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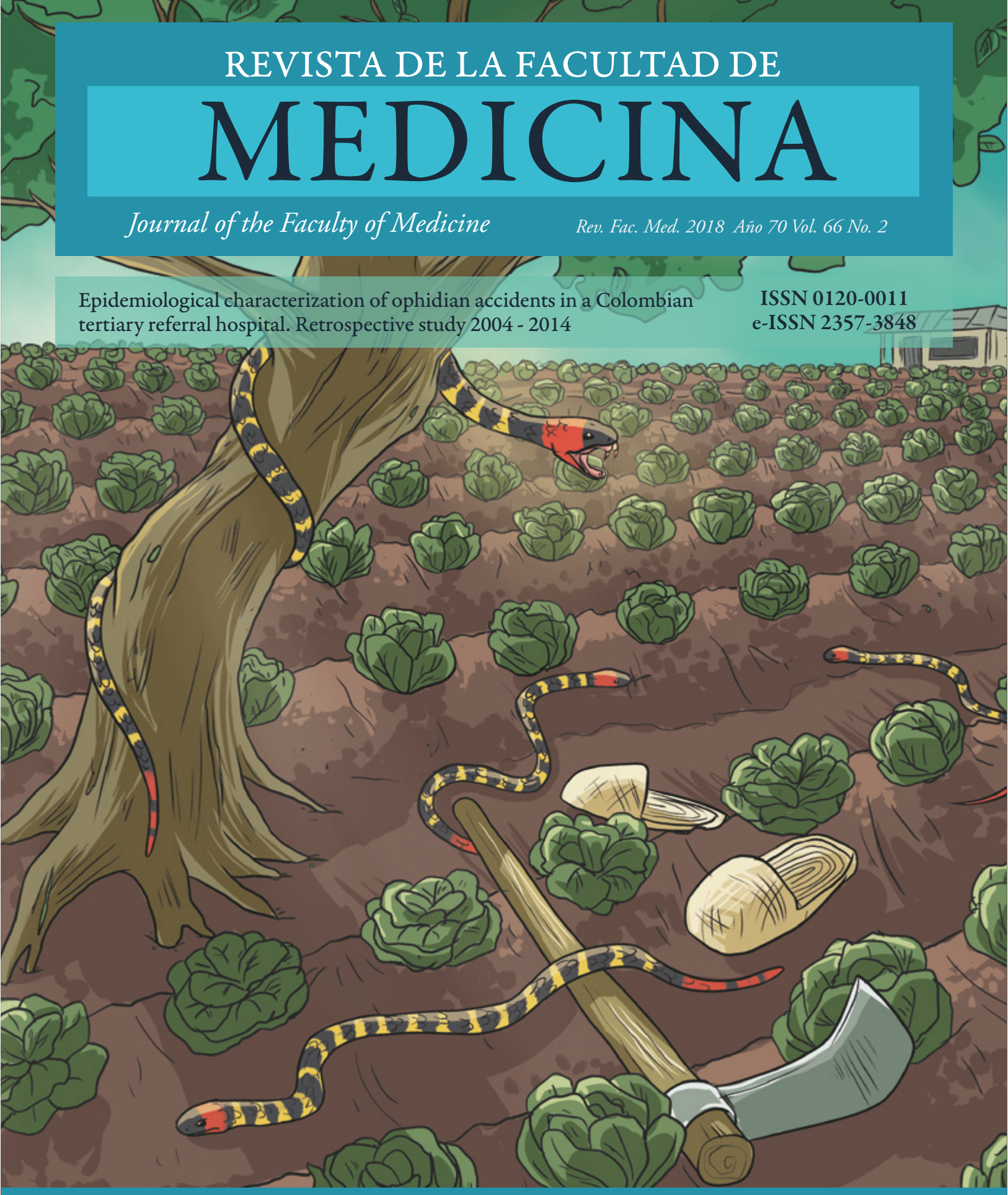

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UNIVERSIDAD NACIONAL DE COLOMBIA

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Contenido

Editorial

Original research

Reflection paper

Review article

Case report

Letter to the editor

Fig. 2.

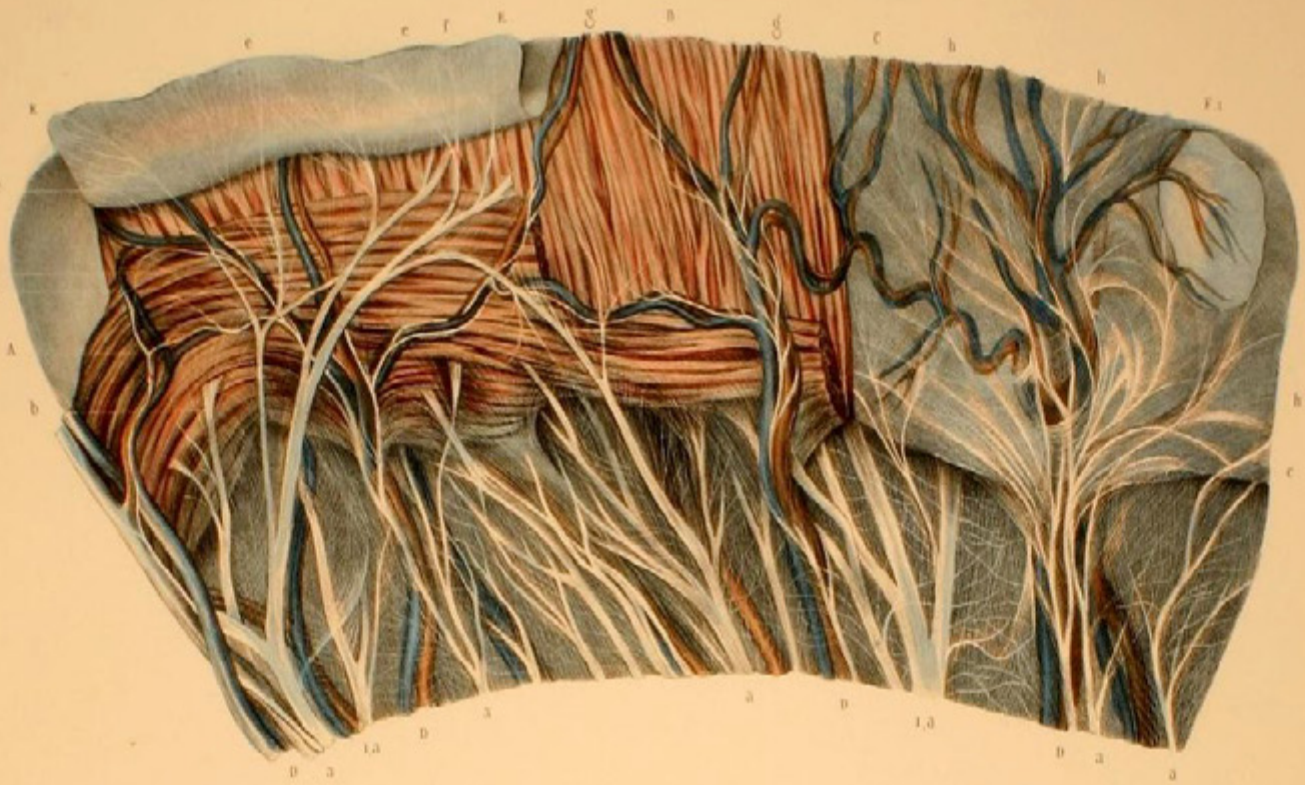
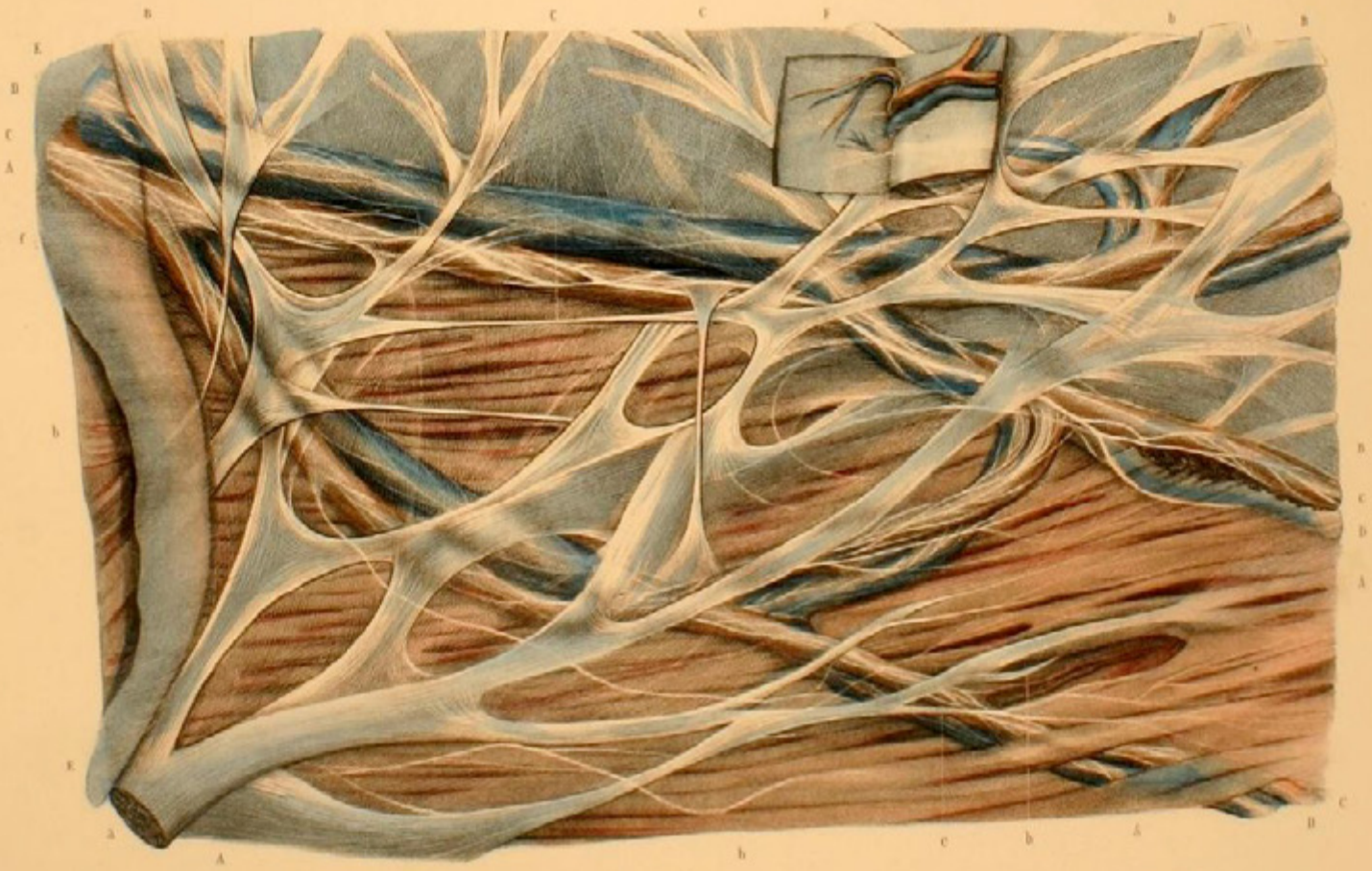


Fig. 1.



Jean Marc Bourgery
"Traité complet de l'anatomie de l'homme"
Paris 1832-1854

Editorial

DOI: http://http://dx.doi.org/10.15446/revfacmed.v66n2.70828

Research on heart failure in Colombia, time to take a step forward

"The mind is not a vessel to be filled but a fire to be kindled"
Plutarch

Cardiovascular diseases are the leading cause of death worldwide. According to the Ministry of Health, in Colombia, cardiac ischemic disease ranks first, followed by stroke, diabetes and hypertensive heart disease, which are in the top ten sources of mortality. (1,2) Almost any pathology that affects the heart can lead to heart failure (HF); however, the most common cause worldwide is ischemic heart disease.

For the period 1998-2011, cardiovascular diseases accounted for 23.5% of all deaths in the country, and cardiac ischemic disease was involved in 56.3% of them. These figures showed an average mortality rate of 104.6 cardiovascular deaths per 100 000 inhabitants per year. (3) A study conducted in Colombia in 4 239 patients treated in heart failure clinics showed that ischemic etiology was the most prevalent (38.7%), followed by idiopathic dilated cardiomyopathy (21.6%) and other less prevalent causes such as valvular heart disease (10.5%), Chagas heart disease (10.3%) and hypertensive heart disease (12.2%). (4)

In 2006, approximately 26 million people worldwide were living with heart failure (5), and an estimated 1.1 million people in Colombia were affected. (4) According to the Ministry of Health, between 2009 and 2012, admissions increased (121%) in emergency services and inpatient care due to HF. (6)

Considering this, we are facing a major issue in Colombia, and its treatment entails significant costs for the health system. Since research is a way to understand and solve health problems, a question arises: what is the state of research on HF in Colombia? In this issue of the Journal of the Faculty of Medicine, Diaztagle *et al.* (7) present the work entitled "Research on heart failure in Colombia 1980-2015: a systematic review", in which the authors identify 35 original studies, for an average of 1 article per year, although the trend shows more publications in the past 5 years, with almost 5 articles per year. These data are alarming because of the small number of investigations on this topic, taking into account that during the same period evaluated in the study, 5 694 original articles on the same topic were published in international indexed journals according to the PubMed database. Furthermore, over half of the studies conducted in our country were descriptive (54.2%).

In the 1996-2017 period, Colombia ranked 47th in the world in terms of production of medical research articles and 42nd in evaluation publications on cardiovascular medicine. (8) This amount of articles is very far from the thirtieth position, occupied by Iran with three times as many publications in this field. In the same period, the country ranked fourth in Latin America, Mexico being the third with twice as many publications. (8) It is evident that our production of original articles is low, even compared to other developing countries.

Diaztagle *et al.* (7) should be congratulated for their hard work to obtain the articles, which included a manual revision in newspaper and periodicals libraries. Although the information that the authors provide is useful, the study is essentially descriptive, like most research on HF, and does not address the causes of low research, and, therefore, does not provide any kind of solution.

Medical research aims to generate new knowledge for the diagnosis, treatment or prevention of a disease. This new knowledge should be directed, ultimately, to solve the problems of patients. Cardiologists, internists, intensivists, emergency physicians, family physicians and general practitioners know that HF is a frequent entity that leads to frequent use of health services. In consequence, the lack of research is not related to the lack of patients; on the contrary, it is very likely that it is related to poor medical research in the country.

I believe that this problem occurs due to the lack of research "culture", because in countries like Colombia we do not believe that we can produce useful information and accept that all the evidence coming from industrialized countries is fully replicable in our population. But, this is not entirely true and we have many examples, such as the case of the use of warfarin with INR between 2 and 3 in patients with atrial fibrillation and at high risk of embolic events to reduce said risk with a low probability of bleeding complications; this was evaluated through several studies conducted on East Asian populations, finding a high index of intracerebral hemorrhagic events (9) that led to recommend lower INR (1.6-2.5) in their guidelines. Another example, in our context, is the lack of reproducibility of risk scores that have shown encouraging results in other studies in patients with syncope attended by emergency services. (1,10) In consequence, although showing that a wheel rotates in every direction is not necessary, it is possible that its rotation is not the same everywhere.

Understanding that part of our problem lies in the lack of resources to investigate is essential. The Administrative Department of Science, Technology and Innovation (Colciencias in Spanish) is the main state contributor of these resources and obtaining them is not easy; therefore, alliances with private companies have to be established in order to develop serious research that produces relevant information for patients. The Ministry of Health should provide funds to hospitals to produce research and hospitals, in turn, should at least grant the necessary time to doctors who want to investigate.

Controlled clinical trials are considered, until now, the culmination of medical research, but I think we are far from conducting this type of large-scale studies in the country. However, we may have records, obtained by scientific societies or cohorts, of patients with follow-ups in university hospitals. The economic assessment of the different diagnostic and therapeutic strategies is also relevant, in

particular regarding the usefulness of high-cost treatments for HF, such as the use of cardioverter defibrillators and resynchronizers or heart transplantation.

Another important aspect is that we have our own problems related to poverty; for example we do not know what the impact of partial adherence to drugs for HF is and how it correlates to delivery issues in health promoting entities or what the impact on these patients is when they also have cardiac devices. We do not know either what the real response of our patients is to the different treatments for HF approved internationally.

Only knowing the research landscape on heart failure in Colombia can we understand what happens when evidence-based medicine is applied in our population. In conclusion, the study of Diaztagle *et al.* (7) is a basis for more and better research in Colombian patients with HF and to take a step forward.

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References

1. **Diaz-Tribalbos DC, Mora G, Olaya A, Marín J, Sierra-Matamoros F.** Determinación del valor pronóstico a 6 meses de puntaje de riesgo OESIL en una cohorte colombiana con síncope evaluada en el servicio de urgencias, primera experiencia latinoamericana. *Arch Cardiol Mex.* In press 2017. http://doi.org/cqm3.
2. Enfermedades cardiovasculares. Bogotá D.C.: Ministerio de Salud y Protección Social; 2010 [cited 2018 Jun 6]. Available from: https://goo.gl/8MebkW.
3. Instituto Nacional de Salud. Enfermedad cardiovascular: principal causa de muerte en Colombia. Bogotá D.C.: Boletín ONS No. 1; 2013 [cited 2018 Jun 6]. Available from: https://goo.gl/61LUqU.
4. **Gómez E.** Capítulo 2. Introducción, epidemiología de la falla cardiaca e historia de las clínicas de falla cardiaca en Colombia. *Rev. Colom Cardiol.* 2016;23(Suppl 1):6-12. http://doi.org/cqm4.
5. **Go As, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, *et al.*** Heart disease and stroke statistics – 2013 update: a report from the American Heart Association. *Circulation.* 2013;127(1):e-e2456. http://doi.org/cqm5.
6. SISPRO. Bodega de datos de SISPRO (RIRS) – Ministerio de Salud y protección Social. Reporte-prestaciones de servicios de salud reportados por las entidades administradoras de planes de beneficio para los años 2009, 2010, y 2011, según resolución 3374/00.
7. **Diaztagle-Fernández JJ, Latorre-Alfonso SI, Maldonado-Álvarez GP, Merchán-Cepeda JS, Centeno-García CD, *et al.*** Research on heart failure in Colombia 1980-2015: a systematic review. *Rev. Fac. Med.* 2018;66(2):139-152. http://dx.doi.org/10.15446/revfacmed.v66n2.60005.
8. SCImago. SJR - SCImago Journal & Country Rank. [Cited 2018 Jun 6]. Available from: https://goo.gl/w6m7FB.
9. **Shen AY, Yao JF, Brar SS, Jorgensen MB, Chen W.** Racial/ethnic differences in the risk of intracranial haemorrhage among patients with atrial fibrillation. *J Am Coll Cardiol.* 2007;50(4):309-15. http://doi.org/fv9jks.
10. **Paz-Meneses MA, Mora-Pabón G.** Use of the ROSE risk score for predicting mortality and cardiovascular events in adult patients at 7 and 30 days of syncope. *Rev. Fac. Med.* 2016;64(3):471-5. http://doi.org/cqm6.

ORIGINAL RESEARCH

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Research on heart failure in Colombia 1980-2015: a systematic review

La investigación en falla cardíaca en Colombia 1980-2015: una revisión sistemática

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| Abstract |

Introduction: Heart failure is one of the most prevalent diseases worldwide. In Colombia, the state of research on the subject is unknown.

Objective: To describe the original publications on heart failure in Colombia.

Materials and methods: Systematic review. Digital search in Embase, PubMed, LILACS and Scielo, using the MeSH terms: "heart failure", "Colombian", "Colombia", "Latin America", "developing countries". Manual search of 58 journals identified in Publindex. Original research that evaluated adult Colombians with heart failure and published between 1980 and 2015 were included.

Results: 2 684 articles were identified, of which 35 met the inclusion criteria. 30 (85.7%) were published since 2009, 30 (85.7%) were conducted in Bogotá and Medellín, 11 (31.4%) had n>200, 19 (54.2%) were descriptive and 5 (14.2%) quasi-experimental. Moreover, 9 (25.7%) described general populations, 9 (25.7%) addressed the issue of self-care, 3 (8.8%) cardiac rehabilitation, 3 (8.8%) perception of the disease and 3 (8.8%) prognostic factors.

Conclusions: The amount of published original research on heart failure is low, and most of them were carried out recently. Descriptive design was the most frequent, while the most frequently addressed topics were self-care and population descriptions.

Keywords: Heart Failure; Research; Colombia; Latin America (MeSH).

| Resumen |

Introducción. La falla cardíaca es una de las enfermedades con mayor prevalencia a nivel mundial. En Colombia no se conoce con certeza el estado de la investigación en torno al tema.

Objetivo. Describir las publicaciones originales en falla cardíaca en Colombia.

Materiales y métodos. Revisión sistemática. Búsqueda electrónica en Embase, PubMed, LILACS Y SciELO, con términos MeSH: "heart failure", "colombian", "Colombia", "Latin America", "developing countries". Búsqueda manual en 58 revistas identificadas en Publindex. Se incluyeron investigaciones originales, publicadas entre 1980 y 2015, que evaluaron población adulta colombiana con falla cardíaca.

Resultados. Se identificaron 2 684 artículos: 35 cumplieron criterios de inclusión; 30 (85.7%) fueron publicados a partir del 2009; 30 (85.7%) se realizaron en Bogotá y Medellín; 11 (31.4%) tuvieron n>200; 19 (54.2%) fueron descriptivos y 5 (14.2%) cuasiexperimentales; 9 (25.7%) describieron poblaciones generales; 9 (25.7%) abordaron el tema del autocuidado, 3 (8.8%), la rehabilitación cardíaca, 3 (8.8%), la percepción de enfermedad y 3 (8.8%), los factores pronósticos.

Conclusión. El número de investigaciones originales publicadas sobre falla cardíaca es escaso; la mayoría se realizó en los últimos años. El diseño descriptivo fue el más común. Los temas abordados con mayor frecuencia fueron el autocuidado y las descripciones poblacionales.

Palabras clave: Insuficiencia cardíaca; Investigación; Colombia; América Latina (DeCS).

Diaztagle-Fernández JJ, Latorre-Alfonso SI, Maldonado-Arenas SE, Manosalva-Álvarez GP, Merchán-Cepeda JS, Centeno-García CD, *et al.* Research on heart failure in Colombia 1980-2015: a systematic review. Rev. Fac. Med. 2018;66(2):139-51. English. doi: http://dx.doi.org/10.15446/revfacmed.v66n2.60005.

Diaztagle-Fernández JJ, Latorre-Alfonso SI, Maldonado-Arenas SE, Manosalva-Álvarez GP, Merchán-Cepeda JS, Centeno-García CD, *et al.* [La investigación en falla cardíaca en Colombia 1980-2015: una revisión sistemática]. Rev. Fac. Med. 2018;66(2):139-51. English. doi: http://dx.doi.org/10.15446/revfacmed.v66n2.60005.

Introduction

Recently, Colombia has presented demographic and epidemiological changes in the population that have determined certain variations in the health profile of its inhabitants. Between 1985 and 2003, a two-fold increase in the number of >60-year-old people and in life expectancy was observed. These changes resulted in a "transitional" epidemiological phase, which led chronic non-communicable diseases to become predominant. For this and other reasons, circulatory system diseases were the leading cause of death by "large groups" in the country between 1997 and 2010, with 28-30% of total deaths. (1) Of these, almost half originated from ischemic heart disease, which is also related to the high prevalence of cardiovascular risk factors such as hypertension, diabetes, smoking, sedentary lifestyle and overweight. (2)

Ischemic heart disease, together with hypertensive heart disease, affects cardiac and vascular function, triggering the condition known as heart failure, a chronic disease that progressively deteriorates the health state of the person. Data obtained in the USA indicated that, between 2011 and 2014, the prevalence of heart failure in people aged ≥20 years was 2.5%, which is equivalent to 6.5 billion people affected. This figure is expected to increase by 46% between 2012 and 2030 (3), a situation that requires the use of a high amount of economic resources for the health system. (4) A study conducted in Colombia estimated that the average monthly cost of outpatient treatment in 2010 was COP 304 318 (about USD 160), while the average cost of hospitalization was COP 6 427 887 (about USD 3 387). (5)

With this in mind, scientific knowledge on heart failure is fundamental to offer a comprehensive clinical approach and to generate innovation processes around the topic. (6) In Colombia, the current status of research and publication about heart failure is unknown, since knowledge may be limited and publications referring to the topics are scarce. (7) Two national consensuses on acute and chronic heart failure have few citations in the bibliographical references of Colombian works. (7,8) As a result, few published studies or publications may not be adequately known due to various circumstances.

For this reason, the objective of this work is to conduct a systematic review of the literature to identify the publications of studies conducted in our country that address the issue of heart failure, expose their methodological characteristics and the most relevant results, and analyze the data provided by the studies.

Materials and methods

A systematic review of the medical literature published in Colombia on heart failure between 1980 and 2015 was carried out. The following search mechanism was used to identify the articles:

Search in domestic scientific journals: A search was made in Colombian health journals acknowledged by the Sistema Nacional de Indexación y Homologación de Revistas Especializadas de CT+I (National Indexing and Homologation System for Journals Specialized in STI) of Colciencias (National Bibliographic Index-Publindex I- 2013 update) that deal with topics related to clinical medicine. (9) The search in this index was filtered using the so-called Great Knowledge Area: Medical and Health Sciences. With this information, a complete list of the journals used to search for the articles was obtained. In addition, the health journals of the universities that had medical faculties in 2014 were searched in their web pages. Journals where publication of original articles of heart failure was considered unlikely were excluded.

