiones". Máximo permitido de palabras 3500, sin contar títulos, resúmenes, tablas y figuras y referencias

**VI. Reporte de caso**

Documento que presenta los resultados de un estudio sobre una situación particular con el fin de dar a conocer las experiencias técnicas y metodológicas consideradas en un caso específico; incluye una revisión breve de la literatura relevante.

La estructura y presentación de los reportes de caso deben cumplir todos los ítéms del checklist de los líneamientos CARE (http://www.care-statement.org/resources/checklist) para presentación de casos.

El envío debe estar acompañado del consentimiento informado del o los pacientes o sus representantes objeto del caso (paso 4 del envío, archivos complementarios)

Máximo permitido de palabras 2000, sin contar títulos, resúmenes, tablas y figuras y referencias

**VII. Carta al editor**

Texto en el que se expresan posiciones críticas, analíticas o interpretativas sobre los documentos publicados en la Revista que, a juicio del Comité Editorial, constituyen un aporte importante a la discusión del tema por parte de la comunidad científica de referencia.

No requiere estructura.

Máximo permitido de palabras 1000, sin contar títulos, resúmenes, tablas y figuras y referencias

## F. Formatos de cesión de derechos, responsabilidad de autoría y compromiso de traducción

Todo envío deberá ir acompañado de los oficios cesión de derechos, responsabilidad de autoría y compromiso de traducción debidamente diligenciados y firmados por todos los autores, los cuales están disponibles para descarga en https://goo.gl/EfWPdX, https://goo.gl/6zztk4 y https://goo.gl/4rhxxh, respectivamente. Dichos oficios podrán cargarse en el paso 4 del envío.

## G. Informe de similitud y plagio

Una vez recibidos, los artículos serán analizados con el Software TurnItin, donde se generará un informe de similitud y plagio, en caso de superar 15% de similitud y no derivarse de un trabajo de grado o tesis de postgrado dicha similitud (no se tienen en cuenta referencias ni coincidencias menores a 7 palabras), el artículo será devuelto para modificación o rechazado según sea el caso.

## H. Declaración de ética y transparencia

La Revista de la Faculta de Medicina acepta y se adhiere a las "Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals" del International Committee of Medical Journal Editors (ICMJE) (www.icmje.org) y a los lineamientos establecidos por Equator (Enhancing the QUAlity and Transparency Of health Research) Network (http://www.equator-network.org/) y por el Committee on Publication Ethics (COPE) (http://publicationethics.org/) con el fin de garantizar la calidad de las publicaciones científicas, su transparencia, integridad y debido respeto de los principios éticos que rigen la investigación biomédica. De acuerdo a lo anterior, los trabajos enviados a la Revista de la Facultad de Medicina se deben ajustar a dichos lineamientos.

Además, cuando se hayan realizado procedimientos en seres humanos o animales debe expresarse de forma explícita que se respetaron los principios éticos para las investigaciones médicas en seres humanos de la Declaración de Helsinki de 2013 (https://goo.gl/C5BPi3) y cualquier otra normativa nacional que aplique, debidamente referenciadas, y que el estudio fue aprobado por el comité de ética de la institución o instituciones donde fue realizado, acompañando el envío con la respectiva carta de aprobación por parte del comité de ética.

En caso de utilizarse imágenes o datos personales en la realización del estudio se debe proteger la identidad y privacidad de estas personas mediante la edición de las imágenes incluidas en el artículo y el uso de términos y convenciones para referirse a sus datos o nombres.

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