Journals were searched individually, in their respective website, identifying the issues published between January 1980 and December 2015. The table of contents of said issues was analyzed, and articles related to heart failure were verified. Inclusion and exclusion criteria were applied to the articles initially identified. In case that the online version of the issues was not found in its entirety, a manual search was carried out in different libraries and national newspaper archives.

Digital search in databases: A digital search was carried out in the Embase, PubMed and Lilacs databases and in the Cochrane Library, using the search structure described in Annex 1.

Manual search of bibliographic references: A manual search was made of the references of all the articles identified in the three previous searches, applying inclusion and exclusion criteria.

Review of CvLac resumes of the main authors: A search of the resumes of the main authors of the identified articles was made on CvLac to verify the existence of additional articles.

Inclusion and exclusion criteria of articles: Original research on patients >18 years of age, diagnosed with acute or chronic heart failure, outpatient or inpatient in Colombia, published in full text, with an observational intervention design or clinical simulation model were included. Case reports, subject reviews, management guidelines and articles published only in summary version were excluded from the analysis.

A data collection tool was designed to carry out the bibliographic documentation, which included the affiliation data of the journal, the type of article described along with the year, issue, number and title of the document. Information on the methodological characteristics of the study, the results and the conclusions of the selected articles was also obtained. The study was approved by the Human Research Ethics Committee of the Hospital of San José of Bogotá and the Fundación Universitaria de Ciencias de la Salud.

Results

Search result

Search in domestic scientific journals: A search of journals was carried out on February 23, 2014 in the National Bibliographic Index-Publindex I-2013 update of the official web page of Colciencias. 73 records were obtained (58 in clinical medicine, 25 in health sciences, 14 in other medical sciences and 3 in basic medicine). Of the total journals identified, 58 were selected to conduct the review. The journal identification process is described in Annex 1. Table 1 shows general information of these journals.

Of 58 journals, 26 were published in full text in an online version. For the remaining 32, it was necessary to complement the search in university and national libraries. It was also necessary to contact editors and administrative staff of some journals to obtain missing issues.

All the issues of 56 journals were reviewed in their entirety. After reviewing all the articles in these issues, 87 studies were found that dealth with heart failure as a central topic, of which 31 met inclusion criteria (Figure 1).

Table 1. Description of selected journals.

Name of the journal	Publishing Institution	First year of publication	City
Acta Médica Colombiana	Asociación Colombiana de Medicina Interna (ACMI)	1977	Bogotá
Actualización en Enfermería	Fundación Santa Fé de Bogotá.	1998	Bogotá
Aquichan	Universidad de la Sabana	2001	Chía
Archivos de Medicina	Universidad de Manizales	2001	Manizales
Área Médica	Universidad de Ciencias Aplicadas y Ambientales (UDCA)	2007	Bogotá
Avances en Enfermería	Universidad Nacional de Colombia	1982	Bogotá
Biomédica	Instituto Nacional de Salud	1981	Bogotá
Biosalud: Revista de Ciencias Básicas	Universidad de Caldas	2002	Manizales
CES Medicina	Universidad CES	1987	Medellín
Ciencia y Cuidado	Universidad Francisco de Paula Santander	2004	Cúcuta
Ciencia y Salud Virtual	Corporación Universitaria Rafael Núñez	2009	Cartagena
Colombia Médica	Universidad del Valle	1970	Cali
Cultura del Cuidado Enfermería	Universidad Libre de Colombia	2004	Pereira
Duazary	Universidad del Magdalena	2004	Santa Marta
Hacia la Promoción de la Salud	Universidad de Caldas	1996	Manizales
Iatreia	Universidad de Antioquia	1988	Medellín
Investigación de Enfermería: Imagen y Desarrollo	Pontificia Universidad Javeriana	1999	Bogotá
Investigación y Educación en Enfermería	Universidad de Antioquia	1983	Medellín
Investigaciones Andina	Fundación Universitaria del Área Andina	2000	Pereira
Investigaciones en Seguridad Social y Salud	Secretaría Distrital de Salud de Bogotá	1999	Bogotá
Manos al Cuidado	Universidad del Tolima	2009	Ibagué
Médicas UIS	Universidad Industrial de Santander	1987	Bucaramanga
Medicina	Academia Nacional de Medicina	1967	Bogotá
Medicina	Corporación Universitaria del Sinú	2002	Montería
Medicina & Laboratorio	Editorial Médica Colombiana S.A.	1989	Medellín
Medicina UPB	Universidad Pontificia Bolivariana (UPB)	1981	Medellín
MedUNAB	Universidad Autónoma de Bucaramanga (UNAB)	1988	Bucaramanga
Perspectiva en Nutrición Humana	Universidad de Antioquia	1999	Medellín
Repertorio de Medicina y Cirugía	Sociedad de Cirugía de Bogotá - Hospital de San José - Fundación Universitaria de Ciencias de la Salud	2000	Bogotá
Revista CES Salud Pública	Universidad CES	2010	Medellín
Revista Ciencias Biomédicas	Universidad de Cartagena	2010	Cartagena
Revista Ciencias de la Salud	Colegio Mayor de Nuestra Señora del Rosario	2003	Bogotá
Revista Clon	Universidad de Pamplona	2002	Pamplona
Revista Colombiana de Cardiología	Sociedad Colombiana de Cardiología y Cirugía Cardiovascular	1989	Bogotá
Revista Colombiana de Enfermería	Universidad del Bosque	2006	Bogotá
Revista Colombiana de Rehabilitación	Escuela Colombiana de Rehabilitación (ECR)	2002	Bogotá
Revista Colombiana de Salud Libre	Universidad Libre de Colombia	2006	Cali
Revista CUIDARTE	Universidad de Santander (UDES)	2010	Bucaramanga
Revista de Gerencia y Políticas de Salud	Pontificia Universidad Javeriana	2001	Bogotá
Revista de la Asociación Colombiana de Gerontología y Geriatría	Asociación Colombiana de Gerontología y Geriatría	1977	Bogotá
Revista de la Facultad de Ciencias de la Salud	Universidad del Cauca	1999	Popayán
Revista de la Facultad de Medicina de la Universidad Nacional de Colombia	Universidad Nacional de Colombia	1932	Bogotá
Revista de Salud Pública	Universidad Nacional de Colombia	1999	Bogotá
Revista ECM Escuela Colombiana de Medicina	Universidad del Bosque	1983	Bogotá
Revista Facultad Nacional de Salud Pública	Universidad de Antioquia	1974	Medellín
Revista Med	Universidad Militar Nueva Granada	1991	Bogotá
Revista Médica de Risaralda	Universidad Tecnológica de Pereira	1995	Pereira
Revista Médica Sanitas	Fundación Universitaria Sanitas	1998	Bogotá
Revista Salud Bosque	Universidad del Bosque	2011	Bogotá
Revista UDCA. Actualidad y Divulgación Científica	Universidad de Ciencias Aplicadas y Ambientales (UDCA)	1998	Bogotá
Revista Vía Salud	Organización para la Excelencia de la Salud	1997	Bogotá
Revista Facultad de Salud-RFS de la Universidad Surcolombiana	Universidad Surcolombiana	2009	Neiva
Salud UIS	Universidad Industrial de Santander	1969	Bucaramanga
Salud Uninorte	Universidad del Norte	1984	Barranquilla
Umbral Científico	Universidad Manuela Beltrán	2002	Bogotá
Universidad y Salud	Universidad de Nariño	2000	Pasto
Universitas Médica	Pontificia Universidad Javeriana	1958	Bogotá
Vitae	Universidad de Antioquia	1991	Medellín

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Source: Own elaboration based on the data obtained in the study.

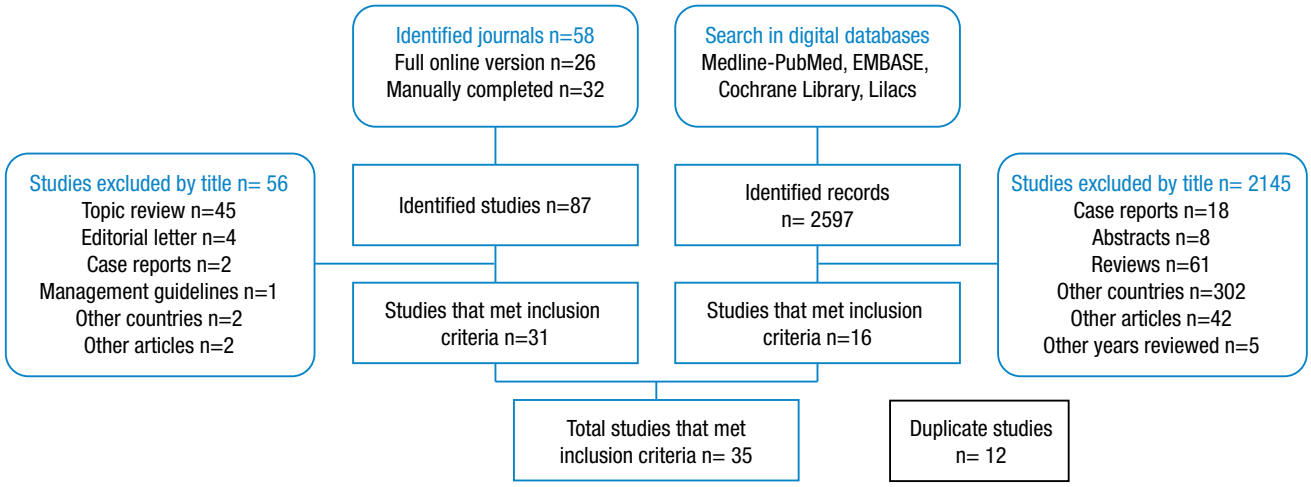

Figure 1. Flowchart of literature search and study selection.
Source: Own elaboration based on the data obtained in the study.

Digital search in databases: This search allowed to identify 2 597 records, of which 16 met the inclusion criteria. Of these, 12 had already been identified in the manual search (Figure 1). Annex 2 describes the digital search strategy. No additional articles were found after searching references and CvLac resumes.

Analysis of identified studies

Of 35 studies published (5,10-43), the largest number (25.7%) was found in the Revista Colombiana de Cardiología with 9, followed by Acta Médica Colombiana with 7 (20%) (Figure 2). The cities with the highest number of publications on heart failure were Bogotá and Medellín, with 15 studies each (42.8%) (Figure 3), and the largest number of publications (85.7%) was observed in 2009 (Figure 4).

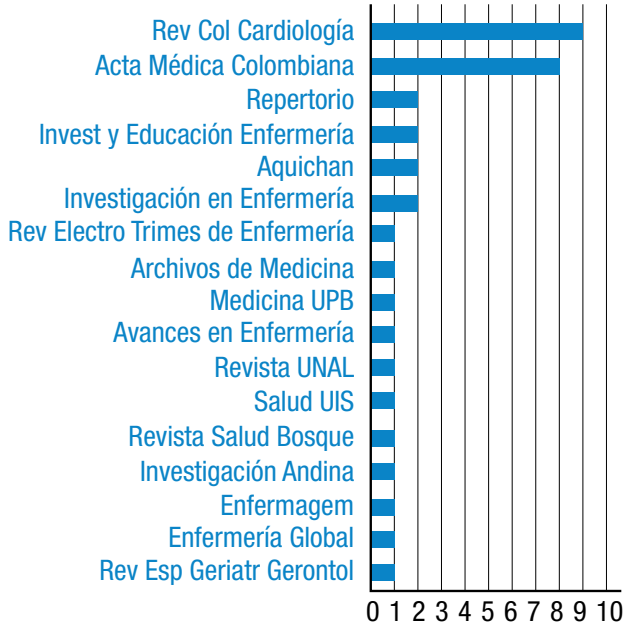

Figure 2. Number of articles per journal.
Source: Own elaboration based on the data obtained in the study.

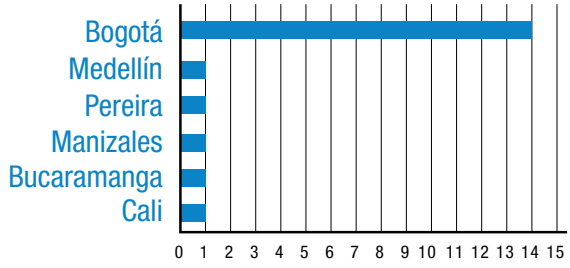

Figure 3. Number of articles per city.
Source: Own elaboration based on the data obtained in the study.

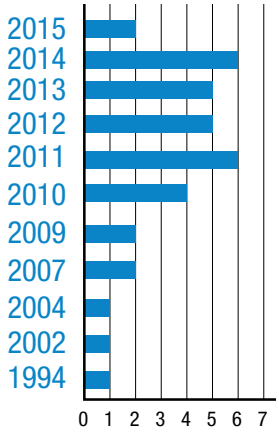

Figure 4. Number of articles per year of publication.
Source: Own elaboration based on the data obtained in the study.

Regarding methodological aspects, 19 (54.2%) studies were descriptive and 5 (14.2%) quasi-experimental. In 13 (37.1%), the sample size was <50, 11 (31.4%) had >200 patients and 9 (25.7%) described general populations (Tables 2-4). On the other hand, 9 studies (25.7%) addressed self-care, 3 (8.8%) evaluated prognostic factors and aspects of cardiac rehabilitation, while 2 evaluated issues related to disease perception, nutritional aspects and therapeutic interventions. No studies related to prevention or treatment for stages I to III, according to the classification of the New York Heart Association (NYHA), were found (Tables 2-4).

Table 2. Observational studies that described populations or established causal relationships with various endpoints in outpatient and inpatient settings.

General characteristics		Main results
Hospital context		
Plata & Angel (10). Prospective cohort n=50.	Patients: hospitalized for HF. Objective: To determine the frequency of malnutrition and to establish its correlation with morbidity and mortality.	Average age: 52.2 years, 56% men. Average weight: 59.3kg ± 13.8. BMI <25: 82%. 10% normal albumin; 52% moderate hypoalbuminemia and 8% severe hypoalbuminemia. Bicipital, triceps, thigh, arm circumference, and Hb fold were greater in survivors than in those who died. In-hospital mortality: 24
Ospina-Serrano & Gamarra-Hernandez (11). Descriptive n=218.	Patients: hospitalized for HF. Objective: To determine clinical and epidemiological characteristics of the patients and their evolution at one year.	Average age: 68 years, 51.6% men. NYHA III: 63%. Average EF: 25%. Comorbidity: AH 73.1%, DM2 21.6%. Causes of hospitalization: lack of adherence to treatment 50%, respiratory infection 15.1%. IH Mortality 16.9%: 31.5%at 3 months, 37.6% at 6 months and 45.2% at 1 year. 40.8% re-admission at 12 months. Factors associated with mortality: age (OR 2.0, 1.27-3.23) and FC (OR 2.6, 1.08-7.08).
Lancheros *et al.* (12). Descriptive, prospective n=129	Patients: decompensated HF. Objective: To describe the population and define factors that may be related to mortality.	Average age: 71.9 years, 56.7% women, AH 80.6%, CAD 19.3%. Previous treatment: 72.1% ACEI/ ARB, 56.5% furosemide, 25.5% BB, 21% spironolactone. Common factors among deceased: age >65 years, creatinine >1.3 mg/dL and HR >90 beats/ min. IH mortality: 4.6%.
Henao *et al.* (13). Prospective n=155	Patient: decompensated HF. Objective: To assess in-hospital death risk using the GWTG-HF scale and the OPTIMIZE HF nomogram	Average age: 72.5 years, 52.2% men. Baseline FC NYHA II 52.9%, EF <40%: 35.3%. Median HS: 8 days, IH mortality: 7.7%. 64.3% were at 1-5% risk according to the GWTG-HF scale and 50.7% according to the OPTIMIZE HF nomogram. No agreement was found between both scales (Lin=0.07).
Senior *et al.* (14). Prospective cohort n=106	Patients: Acute HF admitted to the emergency room. Objective: To describe the epidemiological characteristics of patients.	Average age: 62.4 years, 52.8% men. Hypertensive heart disease 45.2%, idiopathic 31.1%. 11.2% had ACS. Management: digoxin 2.4%, diuretics 73%, ACEI 73.5%, BB 32%, spironolactone 34.9%. FC prior to NYHA II: 26.4%, III: 57.5%. EF ≤40%, 67.2%. Average BNP 2 356pg/mL. Average HS: 11.4 days.
Ramírez *et al.* (15) Retrospective study n=215	Patients: hospitalized with HF. Objective: To determine the incidence of cardiorenal syndrome and to evaluate the clinical characteristics.	Average age: 66.9 years, 63.2% men. Average EF: 23.3%. NYHA III/IV FC: 59.5%. 58.6% had kidney failure and 35.8% had anemia. Prevalence of cardio-renal anemia: 23.3%. Management: diuretics (60.9%), BB (60%) and ACEI (52.6%).
Chaves *et al.* (16) Prospective descriptive n=47	Patients: decompensated chronic HF. Objective: To evaluate compliance with hospital discharge management guidelines.	Average age: 71 years, 55.3% women. NYHA FC II: 59%, III: 19.2%. 80.9% received BB, 76.1% ACEI or ARB and 38% spironolactone. Compliance with the guidelines was adequate in 52.6% for BB, 77.7% for ACEI or ARB and 78.5% for spironolactone. IH mortality: 10.6%
Chaves *et al.* (17) Prospective cohort n=462	Patients: decompensated HF. Objective: To determine the risk factors related to hospital mortality at 30 days.	Average age: 72.4 years, 51.9% women. AH: 80%, COPD: 43%. FC on admission NYHA III: 36.1%, IV: 58.2%. Median HS: 6 days, IH mortality: 8.9%, at 30 days: 13.8%. In the multivariate analysis, BUN >43 mg/dL (OR=3.45, 1.54-7.74) was associated with IH mortality and NT-ProBNP (OR=2.52, 1.25-5.08) and EH >5 days (OR=1.98, 1.04-3.75) at 30 days.
Saldarriaga *et al.* (18) Cross-sectional n=204	Patients: hospitalized with EF <40%. Objective: To evaluate differences in clinical, epidemiological and treatment characteristics according to sex.	36.7% women. Mean age in women (69 vs. 65.4), history of major kidney failure in women (66.7% vs. 51%), 12.7% used ICD. The drugs most used in both sexes were ACEI/ARB, diuretics and BB. In women, BB (54.7% vs. 62%) and ICD (9.3% vs. 14%) were used less frequently.
Ocampo-Chaparro *et al.* (19) Prospective cohort n=106	Patients: aged >75 years and hospitalized. Objective: To describe the clinical characteristics and 30-day survival in a tertiary care university hospital.	Average age: 82 years, FC III and IV: 61.3%. Etiology: AH: 44.3%, ischemic heart disease: 26.4%. Median HS: 10 days. IH mortality: 3.8%. Readmission within the last year: 24.5%. Cause of decompensation: arrhythmia (25%), ischemia and poor adherence (17% each), infection (13%). The use of standardized protocols and aggressive management since admission was related to good clinical outcomes.
Outpatient setting		
Marín *et al.* (20). Descriptive, prospective, n=34	Patients: HF and cardiac resynchronization device. Objective: To determine if BNP is a marker of therapeutic response and prognosis.	Average age: 63.8 years, 56% men. Ischemic heart disease: 50% and idiopathic heart disease: 20%. Management: diuretics (82%), ACEI or ARB (79%), BB (68%), spironolactone (65%). Pre-implant EF: 23.1% and post-implant: 31.9% (p<0.002). Average pre-implant BNP 987.78 pg/mL; at the end: 562.72 pg/mL (p<0.0001).
Castaño-Castrillón *et al.* (21). Cross-sectional n=370	Patients: HF in the first level of care. Objective: To know and analyze the behavior and management in the first level of care	Average age: 69.6 years, 55.4% men. COPD: 31.4%, AH: 21.1%. NYHA FC II: 40%, NYHA III: 27.6%. 27.8% was readmitted at one year, 33.2% had two re-admissions, 15.7% had no re-admissions; 88.7% received ACEI or ARB II, 16.8% BB, 93.2% furosemide and 50.5% spironolactone.
Rodríguez & Gómez (22). Descriptive, retrospective n=557	Patients: HF, with records of weight, age and creatinine. Objective: To estimate the prevalence of kidney failure	Average age: 62 years, 68.2% men. Average creatinine 1.33 mg/dL, creatinine clearance 63.2 mg/min; 82.8% had impaired renal function: creatinine clearance in 37.6% between 60-89 mL/min, in 51.8% between 30-59 mL/min, in 9.1% between 15-29 mL/ min and 1.5% <15 mL/min.
Torres-Navas *et al.* (23). Cross-sectional n=68	Patients: participants in a HF program that attended psychological and social evaluation. Objective: To determine psychosocial characteristics in the first 3 months of admission to the program and its correlation with FC, EF, NT-ProBNP.	Average age: 68.7 years, 60.3% men. Ischemic heart disease: 45.6%. NYHA III-IV FC: 44%. EFLV <40%: 59%. Average NT-ProBNP: 1 665. Patients with higher NYHA FC had a worse quality of life (p<0.001). The emotional state was abnormal in 11.9% and showed direct correlation with NT-ProBNP.
Gómez (24) Cross-sectional n=151	Patients: age >21 years, outpatient, with HF. Objective: To determine the ratio of patients with HF and EF >45% and to compare the clinical characteristics with EF <45%. Analysis for Colombia of the I-PREFER study.	67.5% had EF >45%. Women has a higher incidence (57.8% vs 40.8%, p=0.04) and higher BMI (26.8 kg/m² vs. 24.6 kg/m², p=0.002), HBP (129 mmHg vs. 117 mmHg, p <0.001) and diastolic (76 mmHg vs. 71 mmHg, p=0.014). Data were similar to the global population of I-PREFFER.

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General characteristics		Main results
Outpatient setting		
Arango-Franco *et al.* (25) Cross-sectional n= 70	Patients: Advanced HF with functional electrophysiological device. Objective: To describe patients with advanced HF and the use of electrophysiological devices.	67% men. NYHA FC II: 26%, III: 57.6% IV: 11%. EF >35: 20%, 15-35: 68%. Stage C: 94.2%, QRS width: 75.6%. Resynchronizer: 25.7%, ICD: 41.4%, resynchronizer+ICD: 32.9%. Comorbidities: AH: 91.4%, CAD: 60.9%, DM2: 31%, ventricular arrhythmia: 42.3%.
Triviño *et al.* (26) Cross-sectional n=40	Patients with stage C HF, NYHA FC II and III with EF >45%. Objective: To evaluate the relationship between BMI and cardiorespiratory parameters.	In subjects with BMI ≥25, a negative correlation was observed between the distance reached in the 6-minute walking test (rho=-0.50), the number of steps (rho=-0.45), VO_2max (rho=-0.49) and EF (rho=-0.32).
Senior *et al.* (27) Cross-sectional n=151	Patients: HF who attended a heart failure clinic. Objective: To establish the presence of musculoskeletal pathology in the studied population.	Average age: 68 years, 55.6% men. Etiology: CAD 27.8%, hypertension: 25.8%. NYHA FC I: 26.5%, II: 33.1%, III: 32.5%. Musculoskeletal pathology in 31.8%, the most frequent: osteoarthritis of the hip or knees (6.6%) and rotator cuff tendinitis (4.6%), myofascial and lumbar pain (3.3% each). There was no association between CF and musculoskeletal pathology.

HF: Heart Failure; IH: In-hospital; BMI: Body Mass Index; HBP: High blood preasure; Hb: Hemoglobin; NYHA: New York Heart Association; EF: ejection fraction; EFLV: Ejection fraction of the left ventricle; AH: Arterial Hypertension; DM2: Diabetes *mellitus* tipo 2; FC: Functional Classification; OR: Odds Ratio; CAD: Coronary artery disease; ACEI: Angiotensin converting enzyme inhibitors; ARB: Angiotensin II receptor blockers; BB: Beta blockers; HS: Hospital stay; HR: Heart rate; ACS: Acute coronary syndrome; BNP: Brain natriuretic peptide; BUN: Blood Urea Nitrogen; NT-ProBNP: N-terminal prohormone of brain natriuretic peptide; ICD: Implantable Cardioverter Defibrillator; COPD: Chronic obstructive pulmonary disease; VO_2max: maximum oxygen consumption; GWTH-HF: Get With The Guidelines-Heart Failure
Source: Own elaboration based on the data obtained in the study.

Table 3. Studies related to interventions or costs.

General characteristics		Main results
Núñez *et al.* (28) Prospective cohort n=27	Patients: HF NYHA III or IV. Objective: To determine whether left ventricular reconstruction surgery and annuloplasty or mitral valve replacement technique improve survival and FC at 6 and 12 months.	Average age: 60 years. The Dor technique decreased the ventricular dimensions by 20% and increased EF by 17.3-25%. Mitral preservation techniques did not produce changes in hemodynamic parameters. During follow-up, 92% had FC I, IH mortality was 3.4% and 3.5% at 8 months.
Achury-Saldaña (29). Quasi-experimental study n=50	Patients: Hospitalized for HF Objective: To determine the effect of an educational plan on self-care and adherence.	Average age: 68 years, 54% men, 66% FC II. Training the patient in the treatment, an adequate relationship with the nursing staff and the involvement of the family improved adherence according to the Likert scale from 73 to 89.4 (p=0.0001).
Atehortúa *et al.* (30). Quasi-experimental study n=22	Patients: compensated HF stage C, NYHA II-III, EF <45%. Objective: To evaluate the effect of a cardiac rehabilitation program on functional capacity, NT-proBNP, cardiac function and quality of life.	Average age: 59 years, 77.3% men. Average VO_2max improved from 26.4±6.4 to 34.5±77 mL.kg-1.min-1, (p<0.001). Distance in the 6-minute walk test increased from 438±67.9 meters to 513±83.4 (p<0.001). EF increased from 32.68±8.8% to 38.82±9.16% (p<0.001). Improvement was observed in quality of life in the domain "change in health over time" (p<0.05).
Quiroz *et al.* (31). Cohort study n=224	Patients: HF of ischemic origin. Objective: To establish the impact of cardiac rehabilitation on the modified Borg scale, VO_2, MET and distance in miles.	Average age: 64 years, 81.7% men. Pre-rehabilitation: 63% on Borg scales 1 and 2; post-rehabilitation: 85% on scales 3 and 4 (p<0.001). VO_2 improved from 7.79 to 19.04 (p<0.001), MET from 2.22 to 5.44 (p<0.001) and distance in miles from 1.33h to 2.58 (p<0.001).
Senior *et al.* (32). Case series n=21	Patients: >18 years with severe decompensated chronic HF, Stevenson B or C who received levosimendan. Objective: To evaluate the efficacy and safety of levosimendan in the population.	Average age: 48 years, 81% men. Non-ischemic heart disease: 81.2%. Average EF: 30%. NYHA FC IV: 62.5%, 25% required vasopressors. Levosimendan was well tolerated; no significant side effects were observed. 23.8% required re-admission at 2 months and mortality during this period was 28.6.%.
Arredondo-Holguín *et al.* (33) Quasi-experimental study n=29	Patients: >30 years with HF. Objective: To evaluate the improvement of self-care behaviors after an educational nursing intervention through the Artinian scale.	Average age 65 years, 52.2% women. 82.8% were NYHA FC between II and III. The median scale improved from 40 to 53 (p<0.05). The aspects with the greatest changes were: request for help, adaptation to the disease and adherence to pharmacological treatment. No favorable changes were observed regarding the reduction of salt intake and measurement of the amount of urine eliminated.
Rodríguez-Gázquez *et al.* (34) Diseño: Design: RCT without blinding n=63	Inclusion: >30 years with HF. Objective: To evaluate the effectiveness of an educational nursing program in the improvement of self-care behaviors.	Average age: 67.9 years, 31% men. 80% received family support. EF: intervention group 41.7% and control group 46%. 66% of the intervention group vs. 26.6% of the control group improved by at least 20% in the self-care score (p<0.001). NNT 2.5.
Camargo-Rojas *et al.* (35) Quasi-experimental study n=21	Patients: hospitalized with HF. Objective: To determine if motivational interview is effective to promote self-care in these patients.	Average age: 67 years, 57% men; 52% belonged to low socioeconomic stratum. An overall increase in self-care from medium to high was observed according to the European Heart Failure Self-Care Behaviour Scale in all categories (compliance with the therapeutic scheme, ability to adapt to the disease and seek help in case of exacerbation).
Tamayo *et al.* (5) Cost study n=158	Patients: hospitalized for HF and outpatient. Objective: To carry out an approximation to the determination of direct costs of HF in two hospitals.	Average age: 62 years, 63% men. Average monthly cost of outpatient management COP 304 318; 55.2% spent on medications. The average cost of hospitalization was COP 6 427 887. EH represented the highest proportion of the cost (29.1%).
Romero *et al.* (36) Markov model n=100	Patients: 45 years with HF and AH. Objective: To conduct a cost-effectiveness assessment of metoprolol succinate vs. tartrate vs. carvedilol in patients with HF and AH.	The cost of patients with metoprolol succinate was lower than that for metoprolol tartrate and carvedilol (COP 229 vs. 346 vs. 464 million, respectively). Fewer hospitalizations were observed with metoprolol succinate. Carvedilol had lower mortality.

HF: Heart Failure; NYHA: New York Heart Association; FC: Functional Classification; EF: Ejection fraction; NT-ProBNP: N-terminal prohormone of brain natriuretic peptide; VO_2: Volume of oxygen; MET: Metabolic equivalent of task; COP: Colombian pesos, HS: Hospital stay; RCT: Randomized clinical trial; NNT: Number needed to treat; AH: Arterial hypertension.
Source: Own elaboration based on the data obtained in the study.

Continues.

Table 4. Observational studies that assessed self-care or patient perception.

General characteristics		Main results
Arredondo-Holguín (37). Cross-sectional n=206	Patients: compensated HF NYHA I, II or III. Objective: To describe behaviors and capabilities in self-care agency.	Average age: 60 years, 65.5% male. NYHA FC I: 59.7%, II: 33%. Frequency of self-care: high 14%, average 79% and low 7%. 46.2% had a low self-care frequency in request for help and 43.7% in adaptation to living with the disease.
Uribe *et al.* (38). Case series n=19	Patients: hospitalized for HF. Objective: To perceive the experience lived by patients.	Average age: 67.8 years, 68% women. AH 78.9%, dyslipidemia 52.6%. The patients clearly understood being heart patients and, to a great extent, attributed the onset of the condition to social causes. They recognized healthy lifestyles, but not all of patients implemented them.
Zapata-Gómez (39). Case series n=13	Patients: HF. Objective: To understand how patients perceive, interpret and respond to clinical manifestations.	Death is perceived as a close fact, which is strengthened by the restrictions that the disease imposes on them. This situation leads to important changes in their way of living and relating to people and the environment.
Achury-Saldaña *et al.* (40) Psychometric study. n=192	Patients: HF >18 years. Objective: To determine the reliability and construct validity of the instrument "Evaluation of adherence behaviors to pharmacological and non-pharmacological treatment"	The internal consistency index (Cronbach's alpha) was 0.7213. In the factorial analysis, most of the items coincided with the construct for which it was designed.
Rodríguez & Arredondo (41) Case series n=206	Patients: Compensated HF, NYHA I-III. Objective: To determine the validity and reliability of Nancy Artinian's assessment scale of self-care behaviors.	Average age: 60.6 years, 65.5% men. NYHA FC I: 59.7%. Factorial validation: four domains (request for help, adaptation to living with the disease, adherence to pharmacological treatment and adherence to non-pharmacological treatment) explained 34.2% of the variance of the construct. Final scale reduced to 21 items. Cronbach's apha: 0.75.
Rodríguez-Gázquez *et al.* (42) Cross-sectional n=266	Patients: compensated HF NYHA I, II or III. Objective: To explore the association between self-care agency capacity and factors related to the agency.	Average age: 62.1 years, 62% women. NYHA FC I: 50%, II: 35.3%. Average EF: 31.1%. Self-care capacity was deficient in 47%. Sufficient self-care agency was related to EF, age and married patients.
Arredondo-Holguín *et al.* (43) Descriptive n= 31	Patients: HF. Objective: To describe the difficulties for self-care behaviors related to adherence to non-pharmacological treatment.	Average age: 63 years, 54% women. NYHA FC I: 16.1% II: 38.7% and III: 45.2%. EF <50%: 66.7%. AH (83.9%), CAD (35.5%). All patients had difficulties in self-care related to non-pharmacological treatment. The most frequent: measurement of urine (100%), controlling salt intake (96.7%) and fluid restriction (93.5%).

HF: Heart Failure; NYHA: New York Heart Association; FC: Functional Classification; AH: Arterial Hypertension; EF: Ejection fraction; CAD: Coronary artery disease.
Source: Own elaboration based on the data obtained in the study.

One of the most relevant results was related to in-hospital mortality, with a rate of 3.8-28.6% (10-13,16,17,19,32); one study reported a rate of 13.8% of mortality at one month of and 45.2% at one year. (12) Furthermore, three studies reported data on median hospital stay, which was between 6-10 days (13,17,19); other three studies reported hospital re-admissions rates of 24.5%, 40.8% and 84.3% at one year (13,21,19), and another reported 23.8% re-admission rates at two months. (32) Some studies evaluated specific comorbidities, documenting a high presence of abnormalities in nutritional parameters (10), cardio-renal anemia (15), kidney failure (22), affective disorders (23) and musculoskeletal pathologies. (27)

With reference to interventions, two studies showed the beneficial effects of cardiac rehabilitation plans on patients (30,31), while four others showed an improvement in adherence to management or self-care by patients when performing interventions or educational plans led by nursing. (29,33-35)

An important percentage of works were developed by nursing professionals; 9 (25.7%) corresponded to self-care behavior interventions and adherence to medical treatment for heart failure in quasi-experimental studies in patients.

Discussion

The main motivation to carry out this research was the need to identify domestic studies on heart failure within the framework of the discussions generated based on academic work developed by our institution around this issue. Initial observations of references of domestic guidelines, texts or review articles showed few citations of original studies; therefore, establishing the actual amount of this type of publications and the topics treated was considered important.

The results of this research show that, in fact, there are few studies published based on the observation period, although the number of publications has increased recently. Likewise, almost all designs were observational and only one was a randomized clinical trial. It is important to highlight the lack of the latter design, which offers important results from the point of view of "evidence-based medicine" when evaluating medical interventions.

In Colombia, several investigations have been carried out with the objective of evaluating scientific production in the health area. Jaramillo-Salazar *et al.* (44) evaluated clinical research in the country based on the scientific production recorded in the Thomson-ISI database between 1975 and 2005, while Alvis-Guzmán & De la Hoz (45) analyzed the publications in Medline and LILACS databases in the period between 1993 and 2003. In both studies, there is a significant and progressive increase in the number of publications after the 1990s.

In this study, an increasing number of publications in the last five years was observed. It is important to note that, in the aforementioned research, the number of publications in basic sciences increased more than in clinical areas and, among them, tropical medicine, neurosciences and infectious diseases were the most common. (45) Therefore, the reduced amount of publications on heart failure in the 1990s is related to a lowest amount of publications in the area of clinical medicine in general.

Most of the works were published in Bogotá and Medellín. This is consistent with other reports in health sciences in general, although cities such as Cali provide a significant number of publications in other areas of biomedical research. (45-47)

Among journals evaluated, the Revista Colombiana de Cardiología journal had the highest number of publications, followed by Acta Médica Colombiana, which is an expected result. However, a significant number of articles were found in journals edited by universities. At this point, it is worth noting that, several of these

journals are indexed in Latin American databases such as LILACS or Redalyc, and even some in international databases, but not all of them are, which makes it difficult to access their articles. This was one of the reasons why the digital search did not identify the total number of articles published, leaving manual search as the only option to identify them. This reinforces the importance of quality improvement processes in the journals, highlighted by various editors, to allow them to access international databases and achieve better scientific positioning. (48-51)

Research carried out by nursing professionals deserves special attention, since they contributed a good number of publications focused on self-care and some used qualitative methodology. This allowed obtaining valuable results that must be taken into account when comprehensively approaching the patient. The investigated issues are, in addition to the ones mentioned above, general description studies in inpatient and outpatient populations with heart failure, including studies on prevalence of specific comorbidities such as malnutrition and kidney failure. Although they are few, they offer relevant data on intra-hospital mortality, prevalence of comorbidities and treatment of this disease.

When reviewing Latin American literature, reviews on heart failure that cite studies that address epidemiological, diagnostic and therapeutic aspects were found, especially in Brazil, Chile, Argentina and Mexico. (52-54) Argentina and Chile have national records (55,56) important to evaluate the behavior of the disease in the "real world". (57) Currently, Colombia does not have information on published records of heart failure. With some frequency, the country's institutions have been part of international studies that have evaluated multiple cardiovascular issues (58-62); however, specific data on the Colombian population are not always widely disseminated since there are no specific publications, which would represent a valuable contribution to the knowledge of our patients. The I PREFER record is one of the cases with this kind of publications. (33,63)

It has been established that research should fulfill two important functions. On the one hand, it should make an academic impact, which implies that research should be made public and discussed by the academic community involved and that it should be published in scientific journals, a fundamental part of the process. (64) The objective is to transcend the context of undergraduate and postgraduate programs and conference summaries. In the same way, once published, it should be identified and read by the actors of the community in question. Improving the visibility of published articles and generating an academic discussion around them is a challenge for all people involved in research and teaching processes in health. In this regard, citing more frequently and using domestic investigations as part of discussions of research articles is one of the tasks that should be given more attention. (48)

On the other hand, research should fulfill a social function that occurs when scientific knowledge achieves a benefit for society in general. Therefore, domestic scientific production should be considered when creating social impact policies in a given area. (6,65) In this regard, several studies have been conducted that raise the importance of using the results of research in decision making.

Mosquera *et al.* (66) established that the results of domestic studies did not guide public health decision-making in a departmental health ministry of Colombia and stated that one of the main barriers is the lack of policies and structure for the management of the investigative process. On the other hand, Gómez *et al.* (67) concluded that the potential influence of research on policy decisions depends on multiple factors, some of which may be "governable" by researchers, and stressed the importance of promoting greater contact with decision makers.

The Colombian population has different biological and social realities with respect to cardiovascular risk (68,69), as shown by studies carried out in Latin America; in consequence, it is essential to generate domestic knowledge. While it is true that participation in international research networks is important for strengthening the different scientific groups of the country, strengthening our own work agenda is no less important to enlighten and help provide solutions to our problems. (70,71)

From the academy, validation and local legitimization mechanisms of knowledge application processes that serve to consolidate the scientific tradition of the nation should be sought, without giving so much priority to the "centers of knowledge" that are often seen as models for local scientific activities. (72,73) The idea that "the interpretation of our reality with alien schemes only contributes to making us increasingly unknown, increasingly less free and increasingly lonely" remains valid. (74)

One of the limitations of this review is that it included articles published since 1980, which did not allow identifying articles published prior to this date. However, few Colombian journals began publishing earlier. The review was limited to published studies and did not include results of abstracts or thesis, considered as products of research processes. Abstracts were excluded taking into account that many times they do not provide the data necessary to carry out a complete analysis of the research, while theses were discarded mainly because a systematic way for searching was not identified and, at the moment of carrying out the research, not all universities had a standardized form of thesis file. This undoubtedly generates a potential publication bias, inherent to the research itself. The main strength of this study was that a manual review was carried out which allowed to identify articles that were not found with a digital search.

Conclusion

The amount of original investigations published on heart failure is scarce; most of them were conducted recently, almost all in domestic journals. Descriptive design was the most common form, and the most frequently addressed subjects were self-care and population descriptions.

Conflicts of interests

None stated by the authors.

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References

1. Colombia. Ministerio de Salud y Protección Social. Plan Decenal de Salud Pública 2012-2021. Bogotá D.C.: MinSaliud; 2013 [cited 2014 Jul 12]. Available from: https://goo.gl/BwHFRK.
2. Colombia. Ministerio de la Protección Social. Universidad de Antioquia. Facultad Nacional de Salud Pública. Análisis de la situación de salud en Colombia 2002-2007. Tomo III: Morbilidad y mortalidad de la poblacion colombiana. Bogotá D.C.; Ministerio de Protección social. 2010 [cited 2014 Jul 12]. Available from: https://goo.gl/QRXYa3.
3. **Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, *et al.*** Heart Disease and Stroke Statistics-2017 Update: A report From the American Heart Association. *Circulation.* 2017;135(10):e146-e603. http://doi.org/cck5.
4. **Feitell S, Hankins SR, Eisen HJ.** Adjunctive Therapy and Management of the Transition of Care in Patients with Heart Failure. *Cardiol. Clin*. 2014;32(1):163-74. http://doi.org/chkn.
5. **Tamayo DC, Rodríguez VA, Rojas MX, Rincón M, Franco C, Ibarra MT, *et al.*** Costos ambulatorios y hospitalarios de la falla cardiaca en dos hospitales de Bogotá. *Acta Med. Colomb*. 2013;38(4):208-12.
6. **Ramírez-Martínez DC, Martínez-Ruiz LC, Castellanos-Domínguez OF.** La comunicación científica. In: Divulgación y difusión del conocimiento científico: las revistas científicas. Bogotá D.C: Grupo de Investigación y Desarrollo en Festión, Productividad y Competitividad (BoiGestión),;2012. p. 25-48.
7. **Gómez E, Atehortúa L, editors.** Guías colombianas de cardiologia. Tratamiento de la falla cardíaca aguda. *Rev. Colomb. Cardiol.* 2011;18(Suppl 2):165-99.
8. Sociedad Colombiana de Cardiología y Cirugía Cardiovascular. Consenso colombiano para el diagnóstico y tratamiento de la Insuficiencia cardíaca crónica. Bogotá D.C.; 2014.
9. Sistema Nacional de Indexación Y Homologación de Revistas Especializadas de CT-I. Publindex. Bogotá D.C.*:* Colciencias; 2014. [cited 2014 apr 11]. Available from: https://goo.gl/TJpp9T.
10. **Plata LG, Angel LA.** Prevalencia de la desnutrición en pacientes con insuficiencia cardíaca congestiva y su influencia en la mortalidad. *Rev. Fac. Med.* 1994;42(4):197-202.
11. **Ospina-Serrano AV, Gamarra-Hernandez G.** Características clínicas y epidemiológicas de la insuficiencia cardiaca en el Hospital Universitario Ramón González Valencia de Bucaramanga, Colombia. *Salud UIS.* 2004;36:125-31.
12. **Lancheros A, Valencia Y, Chaves SW.** Insuficiencia cardiaca aguda: factores asociados con mortalidad. *Repert. med. cir.* 2009;18(3):166-74.
13. **Henao C, Benavides-Bermúdez JM, Chaves W, Diaztagle JJ, Sprockel J, Hernández JI.** Falla cardiaca descompensada: estratificación del riesgo de mortalidad intrahospitalaria Hospital de San José de Bogotá D.C. *Repert. med. cir.* 2011;20(4):251-58.
14. **Senior JM, Saldarriaga C, Rendón J.** Descripción clínico-epidemiológica de los pacientes con falla cardiaca aguda que consultan al servicio de urgencias. *Acta Med. Colomb*. 2011;36(3):125-29.
15. **Ramírez JD, Saldarriaga CI, Cardona MC, Aristizábal F, Bahamón CM, Ocampo M, *et al.*** Síndrome de anemia cardiorrenal. Estudio de casos y controles anidado en una cohorte. *Acta Med. Colomb.* 2013;38(1):7-11.
16. **Chaves WG, Diaztagle JJ, Vargas V, Mejía MG, Sprockel JJ, Hernández JI.** Cumplimiento de guías en pacientes hospitalizados con falla cardiaca ¿Cómo estamos? *Acta Med. Colomb*. 2014;39(1):40-5.
17. **Chaves WG, Diaztagle JJ, Sprockel JJ, Hernández JI, Benavidez JM, Henao DC, *et al.*** Factores asociados a mortalidad en pacientes con falla cardiaca descompensada. *Acta Med. Colomb*. 2014;39(4):314-20.
18. **Saldarriaga C, Gonzáles N, Ávila A.** Diferencias de género en el tratamiento de la falla cardíaca. *Rev. Col. Cardiol.* 2014;21(1):27-32. http://doi.org/f2tc75.
19. **Ocampo-Chaparro JM, Badiel M, Casanova ME, Reyes-Ortiz CA, León-Giraldo H, Castaño-Cifuentes O.** Características clínicas y supervivencia a 30 días de pacientes ancianos colombianos hospitalizados por insuficiencia cardíaca descompensada. *Rev. Esp. Geriatr. Gerontol.* 2015;50(3):153-5. http://doi.org/f2572p.
20. **Marín JE, Duque M, Medina LE, Uribe W, Echavarría E, Marín GJ, *et al.*** Utilidad del péptido natriurético cerebral en la evaluación de pacientes con falla cardiaca tratados con resincronización cardiaca y su correlación con la evolución clínica. *Rev. Col. Cardiol.* 2007;14:133-49.
21. **Castaño-Castrillón J, Giraldo JF, Herrera HD, Jaramillo-Jimenez J, Noreña-Villada JM, Restrepo M.** Caracterización de pacientes con insuficiencia cardiaca en el primer nivel de atención de la ciudad de Manizales (Colombia) 2005-2008. *Arch. Med*. 2010;10(2):127-38.
22. **Rodríguez D, Gómez E.** Prevalencia de insuficiencia renal en pacientes que asisten a la clínica de falla cardiaca. *Rev. Col. Cardiol.* 2011;18:144-53. http://doi.org/f2tdgf.
23. **Torres-Navas A, Sierra-Camargo A, Mora-Chaparro B, Durán-Flórez E, Ibáñez-Palacios M.** Influencia de los factores psicosociales sobre el estado clínico de pacientes con insuficiencia cardíaca crónica manejados en una unidad multidisciplinaria. *Revista Salud Bosque.* 2011;1(1):9-16.
24. **Gómez EA.** Identificación de pacientes con falla cardiaca y función sistólica preservada: Un estudio epidemiológico regional (I-PREFER Study) – Colombia. *Rev. Colomb. Cardiol.* 2013;2:58-67. http://doi.org/f2tc8d.
25. **Arango-Franco R, Martínez JW, Cárdenas-Cárdenas JM, Rivera-Toquica AA, Marín-Medina DS, Orozco-Hernández JP, *et al.*** Falla cardíaca avanzada en pacientes tratados con dispositivos electrofisiológicos en una unidad de electrofisología, Pereira (Colombia). *Rev. Investigaciones Andina.* 2014;28(16):978-88.
26. **Triviño L, Ávila JC, Ramírez-Vélez R.** La paradoja de la obesidad y su relación con la aptitud cardiorrespiratoria en pacientes con insuficiencia cardiaca. *Rev. Col. Cardiol.* 2015;22(5):218-23. http://doi.org/f3g7nm.
27. **Senior JM, Plata JA, Navas CM.** Prevalencia de patología musculoesquelética asociada al síndrome de falla cardiaca. *Acta Med. Colomb.* 2014;39(3):233-7.
28. **Núñez F, Sandoval N, Caicedo V, Velasquez O, Orjuela H, Santos H, *et al.*** Nuevas alternativas quirúrgicas al trasplante cardiaco para pacientes en estado terminal con insuficiencia cardiaca. *Rev. Col. Cardiol.* 2002;10(1):32-46.
29. **Achury-Saldaña DM.** Autocuidado y adherencia en pacientes con falla cardiaca. *Aquichan.* 2007;7(2):139-60.
30. **Atehortúa DS, Gallo JA, Rico M, Durango L.** Efecto de un programa de rehabilitación cardiaca basado en ejercicio sobre la capacidad física, la función cardiaca y la calidad de vida, en pacientes con falla cardiaca. *Rev. Col. Cardiol.* 2011;18(1):25-36. http://doi.org/f2tdcc.
31. **Quiroz CA, Sarmiento J, Jaramillo C, Sanabria A.** Impacto de la rehabilitación cardiaca en pacientes con falla cardiaca de origen isquémico. *Rev. Col. Cardiol.* 2011;18(1):10-24. http://doi.org/f2tdcf.
32. **Senior JM, Saldarriaga CI, Aristizábal JM, Rendón JA.** Seguridad y eficacia de la utilización de levosimendán sin dosis de carga en una unidad de falla cardiaca especializada. *Acta Med. Colomb.* 2011;36(2):68-72.
33. **Arredondo-Holguín E, Rodríguez-Gázquez MA, Higuita-Urrego L.** Mejoramiento en los comportamientos de autocuidado después de una intervención educativa de enfermería con pacientes con falla cardíaca. *Invest. Educ. Enferm.* 2012;30(2):188-97.
34. **Rodríguez-Gázquez Mde L, Arredondo-Holguín E, Herrera-Cortés R.** Efectividad de un programa educativo en enfermería en el autocuidado de los pacientes con insuficiencia cardíaca. Ensayo clínico controlado. *Rev. Latino Am. Enfermagem.* 2012;20(2):1-11. http://doi.org/chkr.

35. **Camargo-Rojas C, Córdoba-Rojas DN, Guío-Reyes AM.** La entrevista motivacional como intervención de enfermería para promover el autocuidado en pacientes con insuficiencia cardíaca en una institución de cuarto nivel en Bogotá, Colombia. *Investig. Enferm. Imagen Desarr.* 2013;15(1):31-49.

36. **Romero M, Arango C.** Análisis de costo efectividad del uso de metoprolol succinato en el tratamiento de la hipertensión arterial y la falla cardíaca en Colombia. *Rev. Col. Cardiol.* 2012;19(4):160-8. http://doi.org/f2tdcw.

37. **Arredondo-Holguín E.** Comportamientos y capacidad de agencia de autocuidado de adultos con insuficiencia cardiaca. *Av. enferm.* 2010;28(1):21-30.

38. **Uribe M, Muñoz C, Restrepo J, Zapata A.** Percepción del paciente hospitalizado por falla cardiaca. Institución de salud 2009. *MEDICINA UPB.* 2010;29(2):124-34.

39. **Zapata-Gómez NE.** La experiencia de sufrir una insuficiencia cardiaca crónica: Un padecimiento que acerca a la muerte. *Invest. Educ. Enferm.* 2011;29(3):419-26.

40. **Achury-Saldaña DM, Sepúlveda-Carrillo GJ, Rodríguez-Colmenares SM, Giraldo IC.** Validez y confiabilidad de un instrumento evaluativo de adherencia en pacientes con falla cardíaca. *Enferm. Glob*. 2012;11(26):1-9. http://doi.org/chkv.

41. **Rodríguez-Gázquez M, Arredondo-Holguín E.** Validez y confiabilidad de una escala de valoración de comportamientos de autocuidado en personas con falla cardiaca. *Aquichan.* 2012;12(1):22-31.

42. **Rodríguez-Gázquez Mde L, Arredondo-Holguín E, Salamanca-Azevedo YA.** Capacidad de agencia de autocuidado y factores relacionados con la agencia en personas con falla cardíaca de la ciudad de Medellín (Colombia). *Enferm. Global*. 2013;12(2):183-95. http://doi.org/chkx.

43. **Arredondo-Holguín E, Rodríguez-Gázquez Mde L, Higuita-Urrego LM.** Dificultades con la adherencia al tratamiento no farmacológico de pacientes con falla cardiaca detectados a través de seguimiento telefónico. *Investig. Enferm. Imagen Desarr.* 2014;16(2):133-147. http://doi.org/chkz.

44. **Jaramillo-Salazar H, Latorre-Santos C, Albán-Conto C, Lopera-Oquendo C.** Caracterización de la investigación clínica en Colombia a partir de la producción científica de salud: base de datos Thomson-ISI 1975-2005. In: El hospital como organización de conocimiento y espacio de investigación y formación. Bogotá D.C.: Editorial Universidad del Rosario;. 2008. p.37-50.

45. **Alvis-Guzmán N, De La Hoz-Restrepo F.** Producción Científica en Ciencias de la Salud en Colombia, 1993-2003. *Rev. Salud Pública.* 2006;8(1):25-37.

46. **Rodríguez-Morales AJ, Rendón MA.** Situación de la investigación y publicación científica en Colombia y en el departamento de Risaralda: Revisión de indicadores en el contexto de la creación de la Oficina de Investigación Científica de COODESURIS. *Revista Médica de Risaralda.* 2012;18(1):72-82.

47. **Rosselli-Cock DA.** La investigación biomédica en Colombia: Un análisis de Medline. *Colombia Med.* 1998;29(3):108-111.

48. **Matijasevic E.** Acta Médica Colombiana y las fuerzas de producción social. *Acta Med. Colomb.* 2010;35(3):107-112.

49. **Alfonso F, Almonte K, Arai K, Bacal F, Drago-Silva JM, Galeano-Figueredo J, *et al.*** Revistas cardiovasculares iberoamericanas. Propuestas para una colaboración necesaria. *Rev. Esp. Cardiol.* 2009;62(9):1060-7. http://doi.org/b5z6t7.

50. **Rojas M, León-Galindo J, Echeverri D.** Las bases de datos: un instrumento fundamental. *Rev Col. Cardiol.* 2012;19(3):105-8. http://doi.org/f2tdbs.

51. **Caballero-Uribe CV, Alonso-Palacio LM.** Salud Uninorte inicia la era del Open Journal System (OJS). *Salud Uninorte.* 2010;26(1):i-iv.

52. **Hernández-Leiva E.** Epidemiology of acute coronary syndrome and heart failure in Latin America. *Rev. Esp. Cardiol*. 2011;64(Suppl 2):34-43. doi: http://doi.org/ddfdnv.

53. **Bocchi EA, Arias A, Verdejo H, Diez M, Gómez E, Castro P.** The Reality of Heart Failure in Latin America. *J. Am. Coll. Cardiol.* 2013;62(11):949-58. http://doi.org/f2fnwf.

54. **Cubillos-Garzón LA, Casas JP, Morillo CA, Bautista LE.** Congestive heart failure in Latin America: the next epidemic. *Am. Heart J.* 2004;147(3):412-7. http://doi.org/fpsvrs.

55. **Castro P, Verdejo H, Vukasovic JL, Garcés E, González.** Predictores de mortalidad intrahospitalaria y hospitalización prolongada en la insuficiencia cardíaca: resultados preliminares del registro nacional de insuficiencia cardíaca. Grupo ICARO. *Rev. Med. Chile.* 2006;134(9):1083-91. http://doi.org/bxdhpj.

56. **Fairman E, Thierer J, Rodríguez L, Blanco P, Guetta J, Fernández S, *et al.*** Registro Nacional de Internación por Insuficiencia Cardíaca 2007. *Rev. Argent. Cardiol.* 2009;77(1):33-9.

57. **Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, *et al.*** The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. *J. Am. Coll. Cardiol.* 2014;63(12):1123-33. http://doi.org/f2q42v.

58. **Schargrodsky H, Hernández-Hernández R, Champagne B, Silva H, Vinueza R, Silva-Ayçaguer LC, *et al.*** CARMELA: Assessment of Cardiovascular Risk in Seven Latin American Cities. *Am. J. Med.* 2008;121(1):58-65. http://doi.org/db4rmz.

59. **Miranda JJ, Herrera VM, Chirinos JA, Gómez LF, Perel P, Pichardo R, *et al.*** Major cardiovascular risk factors in Latin America: a comparison with the United States. The Latin American Consortium of Studies in Obesity (LASO). *PLoS One.* 2013;8(1):e54056. http://doi.org/f432cg.

60. **Yusuf S, Rangarajan S, Teo K, Islam S, Li W, Liu L, *et al.*** Cardiovascular Risk and Events in 17 Low-,Middle-, and High-Income Countries. *N. Engl. J. Med.* 2014;371(9):818-27. http://doi.org/xcq.

61. **Lanas F, Avezum A, Bautista LE, Diaz R, Luna M, Islam S, *et al.*** Risk Factors for Acute Myocardial Infarction in Latin America: The INTERHEART Latin American Study. *Circulation.* 2007;115(9):1067-74. http://doi.org/ctkjzt.

62. **Isaza D, Valenzuela D, Plata E.** ACCES: Encuesta de estrategia de manejo en síndrome coronario agudo (SCA). Resultados de los 12 meses de seguimiento en la población de Colombia comparada con Latinoamérica. *Rev. Col. Cardiol.* 2012;19(Suppl 1):35.

63. **Magaña-Serrano JA, Almahmeed W, Gomez E, Al-Shamiri M, Adgar D, Sosner P, *et al.*** Prevalence of heart failure with preserved ejection fraction in Latin American, Middle Eastern, and North African Regions in the I PREFER study (Identification of Patients With Heart Failure and PREserved Systolic Function: an epidemiological regional study). *Am. J. Cardiol.* 2011;108(9):1289-96. http://doi.org/cdhfv8.

64. **Martínez-López E.** Publicar, ¿para qué? *Rev. Fac. Nac. Salud Pública.* 2005;23(1):1.

65. **Rodriguez-Gázquez M.** La transferencia de los resultados de investigación y la generación de bienestar social. *MEDICINA UPB*. 2010;29(2): 85-6.

66. **Mosquera J, Gómez OL, Méndez F.** Uso de los resultados de las investigaciones en salud pública en una entidad territorial de salud en Colombia. *Colomb. Med.* 2005;36(1):16-22.

67. **Gómez RD, Orozco DA, Rodríguez FL, Velásquez W.** Políticas públicas y salud: relación entre investigación y decisión. *Rev. Fac. Nac. Salud Pública.* 2006;24(2):105-118.

68. **López-Jaramillo P.** La epidemia de las enfermedades cardiometabólicas en Latinoamérica: características diferentes que requieren acciones particulares. *Rev. Col. Cardiol.* 2008;15(4):153-60.

69. **López-Jaramillo P, López-López J.** Lecciones aprendidas de dos grandes estudios epidemiológicos de enfermedades cardio-cerebrovasculares en las que ha participado Colombia. *Rev. Col. Cardiol.* 2010;17(5):195-200. http://doi.org/f2tdfv.

70. **Martínez-Herrera E.** La gestión del conocimiento en políticas públicas en salud y participación social. *CES Medicina.* 2007;21(1):101-8.

71. **Martínez E, Franco DF, Villa L.** Las redes de conocimiento en salud pública y el fortalecimiento de capacidades a través de estrategias de cooperación. *Rev. Fac. Nac. Salud Pública.* 2009;27(3):349-55.

72. **Chambers DW.** Locality and Science: Myths of Centre and Periphery. In: Lafuente A, Elena A, and Ortega M, editors. Mundialización de la ciencia y la cultura nacional. Madrid: Doce Calles, 1993. p. 605-617.

73. **Restrepo-Forero OM.** "La mundialización del Darwinismo como proceso y como texto". *Acta biol. Colomb.* 2009;14(4S):41-62.

74. **García-Márquez G.** Nobel Lecture: La soledad de América Latina. Nobelprize.org. 2004. [cited 2017 Dec 18]. Available from: https://goo.gl/scjRRk.

Annex 1

Table A1. Journals of the national bibliographic index-IBN Publindex I 2013 update included for review.

	ISSN number	Name of the journal
Area of knowledge: clinical medicine		
1	0121-0793	IATREIA
2	1657-9534	Colombia Médica
3	2145-1362	RFS. Revista Facultad de Salud Universidad Surcolombiana
4	0123-7047	MedUNAB
5	0041-9095	Universitas Médica
6	0121-0807	Revista de la Universidad Industrial de Santander. Salud
7	0121-0319	MÉDICAS UIS
8	0124-308X	Revista de la Facultad Ciencias de la Salud
9	0122-0667	Revista Médica de Risaralda
10	0123-4250	Revista Médica Sanitas
11	0120-5498	Medicina
12	1692-6323	Revista CLON
13	0123-5583	Actualizaciones en Enfermería
14	0120-5633	Revista Colombiana de Cardiología
15	1692-7273	Revista Ciencias de la Salud
16	0121-7372	Repertorio de Medicina y Cirugía
17	0120-5552	Salud Uninorte
18	0121-0076	Revista ECM Escuela Colombiana de Medicina Órgano Oficial de la Facultad de Medicina, Universidad El Bosque
19	0124-1699	Investigaciones en Seguridad Social y Salud
20	0121-5256	Revista MED
21	0120-8705	CES Medicina
22	1657-9550	BIOSALUD: Revista de Ciencias Básicas
23	1692-0880	Medicina
24	0122-6916	Revista de la Asociación Colombiana de Gerontología y Geriatría
25	2215-7840	Revista Ciencias Biomédicas
26	1900-7841	Revista Colombiana Salud Libre
27	2248-5759	Revista Salud Bosque
28	0123-2576	Medicina & Laboratorio
29	1794-9831	Ciencia y Cuidado
30	1794-5240	Médicas UIS
31	0121-4500	Avances en Enfermería
32	1657-5997	Aquichan
33	1794-5232	Cultura del Cuidado Enfermería
34	1794-5992	Duazary
35	121-7577	Hacia la Promoción de la Salud
36	0124-8146	Investigaciones Andina
37	0124-2059	Investigación en Enfermería: Imagen y Desarrollo
38	0120-5307	Investigación y Educación en Enfermería
39	2145-5244	Manos al Cuidado
40	0124-4108	Perspectivas en Nutrición Humana
41	1909-1621	Revista Colombiana de Enfermería
42	1692-1879	Revista Colombiana de Rehabilitación
43	0124-0064	Revista de Salud Pública
44	0120-386X	Revista Facultad Nacional de Salud Pública
45	1657-7027	Revista Gerencia y Políticas de Salud
46	0123-1782	Revista Vía Salud
47	2145-9932	Revista CES Salud Pública
48	2216-0973	Revista Cuidarte
49	2011-7531	Salud Uninorte
50	0124-7107	Universidad y Salud
Area of knowledge: other medical sciences		
51	0120-2448	Acta Médica Colombiana
52	1692-3375	Umbral Científico
53	0120-0011	Revista de la Facultad de Medicina de la Universidad Nacional de Colombia
54	0120-4157	Biomédica
55	0121-2044	Revista de la Asociación Colombiana de Fisioterapia
56	0121-0041	Revista Colombiana de Medicina Física y Rehabilitación
57	0120-4874	Medicina UPB.
Area of knowledge: basic medicine		
58	0121-4004	Vitae

Continues.

Source: Own elaboration based on the data obtained in the study.

Table A2. Journals identified when searching for medical faculties not included in the Publindex list.

	ISSN number	Name of the journal
1	1657-320X	Archivos de Medicina
2	0123-4226	Revista UDCA Actualidad y Divulgación Científica
3	2145-5333	Ciencia y Salud Virtual

Source: Own elaboration based on the data obtained in the study.

Table A3. Excluded journals.

	ISSN number	Name of the journal
1	0121-8123	Revista Colombiana de Reumatología
2	0121-246X	Revista Facultad de Odontología Universidad de Antioquia
3	0120-3347	Revista Colombiana de Anestesiología
4	0124-3691	Revista Gastrohnup
5	0124-1265	Neuropsicología, Neuropsiquiatría y Neurociencias
6	2011-7582	Revista Colombiana de Cirugía
7	0034-7450	Revista Colombiana de Psiquiatría
8	1900-3080	Revista Nacional de Odontología
9	1657-0448	Revista de la Asociación Colombiana de Dermatología y Cirugía Dermatológica
10	0120-9957	Revista Colombiana de Gastroenterología
11	0120-8748	Acta Neurológica Colombiana
12	0123-9015	Revista Colombiana de Cancerología
13	0120-4319	Universitas Odontológica
14	0120-971X	CES Odontología
15	0123-7810	Revista Odontos Odontología Integral
16	0121-5426	Revista Colombiana de Neumología
17	1692-8415	Ciencia & Tecnología para la Salud Visual y Ocular
18	0120-8845	Revista Colombiana de Ortopedia y Traumatología
19	1692-5106	UstaSalud
20	0122-3429	Revista Colombiana de Menopausia
21	0123-4048	Neurociencias en Colombia
22	0120-789X	Revista Urología Colombiana
23	2145-7735	Revista Colombiana de Investigación en Odontología
24	0121-3873	Revista Estomatología y Salud
25	0120-3444	Universitas Odontológica
26	2145-5333	Ciencia y Salud Virtual
27	0121-2095	Revista Colombiana de Radiología
28	0120-0453	Revista Sociedad Colombiana de Oftalmología
29	2216-0280	Investigación y Educación en Enfermería
30	0034-7434	Revista Colombiana de Obstetricia y Ginecología
31	0120-0445	Revista de la Sociedad Colombiana de Psicoanálisis
32	1900-5121	Típica: Boletín Electrónico de Salud Escolar
33	1794-4732	UstaSalud Optometría
34	1692-7427	Revista Actividad Física y Desarrollo Humano
35	0124-5546	Revista Antioqueña de Medicina Deportiva y Ciencias Aplicadas al Deporte y a la Actividad Física
36	0123-9392	Infectio
37	1794-4333	Palestra
38	1657-2513	Revista Areté
39	0120-8411	Acta de Otorrinolaringología & Cirugía de Cabeza y Cuello
40	0120-2729	Revista Colombiana de Cirugía Plástica y Reconstructiva
41	0034-7418	Revista Colombiana de Ciencias Químico Farmacéuticas

Source: Own elaboration based on the data obtained in the study.

Annex 2.

Table A4. Search strategy - heart failure 1980-2015.

Database	Date	Results	Results after excluding duplicates
Medline–Pubmed	19/07/2016	583	406
Embase-Elsevier	19/07/2016	1 069	1 061
Cochrane Library	19/07/2016	492	492
LILACS	19/07/2016	453	452
Total		2 597	2 411

Source: Own elaboration based on the data obtained in the study.

MEDLINE - PUBMED

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COCHRANE LIBRARY

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#5 Heart Failure, Systolic 3808
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#8 Decompensated heart failure 587
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#10 Congestive heart failure 4897
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#16 Developing countries 5086
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#18 #11 and #17 751
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(tw:(falla cardiaca)) OR (tw:(falla cardiaca aguda)) OR (tw:(falla cardiaca crónica)) OR (tw:(falla cardiaca descompensada)) OR (tw:(falla cardiaca diastólica)) OR (tw:(falla cardiaca sistólica)) OR (tw:(insuficiencia cardiaca)) OR (tw:(insuficiencia cardiaca aguda)) OR (tw:(insuficiencia cardiaca congestiva)) OR (tw:(insuficiencia cardiaca crónica)) OR (tw:(insuficiencia cardiaca diastólica)) OR (tw:(insuficiencia cardiaca sistólica)) AND (tw:(Colombia)) OR (tw:(colombiana)) OR (tw:(colombiano)) OR (tw:(america latina)) OR (tw:(latinoamerica))

Combinado con los siguientes años:

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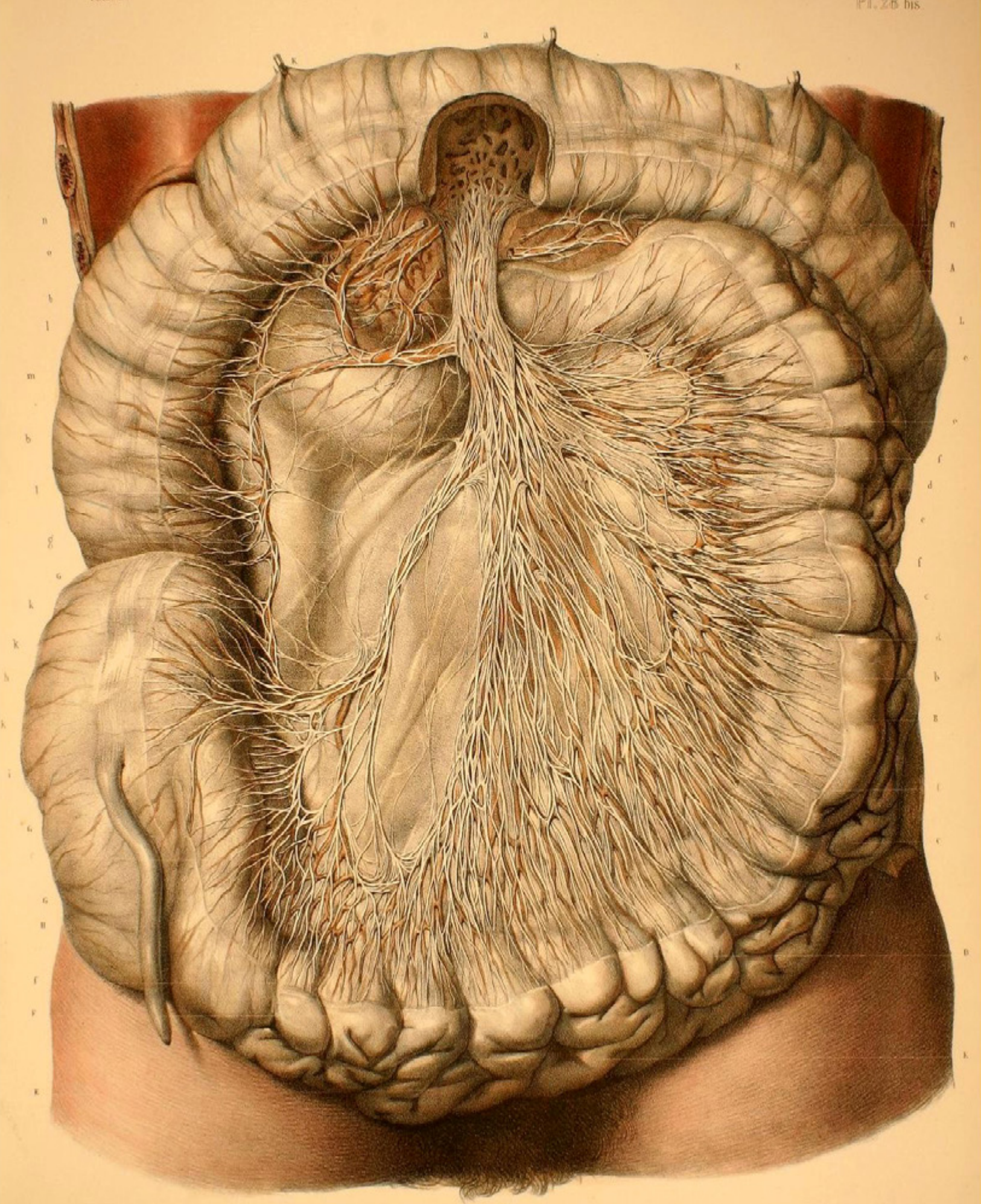

Jean Marc Bourgery
"Traité complet de l'anatomie de l'homme"
Paris 1832-1854

ORIGINAL RESEARCH

DOI: http://dx.doi.org/10.15446/revfacmed.v66n2.61335

Epidemiological characterization of ophidian accidents in a Colombian tertiary referral hospital. Retrospective study 2004-2014

Caracterización epidemiológica de accidentes ofídicos en un hospital de tercer nivel en Colombia. Estudio retrospectivo 2004-2014

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| Abstract |

Introduction: In Colombia, there are 5 000 cases of ophidism per year. This is a public health issue that causes mortality in 8% of cases and disability in 10% due to inadequate clinical attention.

Objective: To describe the clinical and epidemiological characteristics of patients diagnosed with ophidic accident in a tertiary hospital in Colombia.

Materials and methods: A review of clinical charts that included a diagnosis of ophidism during the 2004-2014 period was made at Hospital Universitario de La Samaritana Empresa Social del Estado. The frequency of the variables associated with snake bites, previous treatment and in-hospital management was analyzed.

Results: 42 medical charts were reviewed. Ophidism predominated in male farmers, who presented with bites in the lower limbs and were initially treated by medicine men/women. 90% of patients developed superinfections, 30% wound culture, 74% received antibiotics, 50% underwent fasciotomy and 95.2% were given antivenin.

Conclusions: Significant variability in the management of patients, discrepancy in antivenin dose and in classification of poisoning severity were observed throughout the study, as well as a high incidence of infections despite antibiotic schemes and surgical procedures. Medical management of ophidic accidents must be continuously updated to reduce disability and mortality in patients.

Keywords: Antivenins; Snake Bites; Tertiary Healthcare; Epidemiology; Public Health (MeSH).

| Resumen |

Introducción. En Colombia se presentan 5 000 casos de ofidismo anuales, un problema de salud pública que por manejo inadecuado provoca mortalidad en el 8% de los casos y discapacidad en el 10%.

Objetivo. Describir las características clínicoepidemiológicas de los pacientes diagnosticados con accidente ofídico en un hospital de tercer nivel en Colombia.

Materiales y métodos. Se realizó una revisión de las historias clínicas con diagnóstico de ofidismo del Hospital Universitario De La Samaritana Empresa Social del Estado, en el período 2004-2014, analizando la frecuencia en las variables asociadas a la mordedura de serpiente, el tratamiento previo y el manejo intrahospitalario.

Resultados. Se revisaron 42 historias clínicas. Predominó el ofidismo en hombres agricultores, con mordedura en miembros inferiores y asistidos inicialmente por curanderos. 90% de los pacientes presentó sobreinfección, 30% tuvo cultivo de la herida, 74% recibió antibiótico, al 50% se les realizó fasciotomía y al 95.2% se le suministró antiveneno.

Conclusiones. Se evidenció variabilidad en el manejo de los pacientes y discrepancia en la dosis de antiveneno y la clasificación de severidad del envenenamiento, alta incidencia de infecciones a pesar del esquema antibiótico y procedimientos quirúrgicos reevaluados en ofidismo. El manejo médico del accidente ofídico debe estar en continua actualización para disminuir discapacidad y mortalidad en los pacientes.

Palabras clave: Antivenenos; Mordeduras de serpientes; Atención terciaria de salud; Epidemiología; Salud pública (DeCS).

Sarmiento K, Torres I, Guerra M, Ríos C, Zapata C, Suárez F. Epidemiological characterization of ophidian accidents in a Colombian tertiary referral hospital. Retrospective study 2004-2014. Rev. Fac. Med. 2018;66(2): 153-8. English. doi: http://dx.doi.org/10.15446/revfacmed.v66n2.61335.

Sarmiento K, Torres I, Guerra M, Ríos C, Zapata C, Suárez F. [Caracterización epidemiológica de accidentes ofídicos en un hospital de tercer nivel en Colombia. Estudio retrospectivo 2004-2014]. Rev. Fac. Med. 2018;66(2):153-8. English. doi: http://dx.doi.org/10.15446/revfacmed.v66n2.61335.

Introduction

The clinical picture triggered by the bite of a venomous snake is known as ophidiotoxicosis. (1) Every year, about 2.4 million people are bitten by venomous snakes around the world, causing between 94 000 and 125 000 deaths, as well as 400 000 secondary amputations and other complications such as infections, deformities, psychological sequelae and injuries derived from non-medical cultural practices to prevent the progression of poison. Such practices include the intake of hydrocarbons or alcohol, electrical burns, tourniquets, among others (2), which mostly have a negative impact on the work capacity of the people affected and, therefore, family and regional economy. (2,3)

Colombia is a tropical country characterized by high biodiversity, where venomous snakes are found mainly in areas below 2 500 maml, especially those that generate the greatest risk to populations. For this reason, ophidic accidents occur more frequently in rural areas, being farmers the most affected population, with a higher incidence in young adults and in males. (4)

According to statistics from the Instituto Nacional de Salud (National Health Institute) (1), between 2 000 and 3 000 ophidian accidents occur in Colombia every year, with an incidence of 6.2 cases per 100 000 inhabitants in less populated regions and 20 cases per 100 000 inhabitants in the most populated. (4) For the most part (90-95%), these accidents are caused by snakes of the *Bothrops* genus, and Antioquia and Chocó are the most affected departments. About 5-9% of the events in Colombia are fatal and 6-10% have sequelae. (4)

Although the epidemiological potential of snake bites is not greater than that of diseases transmitted by vectors or other infectious diseases, it is important to note that the impact of mortality caused by ophidiotoxicosis is greater than that attributed to diseases that have been recognized as unattended in tropical regions, which include dengue, cholera, leishmaniasis, chagas, etc. (5), thus turning ophidic accidents into a major public health issue.

In Colombia, some factors that hinder rapid attention of these patients have been identified, namely, geographical features, poor infrastructure for transportation from rural areas to care centers, inadequate cultural practices and lack of thorough medical management of ophidic accidents by health professionals. (6-9)

The treatment of ophidism should be comprehensive and timely, based mostly on the administration of polyvalent antivenin serum specific for the type of venom inoculated according to the genus of the snake. Clinical and paraclinical assessment performed by health personnel is highly important to correlate the semiology with the type and degree of poisoning and, thus, be able to administer sufficient antivenin vials in a timely manner. (5)

The severity of poisoning and the type of venom are determined by factors such as the age of the victim, the size of the bite and sensitivity to the poison, the time elapsed since the bite until receiving medical attention, the location and depth of the bite, the number of bites, the size of the snake and the amount of poison inoculated. (9,10)

Currently, Colombia has a Public Health Surveillance Protocol for Ophidic Accidents (1) and a Guide for the Management of Toxicological Emergencies (5), which establish the basic guidelines for hospital care. However, there is still a high mortality rate and disability secondary to inadequate prehospital treatment.

Therefore, the objective of this study is to perform a clinical characterization of snake bite cases treated in a tertiary hospital in Bogotá between 2004 and 2014, making a comparison with the treatment recommended in national and international management guidelines and review articles, in order to analyze the factors that can provide a continuous improvement in the care of patients with this diagnosis.

Materials and methods

A descriptive, retrospective, cross-sectional study was carried out, with sampling at convenience and evaluation of secondary data sources. The evaluation was made on 42 clinical charts of patients diagnosed with poisonous and non-poisonous snake bites during the aforementioned period, and attended at Hospital Universitario de La Samaritana Empresa Social del Estado (HUS), located in Bogotá, Colombia. Clinical charts with pictures compatible with bites or stings by other animals, blunt trauma to the extremities and poisoning by chemical substances were excluded.

After receiving the authorization from the Ethics Committee, a format was used to collect information regarding the patient's sex, age, geographical area where the bite occurred, occupation, previous morbidities, bite history and use of antiophidic serum, treatment prior to hospital admission, anatomical location of the bite, time of evolution of the condition, time elapsed between the bite and the administration of the antivenin serum, requirement of hospitalization and admission to the intensive care unit, classification of the severity of the ophidic accident, number of days of antibiotic treatment, need for surgical management, complications, antivenin serum side effects, paraclinical evolution of the patient, and alarming signs and symptoms at admission and discharge, such as findings on vital signs, pain, hemorrhages, neurological symptoms and fever.

Once data were collected, information was entered into a spreadsheet in Microsoft Excel 2013. Absolute and relative frequencies of the variables of interest were estimated and grouped into tables. Variables regarding the use of antibiotics and frequency of infections were compared with data from another national hospital-based study using a proportion comparison test. If $p<0.05$, a statistically significant difference was considered.

Results

The most significant results were that the average age was 41.3 years, 76% of the population was male, 42.8% were farmers from the region and Cundinamarca was the main geographical area where ophidic accidents occurred (80.9%). Regarding the anatomical place of the bite, 53% of the patients were bitten in the lower limbs and the remaining patients in the upper limbs (Table 1).

With respect to severity, numerical and (1, 2, 3 and 4) and status records (mild, moderate and severe) were obtained. Taking into account the most used classification, 63.3% of patients were classified in moderate stage, 28% in severe and 7% in mild. The time elapsed from the bite until initiation of medical attention ranged between 1 and 5 hours in 45.2% of the patients, of which 28.5% were in a moderate stage of poisoning.

Regarding the time elapsed from the bite to the administration of antivenin, antivenin was administered between 6 and 11 hours after the bite in 30.9% of patients, of which 21.4% were found in moderate stage, while two patients, with moderate and severe classification, respectively, were not administered any. In relation to previous attention at the HUS, 71.4% of patients were attended first by a medicine men/women and the most frequent procedure (35%) was tourniquet. Of the total patients, 41 required some type of surgical procedure; however, it should be noted that 70% underwent fasciotomy (Table 2).

Table 1. Characteristics of the studied population.

Characteristics		Female	%	Male	%	Total	%
Age	<15 years	1	2.3	0	0	1	2.3
	16-29 years	5	11.9	12	28.5	17	41
	30-59 years	2	4.7	13	30.9	15	35.7
	>60 years	2	4.7	7	16.6	9	21
	Total	10	23.8	32	76.2	42	100
Geographical location of ophidism	Cundinamarca	8	19	26	62	34	81
	Boyacá	1	2.3	0	0	1	2.3
	Vaupés	1	2.3	2	4.72	3	7.5
	Caldas	0	0	1	2.3	1	2.3
	Guainía	0	0	2	4.72	2	4.6
	Guaviare	0	0	1	2.3	1	2.3
Occupation	Not registered	2	4.71	6	14.3	8	19
	Farmer	1	2.3	17	41	18	42.8
	Household duties	4	9.36	5	12	9	21.4
	Student	2	4.71	1	2.3	3	7.5
	Environmental promoter	1	2.3	0	0	1	2.3
	Catechist	0	0	1	2.3	1	2.3
	Snake oil salesperson	0	0	1	2.3	1	2.3
	Merchant	0	0	1	2.3	1	2.3
Anatomical location of the bite	Upper limbs	3	7.14	17	40.5	20	47.6
	Lower limbs	7	16.6	15	35.7	22	52.4

Source: Own elaboration based on the data obtained in the study.

Table 2. Distribution of patients according to characteristics associated with the stage of severity.

Characteristics		Classification of poisoning severity			
		Mild (%)	Moderate (%)	Severe (%)	Total (%)
Bite-medical care	1-5 hours	2 (4.76)	12 (28.57)	5 (11.9)	19 (45.2)
	6-11 hours	1 (2.38)	9 (21.42)	1 (2.38)	11 (26.1)
	12-23 hours	0	2 (4.76)	1 (2.38)	3 (7.14)
	24-47 hours	0	3 (7.14)	3 (7.14)	6 (14.2)
	48-71 hours	0	0	1 (2.38)	1 (2.38)
	>72 hours	0	1 (2.38)	1 (2.38)	2 (4.76)
Bite-antivenin	Not administered	0	1 (2.38)	1 (2.38)	2 (4.76)
	1-5 hours	0	4 (9.52)	1 (2.38)	5 (11.9)
	6-11 hours	1 (2.38)	9 (21.42)	3 (7.14)	13 (30.95)
Bite-antivenin	12-23 hours	2 (4.76)	8 (19.04)	2 (4.76)	12 (28.57)
	24-47 hours	0	3 (7.14)	3 (7.14)	9 (21.42)
	48-71 hours	0	0	1 (2.38)	1 (2.38)
	>72 hours	0	2 (4.76)	1 (2.38)	3 (7.14)
Empirical treatment	No information	0	7 (16.6)	2 (4.76)	9 (21.42)
	Oil	0	3 (7.14)	0	3 (7.14)
	Hot coal	1 (2.38)	1 (2.38)	0	2 (4.76)
	Tourniquet	1 (2.38)	10 (32.8)	4 (9.52)	15 (35.7)
	Alcohol	1 (2.38)	6 (14.2)	6 (14.2)	13 (30.95)
Surgical treatment	No information	0	1(2.4)	0	1 (2.38)
	Amputation	0	0	1 (2.4)	1 (2.38)
	Fasciotomy	0	8 (19.04)	2 (4.8)	10 (32.8)
	Cleaning/ debridement/ drainage	2 (4.8)	11 (26)	2 (4.8)	15 (35.7)
	Fasciotomy and Cleaning/ debridement/ drainage	1(2.4)	4 (9.5)	5 (12)	10 (32.8)
	Fasciotomy and amputation	0	2 (4.8)	0	2 (4.76)
	Cleaning/ debridement/ drainage and amputation	0	1 (2.4)	2 (4.8)	3 (7.14)
Antibiotic treatment	No treatment	1 (2.38)	3 (7.14)	0	4 (9.52)
	1 or 2 antibiotics	1 (2.38)	11 (26.1)	5 (11.9)	17 (40.4)
	3 or 4 antibiotics	1 (2.38)	12 (28.57)	3 (7.14)	16 (38)
	>5 antibiotics	0	1 (2.38)	4 (9.52)	5 (11.9)
Complications	None	1 (2.38)	9 (21.42)	0	10 (32.8)
	Hematologic	0	4 (9.52)	0	4 (9.52)
	Dermatological	0	4 (9.52)	3 (7.14)	7 (16.6)
	Hematologic and dermatological	1 (2.38)	5 (11.9)	2 (4.76)	8 (19.04)
	Hematologic and renal	0	1 (2.38)	2 (4.76)	3 (7.14)
	Hematologic, dermatological, renal and pulmonary	0	2 (4.76)	4 (9.52)	6 (14.2)
	Hematologic, dermatological and pulmonary	1 (2.38)	2 (4.76)	1 (2.38)	4 (9.52)

Source: Own elaboration based on the data obtained in the study.

A prevalence of 90% in in-hospital infectious complications was found, which includes those associated with intradermal and musculoskeletal infectious processes, and of those, 9.5% of the patients without treatment were classified as moderate and mild).

When specifying the antibiotics used, 31 different schemes were observed. The most widely used drug was crystalline penicillin in 17 cases, followed by clindamycin in 16, ampicillin sulbactam in 14, and ciprofloxacin in 12. Additionally, records of patients who were administered piperacillin tazobactam, cefazolin, amikacin, meropenem, gentamicin, vancomycin, imipenem, among others were obtained.

76% of the patients presented some complications, being more frequent hematological and dermatological alterations (25%). The moderate stage included 42% of patients with complications, of which compartment syndrome was the most frequent, followed by dermatological, hematological and musculoskeletal alterations, while patients in severe stage presented multisystemic complications (hematologic, renal and pulmonary) by 33%. Table 3 shows the main complications observed by groups and those observed at least once in patients.

Table 3. Complications observed in patients.

Complications		Patients
Dermatological, musculoskeletal, soft tissue	Compartment syndrome	16
	Abscesses	9
	Soft tissue sepsis	9
	Cellulitis	8
	Rhabdomyolysis	3
	Necrosis	3
	Necrotizing fasciitis	3
	Surgical Site Infection	1
	Infectious tenosynovitis	1
Hematological	Disseminated intravascular coagulation	13
	Hemolytic anemia	8
	Hematemesis	5
	Rectal bleeding	3
	Gynecologic hemorrhage	3
	Septic shock	3
	Ischemic stroke	1
	Hypovolemic shock	1
	Thrombocytopenia	1
	Hyperbilirubinemia	1
	Deep vein thrombosis	1
Pulmonary	Pulmonary edema	7
	Hypoxemia	6
	Pneumatocele	3
	Pulmonary embolism	3
	Pneumonia	1
Renal	Acute renal failure	8
	Emergency dialysis	5
	Proteinuria	3
	Myoglobinuria	2
	Urinary tract infection	1
Others	Acute myocardial infarction	3
	Encephalopathy	2

Source: Own elaboration based on the data obtained in the study.

It was possible to establish that more than 97% of patients were bitten by snakes of the *Viperidae* family, with a mortality rate of 7%, while only one case of coral (*Elapidae*) bite was observed. The number of antivenin vials used per patient was quantified according to the severity of the ophidic accident. It is worth noting that 5 moderate-stage patients received less than 4 vials, while 3 in moderate stage received more than 15, and 3 in severe stage received 4 vials or less. In addition, it was found that the most frequent antivenin side effect was anaphylactic shock with 26.5% (Table 4).

Table 4. Antivenin and side effects presented according to poisoning severity.

Characteristics	Family	Mild (%)	Moderate (%)	Severe (%)	Total
Ophidiotoxicosis	*Viperidae*	3 (7)	26 (61)	12 (28.5)	41 (97.6)
	Elapidae	0	1 (2.3)	0	1 (2.3)
Mortality	*Viperidae*	0	2 (4.6)	1 (2.3)	3 (7)
	Ealpidae	0	0	0	0
Antivenin vials	*Viperidae*				
	< 4	2 (4.6)	5 (12)	3 (7)	10 (23.8)
	5-9	1 (2.3)	13 (31)	1 (2.3)	15 (35.7)
	10-14	0	5 (12)	2 (4.6)	7 (16.6)
	>15		3 (7)	6 (14.2)	9 (21.5)
	Elapidae				
	5-9		1 (2.3)		1 (2.3)
Antivenin side effects	*Viperidae*				
No side effects			2 (4.6)	1 (2.3)	3 (7)
Skin rash		1 (2.3)	6 (14)		7 (17)
Hives		1 (2.3)	4 (10)	2 (4.6)	7 (17)
Fasciculation		1 (2.3)	4 (10)		5 (12)
Increase of blood pressure readings			2 (4.6)	1 (2.3)	3 (7)
Change in the electrocardiogram			3 (7)	1 (2.3)	4 (10)
Anaphylactic shock			4 (10)	7 (16.6)	11 (26.5)
Antivenin side effects	*Elapidae*				
Increase of hypertension figures			1 (2.3)		1 (2.3)

Source: Own elaboration based on the data obtained in the study.

Discussion

Results reveal a scenario in which diverse medical, sociocultural and economic factors converge and lead to an outcome. Epidemiological data obtained from the population studied are similar to those found by some researchers in Colombia (7) and those recorded in the national report of ophidian accidents. (11)

Furthermore, similarities with other studies were found regarding cultural practices that are carried out in cases of ophidism, such as tourniquets, plasters, cuts, suction, burns and alcohol and petroleum intake.

With regard to in-hospital care, about 50% of the patients received antivenin in less than 6 hours after the accident, suggesting that the remaining 50% presented with advanced progression of systemic and local effects of the poison upon admission. (8) Based on the type of ophidian accident, management guidelines (5) and the consensus of

the review articles (6), initiating early antivenin administration is highly recommended to reduce vital organ involvement and mortality.

Fibrinogen uptake and coagulation times were found in 30% of the patients treated, as well as patients with moderate and severe classification who did not receive antivenin. According to the recommendation, coagulation and fibrinogen times should be measured on hospital admission, since the latter is the most useful parameter for determining the severity of poisoning by the *Viperidae* family and the number of initial antivenin vials. (5-7,10)

The most frequent side effect of the drug (antivenin serum) among the entire population was anaphylactic shock with 26.5%, followed by skin rash with 17% and hives in equal proportion. These data coincide with the findings of some researchers when comparing different types of antivenins. (12,13)

Fasciotomy was performed in 70% of the patients; however, this procedure is contraindicated in ophidic accidents due to the absence of a true compartment syndrome and high risk of superinfection. (6,14,15) The most frequent complication in 90% of the patients was local or systemic infection, followed by multisystem failure (50%). Broad spectrum antibiotics were established within the treatment.

Given that current guidelines recommend initiating prophylactic treatment with crystalline penicillin/clindamycin (5) and adjusting antibiotics based on the culture obtained from the affected site (15,16), a comparison of antibiotic management was made against a descriptive study conducted in Hospital Pablo Tobón Uribe (HPTU) of Medellín between 2000 and 2006. (17) Eight HPTU patients who presented with infectious complications were identified out of a total of 52 snake bites; they underwent microbiological isolation of the affected site and prophylactic and in-hospital antibiotic treatment established prior to the culture was observed. This study shows that the most prevalent bacterium in those for whom antibiotic therapy previously indicated was not adequate and also generated resistance was Morganella Morgagni and other Gram-negative bacteria. (17,18)

Additionally, a statistical comparison was made based on hospitals, taking into account the frequency of patients treated with penicillin or clindamycin prior to admission and, at in-hospital level, prior to culture (Table 5). Greater frequency was observed in the use of the recommendation at the HUS, but also greater infectious complications, at hospital level, were found with a statistically significant difference compared to the HPTU.

Table 5. Prophylactic antibiotic treatment used in the Hospital Pablo Tobón Uribe and the Hospital Universitario de La Samaritana Empresa Social del Estado.

Treatment	HPTU	HUS	P
Infectious complication	n=52	n=42	0.0
	8 (15%)	38 (90%)	
No previous antibiotic *	n=8	n=38	0.5
	4 (50%)	23 (60%)	
At least previous penicillin *	3 (37%)	34 (89%)	0.0008
At least previous clindamycin *	0 (0%)	26 (68%)	0.0
At least hospital penicillin *†	1 (12%)	17 (44%)	0.08
At least hospital clindamycin *†	3 (37%)	17 (44%)	0.7

HPTU: Hospital Pablo Tobón Uribe; HUS: Hospital Universitario de La Samaritana Empresa Social del Estado.
* In a patient with an infectious complication.
† Previous to sampling.
Source: Own elaboration based on López *et al.* (17)

Conclusions

Ophidic accidents continue to be an important cause of morbidity and disability in Colombia; therefore, this is a public health issue with consequences that generate disability and limitations in the economic development of the communities. Training the rural population and health personnel is important to avoid secondary complications due to empirical treatments. (9,19,20)

Information regarding ophidian accidents reported in the 2004-2014 period at the HUS allowed to demonstrate variability in management, classification of severity, use of antivenin, examinations and antibiotic and surgical treatment in patients with respect to management guidelines and studies conducted in comparable hospitals.

Clinical management of poisoning by venomous animals should be personalized. (21) However, medical knowledge is part of a continuous updating process, based on studies with a high level of evidence from specialized centers, which promote the re-evaluation of medical practices within care centers for the sole purpose of reducing disability and mortality in patients.

Conflicts of interest

None stated by the authors.

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References

1. Colombia. Instituto Nacional de Salud. Protocolo de Vigilancia en Salud Publica. Accidente Ofídico. Bogotá D.C.: INS; 2014.
2. Organización Mundial de la Salud. Mordeduras de animales. Nueva York: Nota descriptiva No. 373; 2013 [cited 2016 Jul]. Available from: https://goo.gl/bKZ8Dj.
3. **Kasturiratne A, Wickremasinghe AR, de Silva N, Gunawardena NK, Pathmeswaran A, Premaratna R, *et al.*** The global burden of snakebite: a literature analysis and modelling based on regional estimates of envenoming and deaths. *PLoS Med.* 2008;5(11):1591-1604. http://doi.org/b39jmf.
4. **León-Nuñez L.** Informe Del evento accidente ofídico hasta el periodo epidemiológico V, Colombia, 2016. Bogotá D.C.*:* Instituto Nacional de Salud; 2016.
5. **Ayerbe-González S, Rodríguez-Buitrago JR.** Accidentes por animales venenosos y plantas tóxicas. In: Ministerio de la Protección Social. Guías para el manejo de urgencias toxicológicas. Bogotá D.C.: Ministerio de la Protección Social; 2008 [cited 2018 Jan 18]. p. 277-289. Available from: https://goo.gl/n1Ezot.
6. **Sarmiento-Acuña K.** Aspectos biomédicos del accidente ofídico. *Univ. Méd.* 2012;53(1):68-85.
7. **Otero R, Tobón GS, Gómez LF, Osorio R, Valderrama R, Hoyos D, *et al.*** Accidente ofídico en Antioquia y Chocó. Aspectos clínicos y epidemiológicos (marzo de 1989 - febrero de 1990). *Acta Med Colomb.* 1992;17(4):229-49.

8. **Gil-Alarcón G, Sánchez-Villegas MC, Reynoso VH.** Tratamiento prehospitalario del accidente ofídico: revisión, actualización y problemática actual. *Gac Med Mex.* 2011;147:195-208.

9. **Rincon-Torres CE.** Accidentes ofídicos por Micrurus, Colombia, 2011, una mirada desde la salud pública. Bogotá D.C.: Informe Quincenal Epidemiológico Nacional, Instituto Nacional de Salud; 2012.

10. **Perú.** Ministerio de Salud. Norma técnica sobre prevención y tratamiento de accidentes por animales ponzoñosos. Lima: MINSA; 2005.

11. **León-Nuñez L.** Informe final del evento accidente ofídico, Colombia, año 2014. Bogotá D.C.: Instituto Nacional de Salud; 2014.

12. **Otero R, Nuñez V, Barona J, Díaz A, Saldarriaga M.** Características bioquímicas y capacidad neutralizante de cuatro antivenenos polivalentes frente a los efectos farmacológicos y enzimáticos del veneno de Bothrops asper y Porthidium nasutum de Antioquia y chocó. *Iatreia.* 2002;15(1):5-15.

13. **Vázquez H, Olvera F, Alagón A, Sevcik C.** Production of anti-horse antibodies induced by IgG, F(ab´)2 and Fab applied repeatedly to rabbits. Effect on antivenom pharmacokinetics. *Toxicon*. 2013;76:362-9. http://doi.org/f5mwm6.

14. **Pineda D, Ghotme K, Aldeco ME, Montoya P.** Accidentes ofídicos en Yopal y leticia, Colombia, 1996-1997. *Biomédica.* 2002;22(1):14-2. http://doi.org/cjhd.

15. **Hurtado-Zuluaga OA, Urán-Arboleda JE, Villa-Arango JE.** Protocolo de atención prehospitalaria para el manejo integral del accidente ofídico Bothrópico en Colombia [tesis]. Medellín: Universidad CES; 2013.

16. **Muñoz-Porras A, Ovares-Arroyo C.** Antibioticoterapia profiláctica en el accidente ofídico: evidencia actual. *Revista Médica De Costa Rica y Centroamérica.* 2010;67(593):251-4.

17. **López N, Lopera C, Ramírez A.** Características de los pacientes con accidente ofídico y complicaciones infecciosas atendidos en el Hospital Pablo Tobón Uribe entre los años 2000 y 2006. *Acta Med Colomb.* 2008;33(3):127-31.

18. **Blándón-Marín G.** Flora bacteriana asociada a la cavidad bucal en serpientes de la familia Viperidae [tesis]. Manizalez: Universidad de Caldas; 2009.

19. **Zambrano-Ospína AM.** Accidente ofídico como evento de interés en salud pública en Colombia: aportes al diseño de estrategias de gestión [tesis]. Bogotá D.C.: Universidad Nacional de Colombia; 2012.

20. **Lynch JD.** El contexto de las serpientes de Colombia con un análisis de las amenazas en contra de su conservación. *Rev. Acad. Colomb. Cienc.* 2012;36(140):435-49.

21. **Williams D, Gutiérrez JM, Harrison R, Warrell DA, White J, Winkel KD, *et al.*** The Global Snake Bite Initiative: an antidote for snake bite. *Lancet.* 2010;375(9708):89-91.

ORIGINAL RESEARCH

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Epidemiological behavior, geographic distribution and initial clinical management of cutaneous leishmaniasis in Boyacá. 2008-2015

Comportamiento epidemiológico, distribución geográfica y manejo clínico inicial de la leishmaniasis cutánea en Boyacá. 2008-2015

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| Abstract |

Introduction: Leishmaniasis is a reemerging disease that causes more sequelae and disability than any other of its kind in areas where geographical conditions favor the presence of the vector.

Objective: To describe the behavior, geographical distribution and initial clinical management of cutaneous leishmaniasis in the department of Boyacá between 2008 and 2015.

Materials and methods: Observational, retrospective study on a sample of patients diagnosed with cutaneous leishmaniasis in the department of Boyacá, Colombia, registered in the mandatory epidemiological notification sheets of the Colombian public health surveillance system from 2008 to 2015.

Results: 63.6% of patients were men with occupations related to forestry activities and from rural areas. 81% of the reported cases were located in western Boyacá, along the Magdalena River basin, one of the main tributaries of Colombia. Inadequate initial clinical management was observed in 25% of the study sample, which is a risk factor for resistance to pentavalent antimonials.

Conclusion: It is necessary to implement follow-up strategies for patients with cutaneous leishmaniasis in order to verify the cure criteria for the disease and propose strategies for its prevention in the identified populations that are at greater risk.

Keywords: Leishmania; Colombia; Chemotherapy; Public Health; Geographic Information Systems (MeSH).

| Resumen |

Introducción. La leishmaniasis es una de las enfermedades reemergentes que más secuelas y discapacidad causa en zonas donde las condiciones geográficas favorecen la presencia del vector.

Objetivo. Describir el comportamiento, la distribución geográfica y el manejo clínico inicial de la leishmaniasis cutánea en el departamento de Boyacá, Colombia, entre los años 2008 y 2015.

Materiales y métodos. Estudio observacional descriptivo de tipo retrospectivo cuya muestra correspondió a las fichas de notificación epidemiológica obligatoria del Sistema de Vigilancia en Salud Pública pertenecientes a pacientes diagnosticados con leishmaniasis cutánea en Boyacá del 2008 al 2015.

Resultados. De los afectados, el 63.6% correspondió a hombres con ocupaciones afines a actividades forestales y procedentes de zonas rurales. El 81% de los casos se localizaron en el occidente del departamento junto a la cuenca del Rio Magdalena, uno de los principales afluentes del territorio colombiano. Se evidenció un tratamiento clínico inicial inadecuado en el 25% de la muestra, lo que constituyó un factor de riesgo para resistencia a los antimoniales pentavalentes.

Conclusión. Es necesaria la implementación de estrategias de seguimiento a los pacientes con la finalidad de constatar los criterios de curación de la enfermedad y plantear estrategias para su prevención.

Palabras clave: Leishmania; Meglumina; Colombia; Quimioterapia; Salud Pública; Sistemas de Información Geográfica (DeCS).

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Introduction

Leishmaniasis is an infection caused by an intracellular flagellated protozoan transmitted by the bite of hematophagous mosquitoes belonging to the family *Psychodidae*, genera *Phlebotomus* and *Lutzomyia*. (1) Around 20 *Leishmania* species have a pathogenic potential for humans, and also have the ability to infect mammals of different species and generate both cutaneous and visceral involvement. (2-4)

Leishmaniasis is considered an endemic pathology in around 70 countries; however, notifying it as an event in public health is mandatory only in 32 of them, which is why its actual incidence is underestimated. (5) The World Health Organization estimates about 1.3 million new cases and 20 000 to 30 000 deaths per every year, mostly due to visceral involvement. (6) Cutaneous leishmaniasis is the most common form of the disease and occurs in exposed body regions causing ulcerative lesions and poor healing processes. (7,8) 95% of the events related to this form occur in the Americas, the Middle East and Central Asia, being Afghanistan, Iran, Algeria, Syria, Brazil and Colombia the most affected countries. (6)

In Colombia, the incidence of leishmaniasis is high and exceeds 12 000 cases per year; its geographical distribution involves a large part of the country. (9-11) The species *L. panamensis, L. guyanensis, L. braziliensis, L. amazonensis* and *L. mexicana* have been associated with the cutaneous and mucocutaneous form of the disease and are responsible for most cases. (12,13)

According to the epidemiological bulletin of the Instituto Nacional de Salud (National Institute of Health) of Colombia, Boyacá ranks ninth countrywide regarding new cases documented in 2016, which is above the national average, being the municipalities of Otanche, San Pablo de Borbur, Pauna, Quípama and Puerto Boyacá the places with the highest number of cases reported. (14,15) This distribution puts the department at a medium risk for the occurrence of the event.

Currently, several pharmacological treatments are available in the guidelines of the Instituto Nacional de Salud to manage leishmaniasis optimally, which range from local therapies to systemic medications. (16,17) However, there is no single drug that effectively treats all Leishmania species, nor the conditions they cause. (4,18) Furthermore, the development of new compounds is limited because the most affected population is under poverty conditions and, in turn, have greater difficulty for accessing health services. With this in mind, the implementation of new drugs may represent a high acquisition cost, thus affecting mostly this type of population. (19)

Pentavalent antimonials used as pharmacotherapy to treat cutaneous leishmaniasis continue to be the first management option. (16,20) Meglumine antimonate is the most used and is recommended in the guidelines of the Instituto Nacional de Salud as the first option for the management of this disease in Colombia. (3,21,22) The average dose is 20 mg/k once a day, though local or systemic application for 20 or 30 days, depending on the route of administration of the drug, being shorter in the case of systemic therapy and longer in the case of local application. (3,19)

It is possible to observe therapeutic failures caused by low adherence, drug resistance and the use of subtherapeutic doses, which, in turn, are related to three factors: lack of knowledge on the part of the treating health personnel about the doses and presentation of the drugs; lack of dose adjustment according to the patient's weight during the treatment; and lack of follow-up. (19) Moreover, another factor is treatment abandonment due to local side effects such as pain at the site of application, arthralgias, myalgias and even organic involvement manifested through liver and kidney failure and disorders in the electrical conduction system of the heart, which in some cases may seriously compromise the health of patients. (8,23)

This study aimed to make an epidemiological approach, not only to the distribution of the disease in Boyacá, but to its behavior and the factors that determine its occurrence in the affected population. In short, the objective is to describe the behavior, geographical distribution and initial clinical management of cutaneous leishmaniasis in the department of Boyacá between 2008 and 2015.

Materials and methods

A descriptive, retrospective study was carried out. Considering that the event is notifiable, the information generated on a regular basis through the notification form of the Epidemiological Surveillance System (SIVIGILA by its acronym in Spanish) allowed obtaining data on sociodemographic, clinical and geographical distribution conditions of the patients diagnosed with cutaneous leishmaniasis.

The study included users who were reported to SIVIGILA as confirmed cases of cutaneous leishmaniasis in the 123 municipalities of Boyacá between 2008 and 2015 and had complete epidemiological records. Patients that acquired the infection in a department other than Boyacá were excluded.

The analyzed variables were age, sex, weight, occupation, place of occurrence of the case, health insurance system, ethnicity, place of origin, number and location of cutaneous leishmaniasis lesions, previous hospitalization, previous treatment, estimated dose per day and total number of vials administered.

Statistical analysis

Statistical analysis of demographic and clinical conditions was performed using the IBM SPSS program (Chicago, Illinois) version 23. Univariate and bivariate analyses of the aspects established in the categorization of the variables were carried out. Qualitative variables such as sex, geographic area, ethnicity, health insurance system, among others, were analyzed using absolute and relative frequencies. On the other hand, quantitative variables were processed through measures of central tendency.

An analysis was made taking into account the geographical distribution of the cases reported in Boyacá between 2008 and 2015. A color scale was used: green for municipalities with 1 to 8 cases, yellow for 9 to 16 cases, orange for 17 to 24 cases and red more than 25 cases. To elaborate the maps with the geographic distribution of the patients affected by cutaneous leishmaniasis, the EpiMap extension of EpiInfo was used.

Regarding clinical management of patients, criteria for locating the lesions were determined by means of frequency analysis. This was confirmed by weight and the amount of doses in milligrams —if the patients received an adequate initial dose—, and the amount of vials during the chemotherapy period established according to the protocol of the Instituto Nacional de Salud (National Health Institute) of Colombia. Data were obtained from calculating the initial dose per day adjusted by weight for each patient. Then, the number of vials that should be administered during the 20 days of treatment was established taking into account that the excess content of each vial per day should be discarded and compared with the estimated initial dose recorded in the notification form and the total amount of vials administered to each patient.

Ethical considerations

This study was elaborated following the guidelines of the Council for International Organizations of Medical Sciences. This research is risk-free according to Resolution 8430 of 1993 of the Ministry of Health

Colombia, which establishes scientific, technical and administrative regulations for health research. (24) Moreover, confidentiality, respect and security of the information were preserved at all times during its processing. However, authorization from the Ministry of Health of Boyacá, Public Health Surveillance Area, was requested to access the databases. The research protocol was presented to the Ethics Committee of the Universidad de Boyacá.

Results

Sociodemographic conditions

Out of 949 epidemiological records found, 40 were excluded due to poor quality of the data or lack of data. The analysis included 909 files correctly entered in the system. The average age was 23 years (σ: 19, min-max: 4-52), and 429 cases (47.2%) occurred in the 0-18 age range; of these, 155 cases (17%) occurred in the 0-5 range. The general distribution of affected individuals determined by life cycle is shown in Table 1, which makes evident that adults (29 to 59 years) were involved in 26.5% of the cases. Regarding sex, except for children (6 to 11 years), men (63.6% of the total sample) were more involved in this type of cases than women.

According to the place of residence of the patients, three classifications were used: municipal head, population center and dispersed settlement, the latter being the most affected with 75% of the cases.

Most subjects affected (71.9%) were students, people without a specific occupation and workers in rural areas, most of them enrolled in the subsidized system (70.5%) of the General System of Social Security in Health. The most frequent ethnicity (96.9%) was specified as "other" in the compulsory notification sheet, which corresponds to cross-breeding between natives and Europeans during colonial times (mestizo).

Table 1. Sociodemographic conditions and age group of patients diagnosed with cutaneous leishmaniasis in Boyacá, Colombia. 2008-2015.

Conditions		Life cycle in years													
		0-5	%	6-11	%	12-17	%	18-28	%	29-59	%	60-99	%	Total	%
Population	Women	72	8	80	8.8	48	5.3	42	4.6	68	7.5	21	2.3	331	36.4
	Men	83	9.1	61	6.7	85	9.3	132	14.5	173	19	44	4.9	578	63.6
	Total	**155**	**17.1**	**141**	**15.5**	**133**	**14.6**	**174**	**19.1**	**241**	**26.5**	**65**	**7.2**	**909**	**100**
Occupation	Rural work	0	0	0	0	1	0.1	46	5	104	11.4	36	4	187	20.5
	Student	42	4.6	125	13.7	122	13.4	11	1.2	1	0.1	0	0	301	33.1
	Domestic work	1	0.1	0	0	1	0.1	32	3.5	57	6.3	16	1.6	107	11.8
	Mining	0	0	0	0	0	0	4	0.4	16	1.8	2	0.2	22	2.4
	Military	0	0	0	0	0	0	53	5.9	14	1.5	0	0	67	7.4
	Other occupations	1	0.1	0	0	0	0	16	1.8	36	4	6	0.7	59	6.5
	Unemployed	111	12.2	16	1.8	9	1	12	1.3	13	1.4	5	0.6	166	18.3
	Total	**155**	**17.1**	**141**	**15.5**	**133**	**14.6**	**174**	**19.1**	**241**	**26.5**	**65**	**7.2**	**909**	**100**
Place of origin	Municipal head	14	1.5	13	1.4	13	1.4	41	4.5	33	3.6	5	0.6	119	13.1
	Population center	11	1.2	9	1	12	1.3	24	2.6	25	2.7	4	0.4	85	9.3
	Dispersed settlement	130	14.4	119	13.1	108	11.9	109	12	183	20.2	56	6.2	705	77.6
	Total	**155**	**17.1**	**141**	**15.5**	**133**	**14.6**	**174**	**19.1**	**241**	**26.5**	**65**	**7.2**	**909**	**100**
Health insurance system	Contributive	10	1.1	15	1.6	9	1	17	1.9	45	5	6	0.7	102	11.2
	Subsidized	131	14.5	118	13	115	12.6	79	8.7	151	16.6	47	5.2	641	70.5
	Exceptional system	0	0	0	0	0	0	50	5.5	17	1.9	0	0	67	7.4
	No insurance	14	1.5	8	0.9	9	1	28	3	28	3	12	1.3	99	10.9
	Total	**155**	**17.1**	**141**	**15.5**	**133**	**14.6**	**174**	**19.1**	**241**	**26.5**	**65**	**7.2**	**909**	**100**
Ethnicity	Indigenous	0	0	0	0	0	0	2	0.2	6	0.7	1	0.1	9	1
	Gypsy	0	0	0	0	0	0	0	0	1	0.1	0	0	1	0.1
	Palenque	2	0.2	0	0	0	0	0	0	0	0	0	0	2	0.2
	Afro-Colombian	7	0.8	1	0.1	3	0.3	3	0.3	1	0.1	1	0.1	16	1.8
	Mestizo	146	16.1	140	15.4	130	13.3	169	18.6	233	25.6	63	6.9	881	96.9
	Total	**155**	**17.1**	**141**	**15.5**	**133**	**14.6**	**174**	**19.1**	**241**	**26.5**	**65**	**7.2**	**909**	**100**

Source: Own elaboration based on the data obtained in the study.

Geographical distribution

When analyzing notifications issued during the 8-year period under study, a varied behavior was observed, showing two major peaks in 2010 with 187 cases and 2014 with 173 cases, in contrast to 2011, when only 58 cases were recorded (Figure 1).

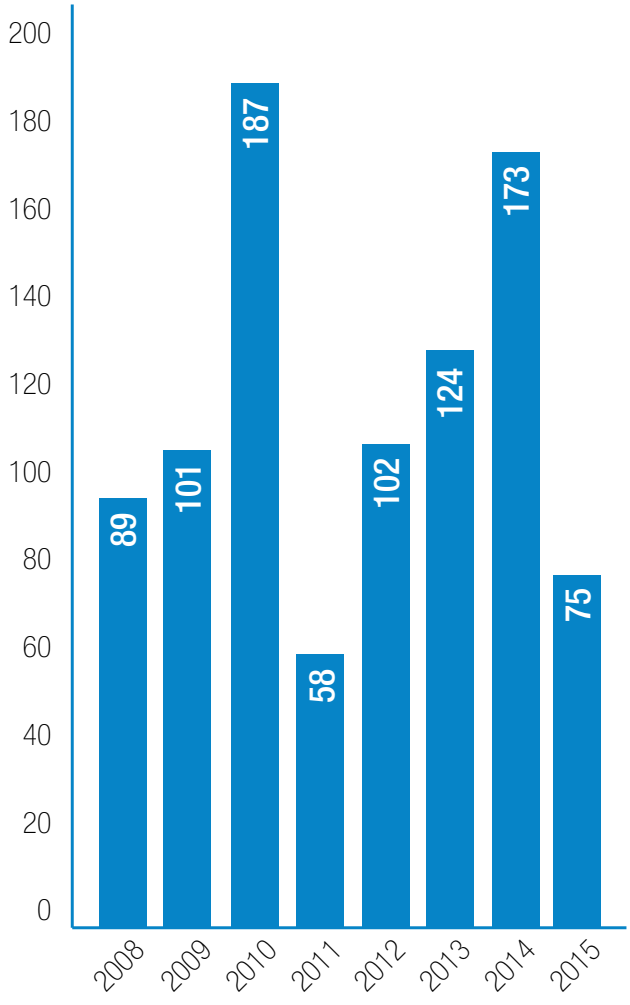

Figure 1. Number of cutaneous leishmaniasis cases reported per year in Boyacá, Colombia. 2008-2015.
Source: Own elaboration based on the data obtained in the study.

Figure 2 shows the behavior in the municipalities that reported cases of cutaneous leishmaniasis during the study period. This information allowed to determine that 5 of the 123 municipalities of the department presented the highest number of cases, being the municipality of Otanche the one that reported the highest prevalence with 344 cases (37.8%), followed by San Pablo de Borbur with 139 (15.3%). It should be noted that these five municipalities account for 81% of the total cases reported during the study period.

According to the geographical distribution analysis, the municipalities with the highest number of cases are located in the western province during the entire period, especially in the municipalities of Otanche, San Pablo de Borbur, Puerto Boyacá and Pauna. The maps also show some cases of municipalities that have no risk for the event, among them Chiquinquirá, Chita, Duitama, El Cocuy, Nobsa, Panqueba, Saboya, Sogamoso, Tibasosa and Ventaquemada (Figure 3).

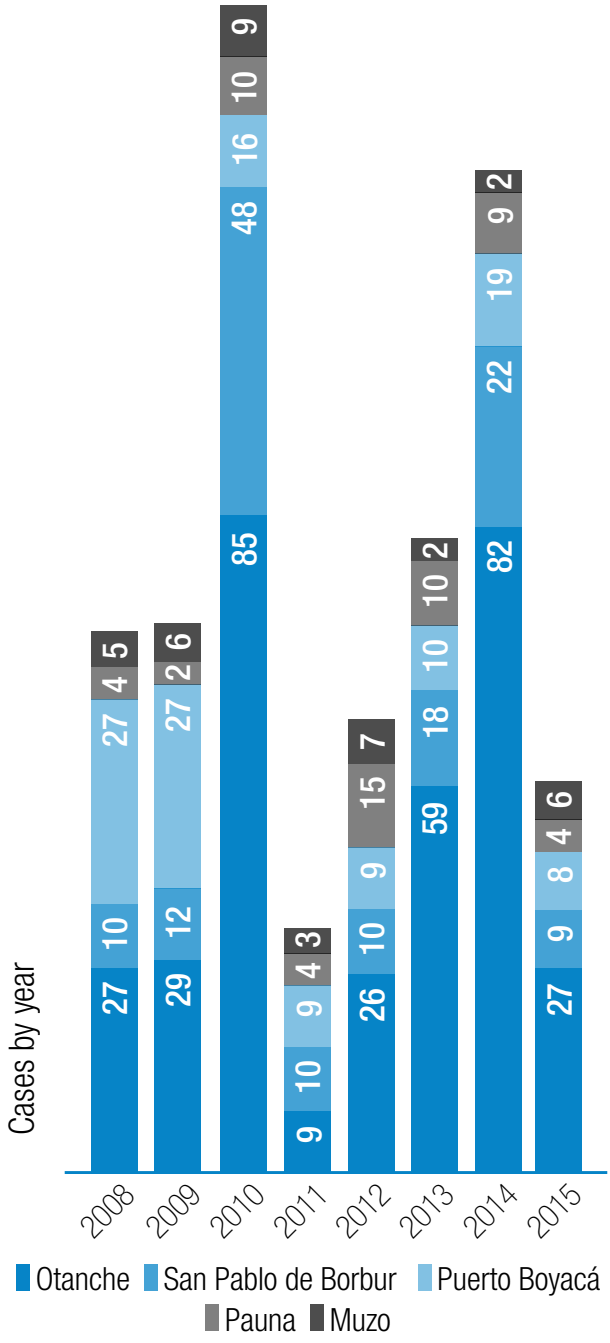

Figure 2. Municipalities with reports of patients with leishmaniasis in Boyacá, Colombia. 2008-2015.
Source: Own elaboration based on the data obtained in the study.

Initial clinical management

The number of cutaneous leishmaniasis lesions is variable: 665 cases (73.1%) had a single lesion; 179 (19.7%) had two; 57 (6.3%) had three and 8 (0.8%) had four or more. The presence of lesions was greater in upper and lower limbs with a total of 482 (53%) and 333 (36.6%) cases, respectively. 247 (27.2%) patients had lesions on the face and 162 (17.8%) on the trunk. The sum of injuries is greater than the number of patients because some individuals were affected by injuries that involve more than one body segment or have more than one injury.

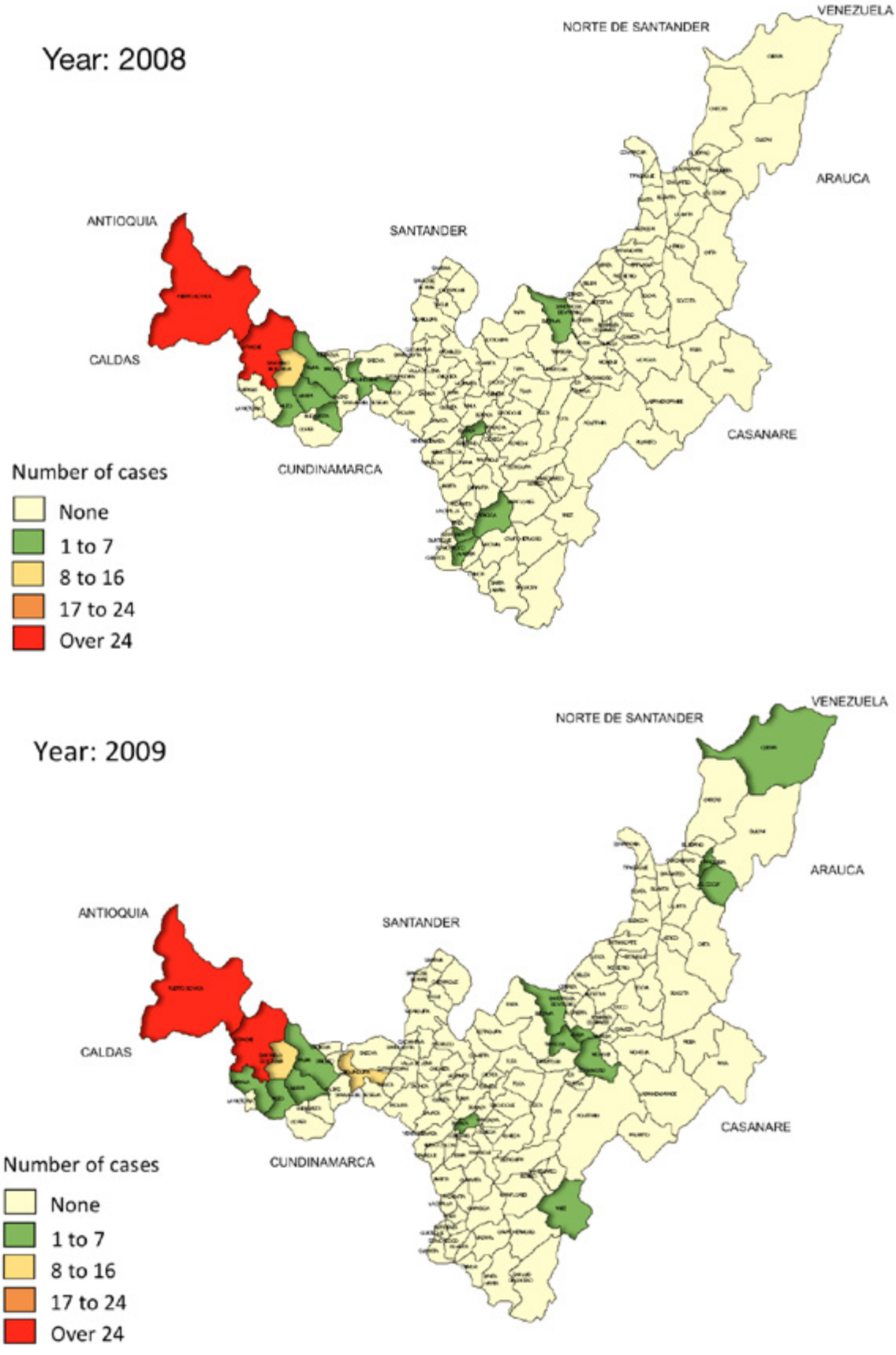

Figure 3. Geographical distribution of cutaneous leishmaniasis cases in Boyacá, Colombia. 2008-2015.
Continues.

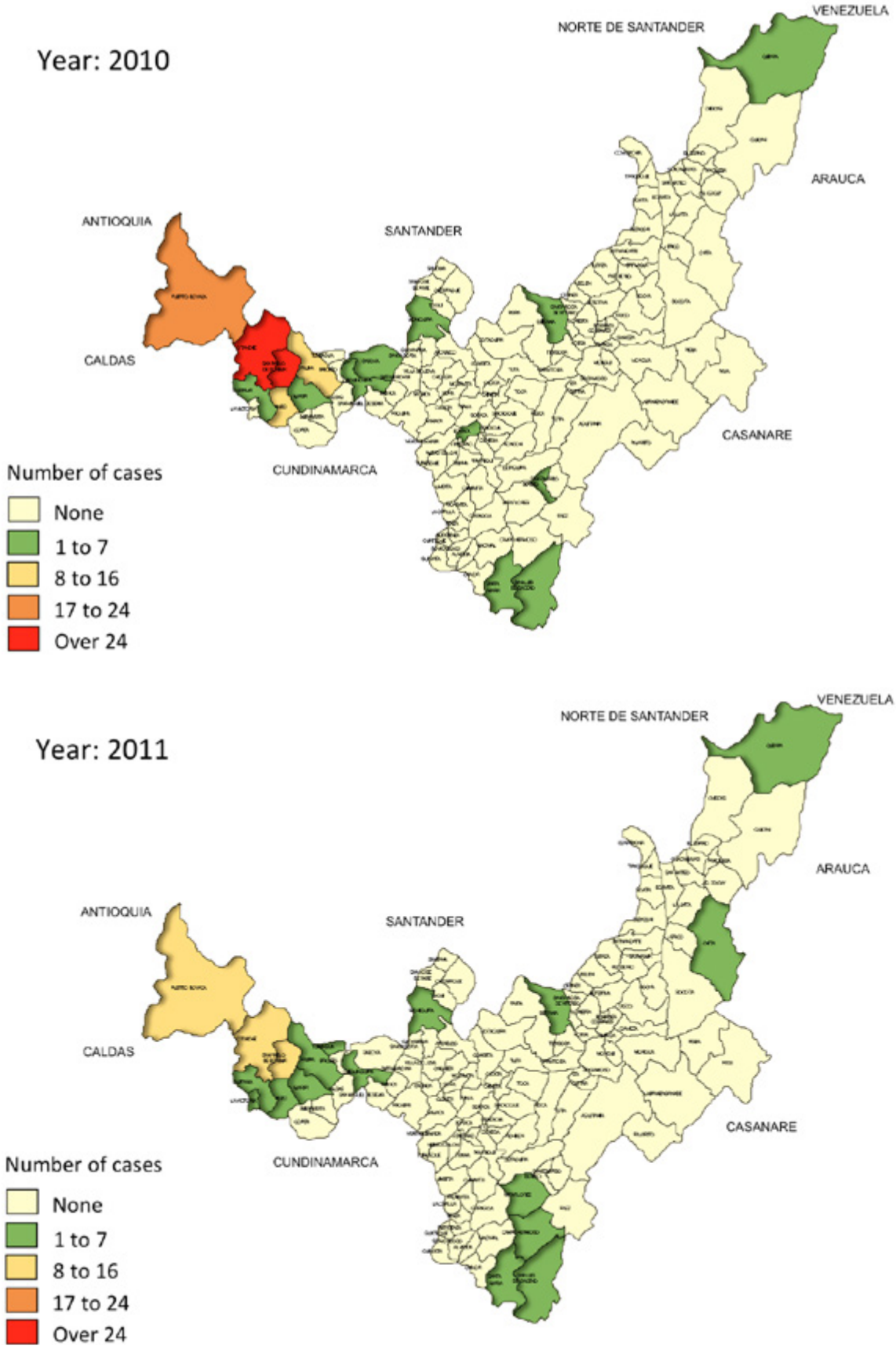

Figure 3. Geographical distribution of cutaneous leishmaniasis cases in Boyacá, Colombia. 2008-2015.
Continues.

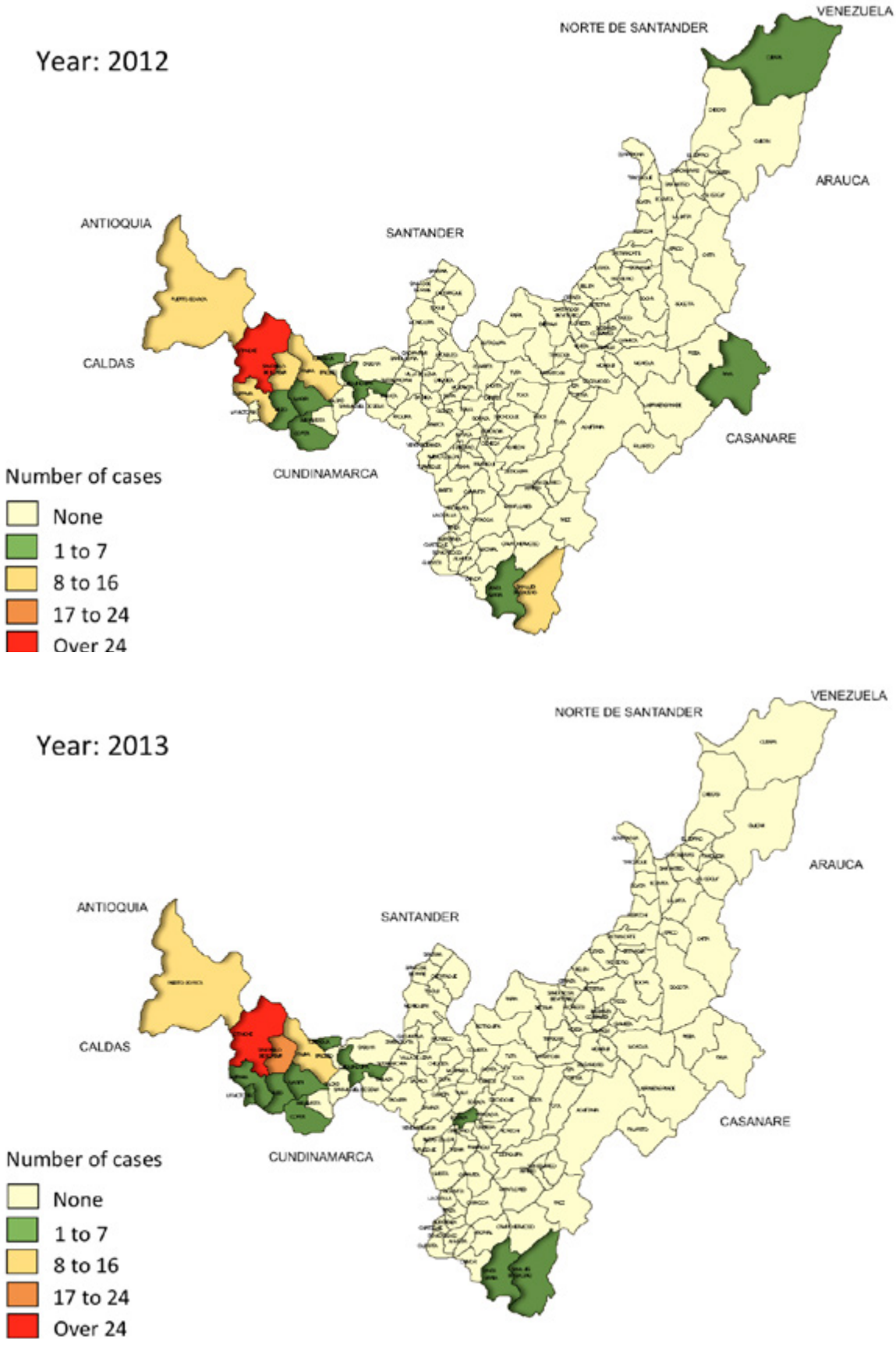

Figure 3. Geographical distribution of cutaneous leishmaniasis cases in Boyacá, Colombia. 2008-2015.
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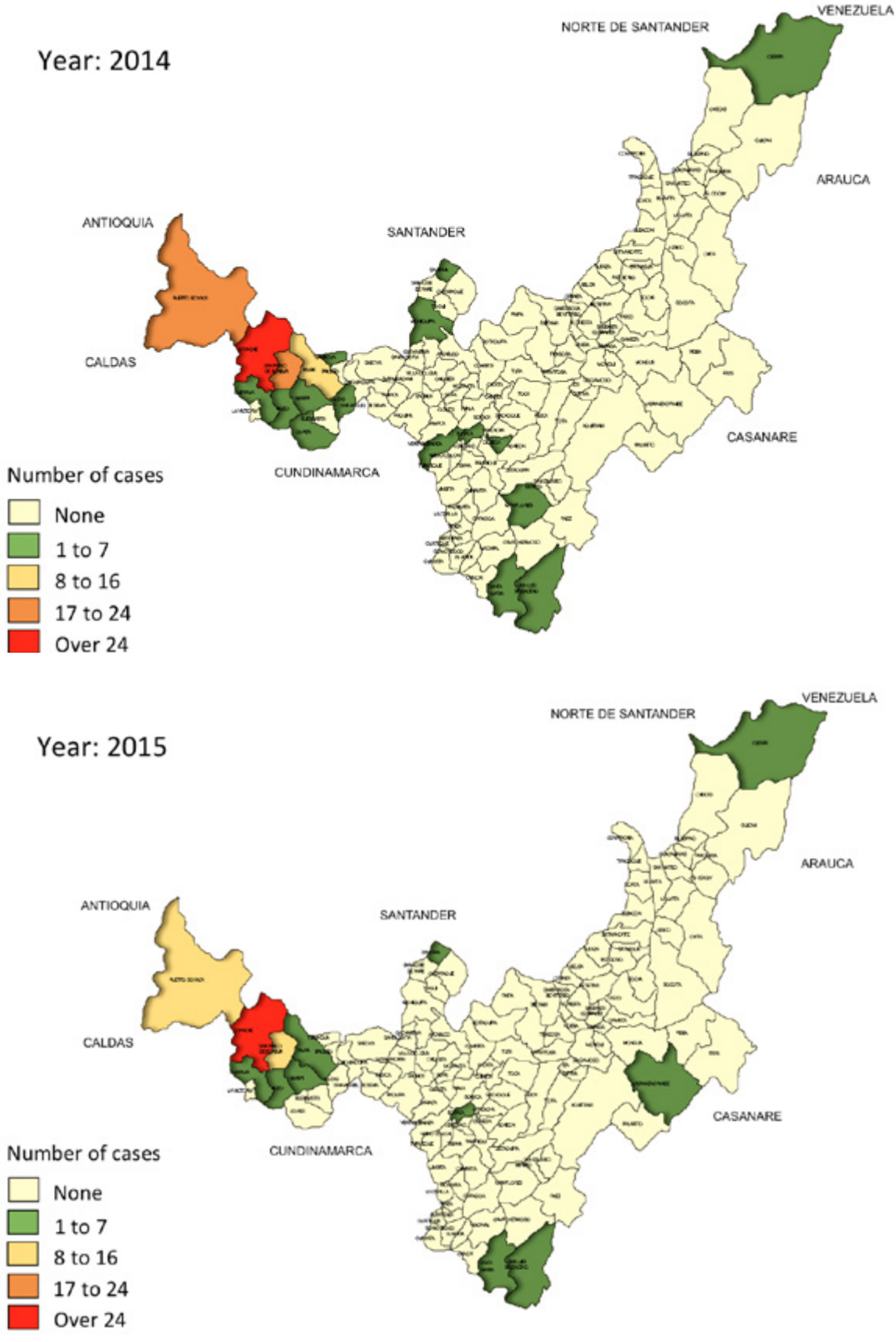

Figure 3. Geographical distribution of cutaneous leishmaniasis cases in Boyacá, Colombia. 2008-2015.
Source: Own elaboration based on the data obtained in the study.

Initial clinical management

The number of cutaneous leishmaniasis lesions is variable: 665 cases (73.1%) had a single lesion; 179 (19.7%) had two; 57 (6.3%) had three and 8 (0.8%) had four or more. The presence of lesions was greater in upper and lower limbs with a total of 482 (53%) and 333 (36.6%) cases, respectively. 247 (27.2%) patients had lesions on the face and 162 (17.8%) on the trunk. The sum of injuries is greater than the number of patients because some individuals were affected by injuries that involve more than one body segment or had more than one injury.

The percentage of patients infected and previously hospitalized due to leishmaniasis was 3%. Similarly, a history of previous treatment was found in 9.6% of the total of patients included in this study. Figure 4 shows the number of subjects who received adequate and inadequate treatment regarding the therapeutic dose according to the weight in kilograms discriminated per year. Of the total cases, 73.9% received the number of vials required according to their weight during the study period. The lowest rate of error in the calculation of the initial dose (12%) was observed in 2015.

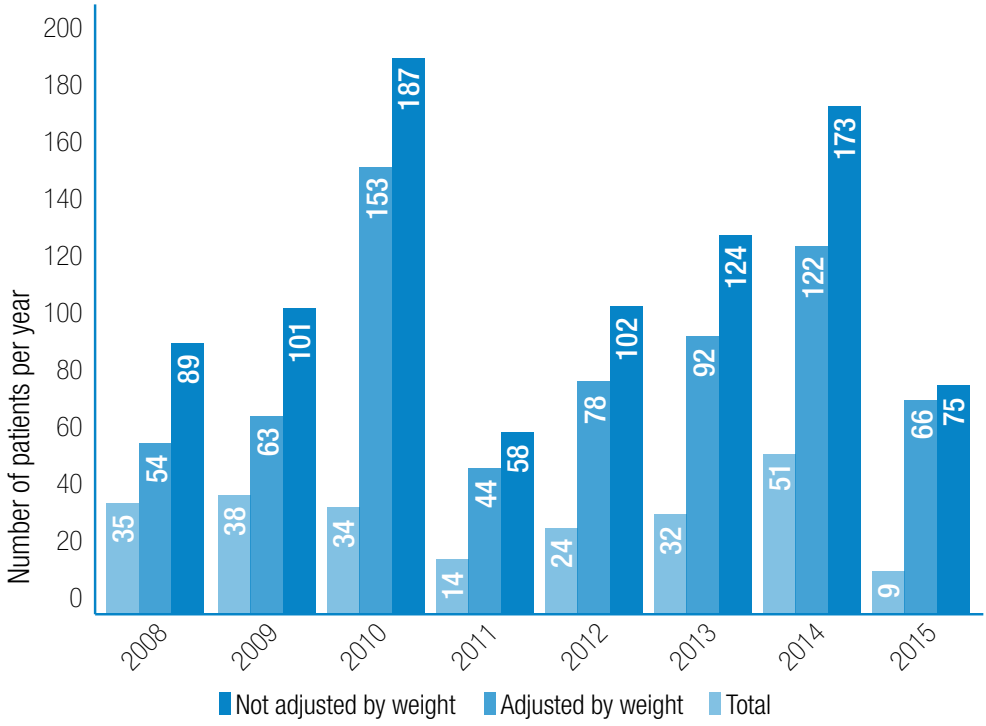

Figure 4. Pharmacological treatment with meglumine antimonate, calculated according to the guidelines of the Colombian Ministry of Health and Social Protection and discriminated by year in patients with cutaneous leishmaniasis from Boyacá, Colombia. 2008-2015.
Source: Own elaboration based on the data obtained in the study.

Discussion

The results of this study indicate that leishmaniasis is a disease that affects young people, residents of rural areas, who work in forested areas, which coincides with Cella *et al.* (25) and Bsrat *et al.* (26) Regarding sex, it was more frequently observed in men, which is similar to the reports found in the works carried out by Cella *et al.* (25), Soares *et al.* (27), Aguado *et al.* (28) and Cota *et al.* (29)

As in the studies of Cota *et al.* (29) and Pontello *et al.* (30), the body areas most affected by cutaneous leishmaniasis are the upper and lower limbs. The number of predominant lesions in the subjects of this study was one injury, which coincides with Blanco *et al.* (31).

Regarding geographical distribution, a high number of cases was observed in the western province, especially in the municipalities of Otanche, San Pablo de Borbur, Puerto Boyacá and Pauna, which have been classified by other studies as critical sites for the presence of vectors infected by the *Leishmania* parasite. (32)

Pentavalent antimonials were the drugs used in the patients included in this study, mainly meglumine antimoniate. Some findings include inadequate dosing in over 25% of the cases due to deficiencies in the calculation of the initial dose of the treatment. Such situation may have a negative impact on the health of patients since it is considered a risk factor for resistance to the action of the compounds used in the management of leishmaniasis. (33,34) Inadequate pharmacological therapy for this pathology is a widely recognized problem in the current medical literature; however, there are no studies to compare our results in this regard, since no research addresses the initial clinical management performed on patients affected by cutaneous leishmaniasis. Mohapatra (33) states that the lack of knowledge of physicians about the presentation, dose and duration of treatment is one of the main causes of resistance to antileishmanial drugs in developing countries.

This study did not include any follow-up information regarding the treatment of patients because data were taken from the SIVIGILA notification sheets and there are no sections that allow for a clinical follow-up or cure criteria; therefore, it was impossible to assess the efficacy of pharmacological management and verify the healing process of patients whose cases were notified as confirmed leishmaniasis. Furthermore, there was no record of the doses applied to patients per day, which is decisive for the management of this pathological entity, since a 20-day duration and not proving its application may lead to failures during the administration of the treatment and complications such as drug resistance.

One of the limitations of this study is the lack of an instrument for monitoring the clinical picture of patients affected by cutaneous leishmaniasis in Boyacá, Colombia. In spite of that, this study aimed at updating the existing information regarding the epidemiological behavior and geographical distribution of leishmaniasis in Boyacá. In addition, a description of the initial pharmacological treatment was established to provide recommendations to health decision-makers at the regional and national levels in order to correct inadequate behaviors and encourage other authors to study vector-borne diseases in greater depth. There are still shortcomings in the identification and management of these cases, which constitutes a problem of interest for public health.

Conclusions

Findings related to the type of presentation and behavior of the disease are similar to other works, which lead to believe that its behavior is as expected. West Boyacá is the region most affected by leishmaniasis in the department; five of the municipalities in this area are classified as critical due to the high presence of infected vectors, which may be related to the geographical location and the influence of fluvial sources. This last point must be taken into account when developing strategies for the epidemiological control of the disease.

Regarding initial management, and in spite of the guidelines for diagnosis and management, the lack of knowledge of the treating medical personnel has led to inadequate management in 1 of every 4 patients diagnosed who have been treated with subtherapeutic doses, causing failures that result in recurrences.

Once again, there is a need to create a public health surveillance instrument that not only collects report data but also adherence monitoring and medication administration, as well as the occurrence and management of collateral effects and complications of the disease.

Regulating entities should detect failures in the notification files of the disease, because when a clinical and pharmacological follow-up is required, it is necessary to modify these documents to improve surveillance and control processes of cutaneous leishmaniasis. Efficient training of the treating medical personnel and the health team that interacts with these patients is essential to reduce the rates of treatment failure.

Conflicts of interest

None stated by the authors.

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References

1. **Reveiz L, Maia-Elkhoury AN, Nicholls RS, Sierra-Romero GA, Yadon ZE.** Interventions for American Cutaneous and Mucocutaneous Leishmaniasis: A Systematic Review Update. *PLoS One.* 2013;8(4):e61843. http://doi.org/cjbw.

2. **Murray HW.** Leishmaniasis in the United States: Treatment in 2012. *Am J Trop Med Hyg.* 2012;86(3):434-40. http://doi.org/cjbx.

3. **McGwire BS, Satoskar AR.** Leishmaniasis: Clinical syndromes and treatment. *QJM.* 2014;107(1):7-14. http://doi.org/f5m2ds.

4. **Copeland NK, Aronson NE.** Leishmaniasis: treatment updates and clinical practice guidelines review. *Curr Opin Infect Dis.* 2015;28(5):426-37. http://doi.org/f78fwb.

5. **Giavedoni P, Iranzo P, Fuertes I, Estrach T, Alsina-Gibert M.** Leishmaniasis cutánea. Experiencia de 20 años en un hospital español de tercer nivel. *Actas Dermosifiliogr.* 2015;106(4):310-6. http://doi.org/f25s6x.

6. Organización Mundial de la Salud. Leishmaniasis. Nueva york; 2016 [cited 2018 Jan 15]. Available from: https://goo.gl/ekf6Xg.

7. **van Griensven J, Gadisa E, Aseffa A, Hailu A, Beshah AM, Diro E.** Treatment of Cutaneous Leishmaniasis Caused by Leishmania aethiopica: A Systematic Review. *PLoS Negl Trop Dis.* 2016;10(3):e0004495. http://doi.org/f8th4h.

8. **Barberis F, Vélez-Bernal ID.** Opciones terapéuticas para el manejo de la Leishmaniasis cutánea americana. *Rev Panam Infectol.* 2014;16(2):113-22.

9. **Carrillo-Bonilla LM, Trujillo JJ, Álvarez-Salas L, Vélez-Bernal ID.** Estudio de los conocimientos, actitudes y prácticas de la leishmaniasis: evidencias del olvido estatal en el Darién Colombiano. *Cad Saúde Pública.* 2014;30(10):2134-44. http://doi.org/cjbz.

10. Colombia. Ministerio de la Protección Social, Instituto Nacional de Salud. Guía para la atención clínica integral del paciente con Leishmaniasis. Bogotá D.C.: Organización Panamericana de la Salud; 2010 [cited 2018 Jan 15]. Available from: https://goo.gl/n3raAC.

11. **Guerra JA, Maciel MG, Guerra MV, Talhari AC, Prestes SR, Fernandes MA, *et al.*** Tegumentary leishmaniasis in the state of amazonas: What have we learned and what do we need? *Rev Soc Bras Med Trop.* 2015;48(Suppl 1):12-9. http://doi.org/f7gjjv.

12. **Montalvo AM, Fraga J, Montano I, Monzote L, Van der-Auwera G, Marín M, *et al.*** Identificación molecular con base en el gen hsp70 de aislamientos clínicos de *Leishmania spp.* en Colombia. *Biomedica.* 2016;36(suppl 1):37-44. http://doi.org/cjb2.

13. **Akhoundi M, Kuhls K, Cannet A, Votýpka J, Marty P, Delaunay P, *et al.*** A Historical Overview of the Classification, Evolution, and Dispersion of Leishmania Parasites and Sandflies. *PLoS Negl Trop Dis.* 2016;10(3):1-40. http://doi.org/f8th65.

14. Colombia. Instituto Nacional de Salud. Enfermedades transmitidas por vectores. Bogotá D.C.: Boletín epidemiológico semanal 46; 2016.

15. Gobernación de Boyacá, Dirección Técnica de Salud Pública y Vigilancia en Salud Pública. Boletín epidemiológico de Boyacá semana 48. Tunja: Grupo Vigilancia en Salud Pública SESALUB; 2016 [cited 2016 Dec 13]. Available from: https://goo.gl/o7iRqB.

16. **López-Carvajal L, Palacio-Barco MA, Cardona-Arias JA.** Eficacia de Los Azoles en el Tratamiento de la Leishmaniasis Cutanea. *Arch Med.* 2016;12(2):1-10.

17. **Goto H, Lauletta-Lindoso JA.** Cutaneous and Mucocutaneous Leishmaniasis. *Infect Dis Clin North Am.* 2012;26(2):293-307. http://doi.org/f34fz8.

18. **de Menezes JP, Guedes CE, Petersen AL, Fraga DB, Veras PS.** Advances in development of new treatment for leishmaniasis. *Biomed Res Int.* 2015;2015:815023. http://doi.org/gb573t.

19. Organización Panamericana de la Salud. Leishmaniasis en las Américas: Recomendaciones para el tratamiento. Washington D.C.: OPS; 2013.

20. **de Vries HJ, Reedijk SH, Schallig HD.** Cutaneous leishmaniasis: recent developments in diagnosis and management. *Am J Clin Dermatol.* 2015;16(2):99-109. http://doi.org/gcbtc6.

21. **García-Bustos MF, Barrio A, Parodi C, Beckar J, Moreno S, Basombrio MA.** Mitelfosina versus antimoniato de meglumina en el tratamiento de la leishmaniasis mucosa. *Medicina.* 2014;74(5):371-7.

22. **Perez-Franco JE, Cruz-Barrera ML, Robayo ML, Lopez MC, Daza CD, Bedoya A, *et al.*** Clinical and Parasitological Features of Patients with American Cutaneous Leishmaniasis that Did Not Respond to Treatment with Meglumine Antimoniate. *PLoS Negl Trop Dis.* 2016;10(5):e0004739. http://doi.org/f8rptw.

23. **Gamboa-Latorre LF, Becerra-Mateus JA.** Cardiotoxicidad por antimoniales. *Rev Salud Bosque.* 2012;2(2):69-74.

24. Colombia. Ministerio de salud de Colombia. Resolución 8430 de 1993 (octubre 4): Por la cual se establecen las normas científicas, técnicas y administrativas para la investigación en salud. Bogotá D.C.: octubre 4 de 1993 [cited 2018 Jan 15]. Available from: https://goo.gl/utLcMC.

25. **Cella W, Melo SC, Dell agnolo CM, Pelloso SM, Silveira TG, Carvalho MD.** Seventeen years of American cutaneous leishmaniasis in a Southern Brazilian municipality. *Rev Inst Med Trop Sao Paulo.* 2012;54(4):215-8. http://doi.org/f358mg.

26. **Bsrat A, Berhe N, Balkew M, Yohannes M, Teklu T, Gadisa E, *et al.*** Epidemiological study of cutaneous leishmaniasis in Saesie Tsaeda-emba district, eastern Tigray, northern Ethiopia. *Parasit Vectors.* 2015;8(1):149. http://doi.org/cjb3.

27. **Soares L, Abad-Franch F, Ferraz G.** Epidemiology of cutaneous leishmaniasis in central Amazonia: A comparison of sex-biased incidence among rural settlers and field biologists. *Trop Med Int Heal.* 2014;19(8):988-95. http://doi.org/f583zh.

28. **Aguado M, Espinosa P, Romero-Maté A, Tardío JC, Córdoba S, Borbujo J.** Brote de leishmaniasis cutánea en el municipio de Fuenlabrada. *Actas Dermosifiliogr.* 2013;104(4):334-42. http://doi.org/f2h82k.

29. **Cota GF, de Sousa MR, Fereguetti TO, Saleme PS, Alvarisa TK, Rabello A.** The cure rate after placebo or no therapy in American cutaneous leishmaniasis: A systematic review and meta-analysis. *PLoS One.* 2016;11(2): e0149697. http://doi.org/f8sszx.

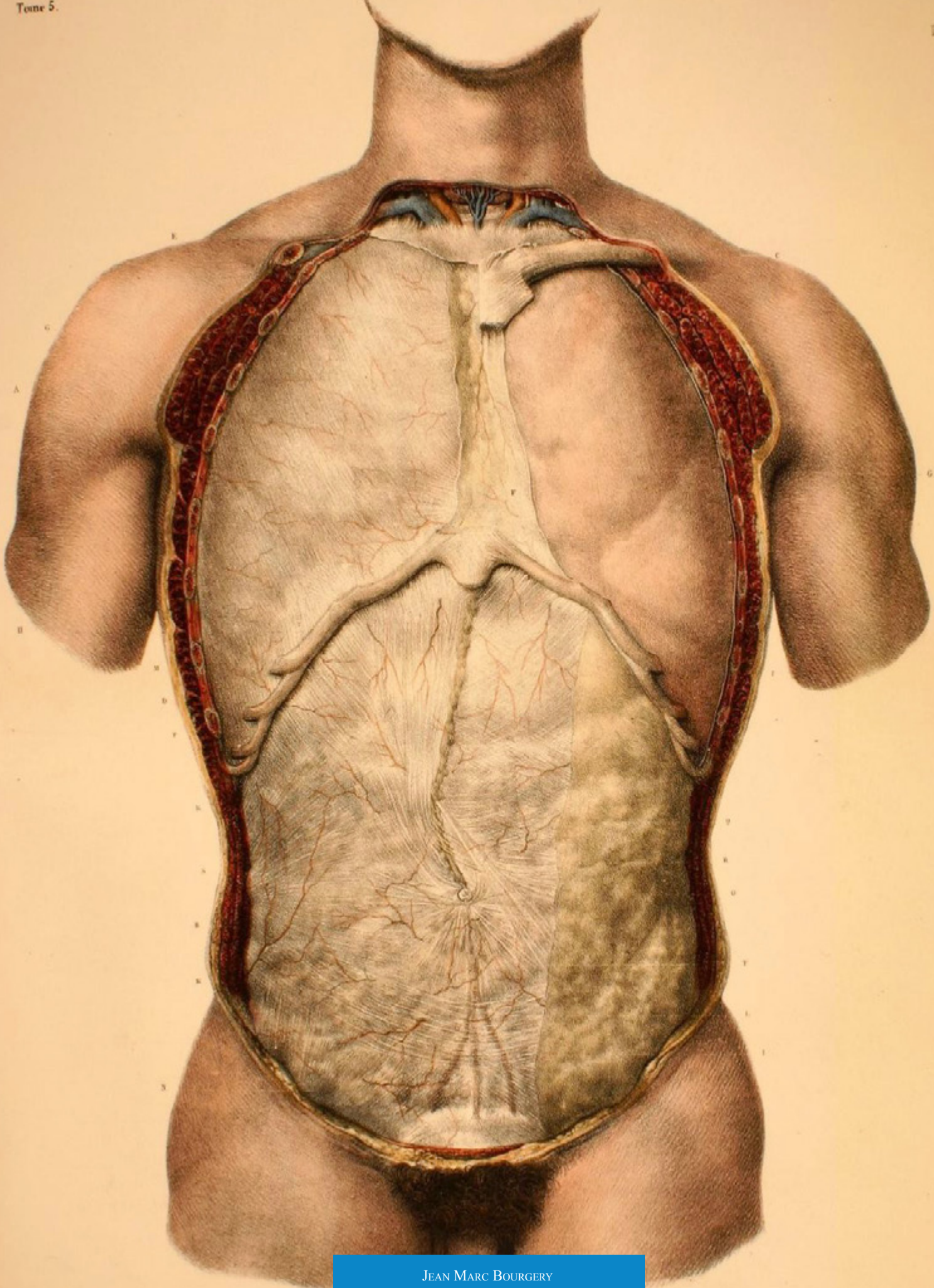
30. **Pontello R, Gon-Ados S, Ogama A.** American cutaneous leishmaniasis: epidemiological profile of patients treated in Londrina from 1998 to 2009. *An Bras Dermatol.* 2013;88(5):748-53. http://doi.org/gcbvc4.

31. **Blanco VM, Cossio A, Martinez JD, Saravia NG.** Clinical and epidemiologic profile of cutaneous leishmaniasis in Colombian children: Considerations for local treatment. *Am J Trop Med Hyg.* 2013;89(2):359-64. http://doi.org/f46b7w.

32. **Santamaría E, Ponce N, Zipa Y, Ferro C.** Presencia en el peridomicilio de vectores infectados con Leishmania (Viannia) panamensis en dos focos endémicos en el occidente de Boyacá, piedemonte del valle del Magdalena medio, Colombia. *Biomédica.* 2006;26(1):82. http://doi.org/cjb5.

33. **Mohapatra S.** Drug resistance in leishmaniasis: Newer developments. *Trop Parasitol.* 2014;4(1):4-9. Available from: http://doi.org/cjb6.

34. **Alvar J, Vélez ID, Bern C, Herrero M, Desjeux P, Cano J, *et al.*** Leishmaniasis worldwide and global estimates of its incidence. *PLoS One.* 2012;7(5):e35671. http://doi.org/f35m7j.



Jean Marc Bourgery
"Traité complet de l'anatomie de l'homme"
Paris 1832-1854

ORIGINAL RESEARCH

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Alcohol consumption in Spanish mental health patients vs. working population

Consumo de alcohol en España en pacientes de unidades de salud mental versus trabajadores en general

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| Abstract |

Introduction: Alcohol consumption has a high prevalence in society and its chronic consumption is one of the main factors related to health condition in an individual, along with other aspects concerning lifestyle. Regarding the health-disease correlation, it is one of the main determinants of health, from an epidemiological point of view, and has been a traditional object of study from different perspectives and in diverse population groups.

Objective: To compare consumption patterns and related variables in two different groups: patients in mental health units and workers in general.

Materials and methods: Cross-sectional study in a population of 1 180 service workers and 304 patients in a mental health unit. Sociodemographic and work aspects, as well as pattern of alcohol consumption were analyzed for both populations.

Results: Differences in both groups were observed regarding the number of consumers, quantity of consumption and type of beverages consumed, differences that disappear, in part, when comparing groups of workers of both population samples.

Conclusions: Differences in the consumption pattern of both populations lead to different preventive-assistance strategies and to the need for implementing coordinated actions by specific programs among those affected.

Keywords: Alcoholism; Public Health; Occupational Health; Mental Health (MeSH).

| Resumen |

Introducción. El consumo de alcohol tiene una elevada prevalencia en la sociedad y su consumo crónico es uno de los principales factores relacionados con el estado de salud de los individuos, junto a otros aspectos concernientes al estilo de vida. Debido a su importancia, este tema ha sido objeto tradicional de estudio desde diferentes perspectivas epidemiológicas y en diversos colectivos poblacionales.

Objetivo. Realizar una comparativa de patrones de consumo y variables relacionadas en dos colectivos diferenciados: pacientes de unidades de salud mental y trabajadores en general.

Materiales y métodos. Estudio transversal realizado en una población de 1 180 trabajadores del sector servicios de la administración pública y 304 pacientes de una unidad de salud mental. Se analizaron variables sociodemográficas y laborales y el patrón de consumo de alcohol.

Resultados. Existen diferencias en ambos colectivos en cuanto al número de consumidores, cantidad de consumo y tipo de bebidas consumidas, diferencias que desaparecen en parte cuando se comparan colectivos de trabajadores de ambas muestras poblacionales.

Conclusiones. Las diferencias en el patrón de consumo de ambas poblaciones orientan hacia actuaciones preventivo-asistenciales distintas en ambos grupos y hacia una necesidad de implementar actuaciones coordinadas entre todos los afectados mediante programas específicos.

Palabras clave: Alcohol; Salud pública; Salud laboral; Salud mental (DeCS).

Ruiz-Flores Bistuer M, Vicente-Herrero MT, Lladosa-Marco S, Capdevila-García LM, López-González AA. Alcohol consumption in Spanish mental health patients vs. working population. Rev. Fac. Med. 2018;66(2):171-7. English. doi: http://dx.doi.org/10.15446/revfacmed.v66n2.63324.

Ruiz-Flores Bistuer M, Vicente-Herrero MT, Lladosa-Marco S, Capdevila-García LM, López-González AA. [Consumo de alcohol en España en pacientes de unidades de salud mental versus trabajadores en general]. Rev. Fac. Med. 2018;66(2):171-7. English. doi: http://dx.doi.org/10.15446/revfacmed.v66n2.63324.

Introduction

Alcoholic beverages are highly consumed worldwide. Although most adults have a low risk drinking pattern, there are people who present harmful alcohol consumption patterns, which range from daily heavy drinkers to occasional/social risk consumers. Given the danger they pose to health, these types of patterns create a public health and safety issue in almost all countries, with estimated figures of 3.3 million deaths per year attributable to alcohol consumption. (1) Nearly 5.9% of the deaths recorded in 2014 in the world were related to alcohol consumption (7.6% for men and 4% for women). (2)

Bearing in mind that there are different modes of consumption, different types of beverages and different social and cultural characteristics in each subpopulation, morbidity and mortality may vary greatly, since they do not depend only on the amount of alcohol consumed, which may affect the estimates and the methodology used in various studies. (3) If the International Classification of Diseases ICD-10 codes (4) are taken as a basis, it is possible to see that there are more than 30 codes directly related to alcohol. Furthermore, alcohol is a leading cause of disease in more than 200 of them.

Different consumption patterns give way to very different outcomes in relation to the health condition of different population groups. Therefore, this work aims to define the consumption patterns in two well-differentiated populations: a population of workers in general and a population of patients-users of a mental health unit (MHU), regarding the quantity of measured consumption and the subjective perception of said consumption. Both concepts will be expanded to explain more precisely the impact of alcohol consumption and, in this way, identify harmful consumption patterns as quickly as possible and propose differentiated interventionist strategies. This type of intervention is recommended among psychiatric patients depending on their diagnoses. (5)

Methodology

Cross-sectional observational study in which data were collected from two different groups: workers of public administration companies in the Balearic Islands and the Valencian Community (Spain) and patients of a MHU of the Balearic Islands (Spain). In the workers population, the study was carried out during the application of specific health surveillance surveys by the companies; this procedure was carried out between January and November 2011. Informed consent was obtained from all the people involved, who participated voluntarily. Sampling was randomly obtained and it was brought to the attention of the health and safety committees. Data of MHU patients were collected between February and October 2014 during a clinical interview made by a psychiatrist, without previous selection, with voluntary participation, random sampling and informed consent for subsequent epidemiological use.

Age, sex, educational attainment (elementary, secondary and higher education), type of work (manual and non-manual) and social class (1: high, 2: medium and 3: low) were studied in both groups —as proposed by the working group of the Spanish Society of Epidemiology and the Spanish Society of Family and Community Medicine (6)—, days of consumption per week, drinks consumed and type of alcohol (wine, beer, spirits and various/all, both fermented and distilled beverages). In the case of MHU patients, social and work conditions were established (housewife, unemployed, retired, permanent worker and casual worker).

To quantify consumption, standard drinking units (SDU) were used to measure consumption/day/person. (7) The Spanish Scientific Society for Research on Alcohol, Alcoholism and Other Drug Addictions established that a SDU is equivalent to 10g of pure alcohol. (8) It should be noted that, in countries such as the USA, drinks express their alcohol content in grams of ethanol/100mL of beverage, instead of 1mL of ethanol/100mL of beverage (mL%), a formula used in almost all countries, which lowers figures by 20%. Based on this, three consumption profiles are defined: *low risk* (<14 SDU/week in women and <21 SDU/week in men), *risky* (14-20.9 SDU/week in women and 21-34.9 SDU/week in men) and *abusive* (>21 SDU/week in women and >35 SDU/week in men).

Diagnoses of MHU patients were grouped according to the ICD-10 chapters F00-F09, Organic, including symptomatic, mental disorders; F10-F19, Mental and behavioral disorders due to psychoactive substance use; F20-F29, Schizophrenia, schizotypal and delusional disorders; F30-F39 Mood [affective] disorders; F40-49, Neurotic, stress-related and somatoform disorders; F50-59, Behavioral syndromes associated with physiological disturbances and physical factors; F60-69, Disorders of adult personality and behavior; F70-79, Mental retardation; F80-89, Disorders of psychological development; and F90-98, Behavioral and emotional disorders with onset usually occurring in childhood and adolescence.

Non-drinkers were separated into abstainers and ex-drinkers (those who quit drinking within the past year). To assess the perception of consumption, the validated version of the AUDIT questionnaire was applied (9) and a descriptive analysis was carried out using frequency tables for categorical variables and descriptive statistics (mean, median, quartiles and standard deviation) for quantitative variables. A bivariate analysis was carried out for statistical inference, using the t-Student and Wilcoxon tests for continuous variables, depending on the nature of the variables.

Normality hypotheses were verified using Kolmogorov-Smirnov or Shapiro-Wilk test. In the case of categorical variables, the Chi-square or Fisher test was used depending on whether applicability conditions for the expected values were met or not. Regression models (logistic or linear) were used for multivariate analysis.

Results

The population sample included 1 180 workers and 304 patients from a MHU. The characteristics of both samples are described in Table 1.

Table 1. Characteristics of the sample.

Characteristics		WP (n=1180)		MHUP (n=304)	
Age		minimum 22; maximum 67; average 46.03		minimum 19; maximum 85; average 47.81	
Sex	Women	438	37.12%	175	57.57%
	Men	742	62.88%	129	42.43%
Educational attainment	Elementary	309	26.19%	179	58.88%
	Secondary	729	61.78%	122	40.13%
	Higher	142	12.03%	3	0.99%
Type of job	Manual	778	65.93	86	28.29%
	Not manual	402	34.07	40	13.16%
	Unemployed	0	0%	178	58.55%
Social class *	I	184	15.59	9	2.96%
	III	941	79.75	31	10.20%
	VII	55	4.66	86	28.29%

WP: working population; MHUP: mental health unit patients.
* Class I: directors/managers, university professionals, athletes and artists; class II: intermediate occupations, self-employed workers, unemployed individuals; Class III: unskilled workers.
Source: Own elaboration based on the data obtained in the study.

Considering the classification described above, according to the National Occupational Classification 2011 (NOC-11), differences were found in both populations regarding the characteristics of alcohol consumption. It is worth noting that the working population consumes alcohol by 81.19%, with a weekend consumption pattern, and mainly wine and beer, while 57.24% of MHU patients report not consuming alcohol in the past year (Table 2).

Furthermore, a striking discrepancy was observed regarding the subjective perception of alcohol consumption, since MHU patients, despite having a lower quantified alcohol consumption in comparison to the working population, have a greater consumption perception, in other words, they are more aware and accurate when it comes to assessing alcohol consumption (Figure 1). Moreover, differences were found in relation to the type of beverage consumed in both population groups (Figure 2).

Table 2. Levels of consumption among the population.

Variable		WP		MHUP	
		n	%	n	%
Frequency	Never	215	18.22%	174	57.24%
	Monthly	164	14.40%	43	14.14%
	Weekly	4	0.34%	17	5.59%
	Weekends	472	40.00%	17	5.59%
	3 days/week	29	2.46%	7	2.30%
	Every day	298	25.25%	46	15.13%
Number of drinks/day	0	215	18.22%	174	57.24%
	1	280	23.73%	59	19.41%
	2	599	18.22%	34	11.18%
	3	70	5.93%	16	5.26%
	>3	16	23.73%	21	6.91%
Type of alcohol	Beer	450	38.14%	55	18.09%
	Wine	322	27.29%	33	10.86%
	Spirits	41	3.47%	15	4.93%
	Several/all of them	152	12.88%	27	8.88%
	None	215	18.22%	174	57.24%
SDU score	Low risk	97	10,05%	104	80%
	Risky consumption	349	36.17%	15	11.54%
	Abusive consumption	519	53.78%	11	8.46%

WP: working population; MHUP: mental health unit patients; SDU: standard drinking units.
Source: Own elaboration based on the data obtained in the study.

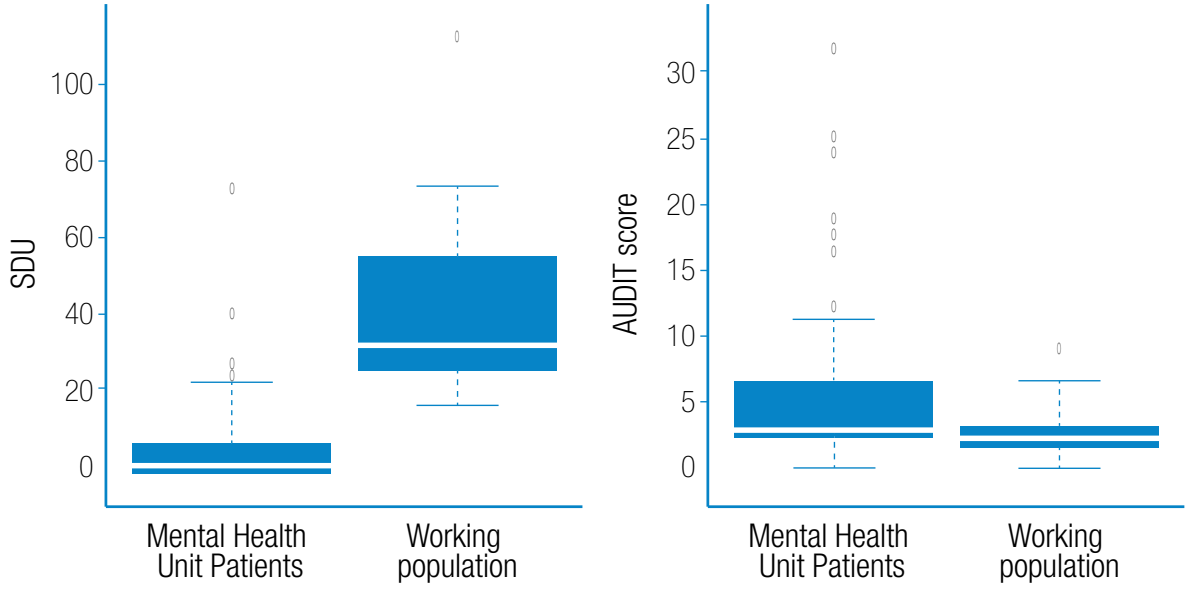

Figure 1. Quantified consumption (SDU) versus perceived consumption (AUDIT) in both populations.
Source: Own elaboration based on the data obtained in the study.

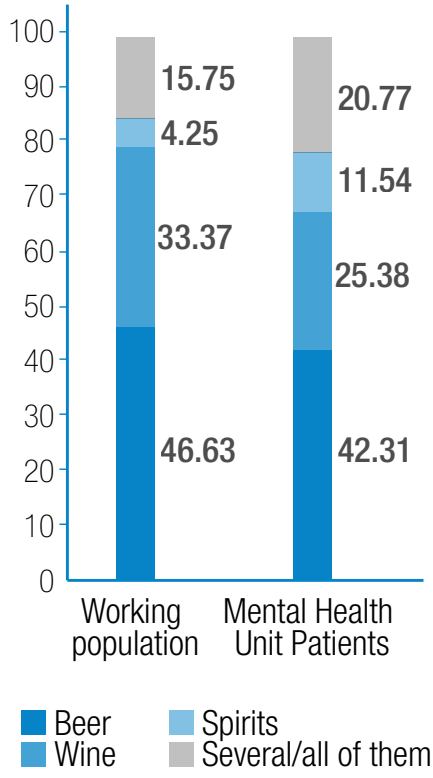

Figure 2. Comparison of type of alcohol consumed in both populations.
Source: Own elaboration based on the data obtained in the study.

The differences were modified when the workers of both samples were compared selectively by types of beverage consumed (Figure 3). However, differences in consumption perception between both populations studied remained (Figure 4).

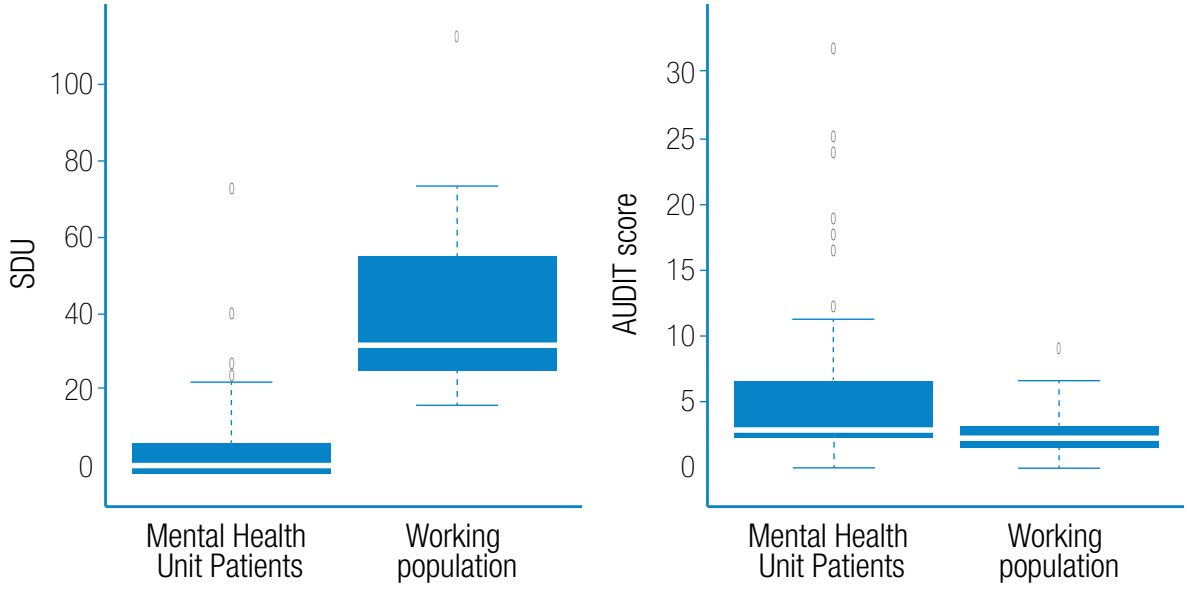

Figure 3. Comparison of workers of both populations. Quantified consumption (SDU) vs. Perceived Consumption (AUDIT).
Source: Own elaboration based on the data obtained in the study.

The comparison of current MHU consumers and the status of former drinkers before the study can be seen in Figure 5.

Discussion

The main objective of this study is to compare alcohol consumption and the perception of consumption in two well-differentiated groups of the Spanish population: working population in general and MHU patients. It is based on the hypothesis that there are qualitative and quantitative differences between them that are related to their personal, cultural, social and work conditions —in the case of those who are part of the work force. (10)

The findings of this research show high alcohol consumption among workers, which coincides with other previous investigations

with different study groups; in consequence, higher consumption figures are obtained in the hotel or construction industry, than those obtained here. (11) Aspects assessed as occasional do not coincide either, since other studies consider aspects related to work stress or work shifts —which were not assessed in this research— as predisposing factors for greater consumption. (12)

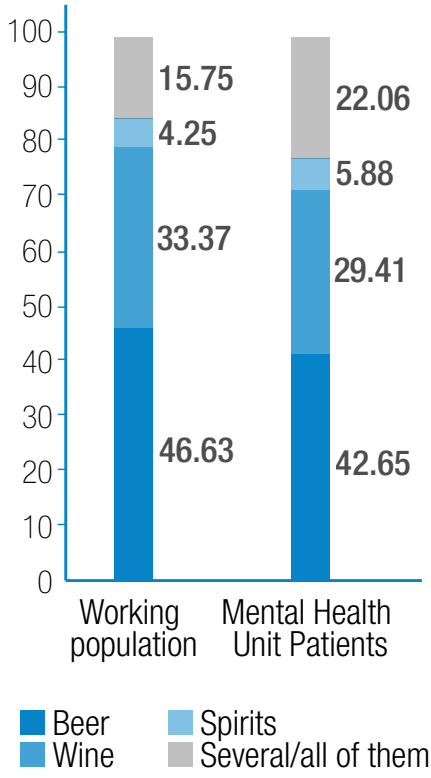

Figure 4. Comparison of type of alcohol consumed by the workers of both populations.
Source: Own elaboration based on the data obtained in the study.

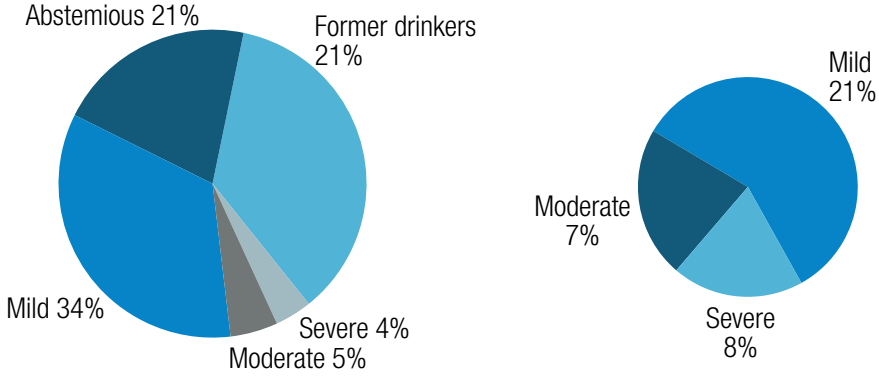

Figure 5. Comparison of consumption in former drinkers at the mental health unit: quantified consumption (SDU) versus perceived consumption (AUDIT) in workers of both populations.
Source: Own elaboration based on the data obtained in the study.

Low consumption perception observed in the workers group had already been pointed out by other authors, who were oriented towards educational interventions to support prevention. (13) Regarding the type of beverage consumed as a priority in both groups (wine and beer), there are coincidences with other researches, both in men and women (14), although Finnish authors highlight greater consumption of wine and beer among men and other types of liqueurs in women. (15)

Furthermore, the so-called *blue collar worker* is another common point in relation to greater consumption among manual workers of both groups, which coincides with other works; this may be caused by greater permissiveness and lack of skills on the part of supervisors regarding the management of abusive consumption and to the lower work risks increased by consumption. Additionally, it is pointed out that the greater the isolation of these workers, the greater the consumption of alcohol. (16)

Knowing about consumption perception favors more effective preventive actions on predictive factors. (17) In MHU patients, there was a significant ratio of non-consumers at the time of the interview (regarding consumption in the past year). However, among alcohol consumers, high levels of consumption —above the working population in general— were detected, at the expense of high-alcohol-content beverages, although beer and wine are the most common.

The correlation with greater vulnerability to alcohol consumption in psychiatric patients had already been evidenced in previous

studies and had been oriented towards coordinated actions between psychiatrists and addictologist to achieve better results. (18) However, proper consumption perception among MHU patients contrasts with the low perception among workers in general.

After inquiring about previous alcohol consumption, it was possible to see that there was a high previous consumption among the patients, being higher in lower educational levels. During the visit paid to the patients, the psychiatrist usually advised them to quit drinking, which would explain the high percentage of former drinkers. It must be taken into account that the association of both pathologies hinders the prognosis in the psychiatric process that motivates consultation and delays recovery. (19) In fact, the psychiatric pathology itself can lead to a relapse in alcohol consumption or in other types of addictions, so the psychiatric interview should consider these aspects altogether based on structured clinical interviews. (20)

Among working population in general, consumption levels are lower, but the perception of consumption is also lower, which may hinder the effectiveness of intervention programs in this group as it is considered a *falsely healthy population* and include alcohol consumption in their daily life habits.

The perception of alcohol consumption is relevant to establish prevention programs and avoid side effects and even associated deaths. Most alcohol users are unaware of health service programs or social services and, in most cases, interventions are linked to the mediation of legal services. Better management for early detection and assessment of problems associated to consumption is necessary in the light of guidelines based on evidence. (21) American authors advocate interventions from primary health services and from public health in high-risk consumers, where intervention strategies are implemented and incorporated as a routine in primary care and preventive medicine. (22-24)

The differences observed regarding consumption in relation to social class support the hypotheses of other works that seek to initiate combined actions to reduce alcohol consumption, in which additional measures are included to facilitate reaching all social groups. (25)

Differences found in this work, in terms of alcohol consumption based on social status, had already been exposed in other studies. However, in order to understand better the mechanisms and pathways that influence the differential risk among people in low and high socioeconomic statuses, all authors suggest the need for more research to characterize better the correlation between alcohol consumption, socioeconomic status and risk of disease attributable to alcohol. (26)

One of the strengths of this work is the comparison made between quantified and perceived alcohol consumption and the conditioning factors studied. Also, the comparison between two distinctly different population groups and the scores of a "healthy" population versus a group of "patients" is highlighted.

On the other hand, individual information provided by the worker or by the MHU patient is a limitation as a reference for consumption, since it may be subjective and may lead to bias of the results. Additionally, the impossibility of extrapolating the results to the working population in general is also considered a limitation since all participants are subject of the same work sector.

Conclusions

Knowledge on alcohol consumption, as well as on the subject's perception of how much they consume and the variables that influence said consumption provide basic information to design preventive strategies and more effective interventions. Future research should include other groups and aspects not covered in this work in order to modulate the results obtained here.

Conflicts of interests

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References

1. World Health Organization. Global status report on alcohol and health-2014. Geneva: WHO; 2014 [cited 2015 Sep 1]. Available from: https://goo.gl/EXK8Et.
2. World Health Organization. Alcohol. Nueva York: Nota descriptiva No. 349; 2015 [cited 2017 Sep 19]. Available from: https://goo.gl/aXwhgA.
3. **Courtney KE, Polich J.** Binge drinking in Young adults: Data, definitions, and determinants. *Psychol Bull.* 2009;135(1):142-56. http://doi.org/fghvmv.
4. World Health Organization. CIE-10: Trastornos mentales y del comportamiento: descripciones clínicas y pautas para el diagnóstico. Madrid: Meditor; 1992.
5. **Bradizza CM, Stasiewicz PR, Paas ND.** Relapse to alcohol and drug use among individuals diagnosed with co-occurring mental health and substance use disorders: a review. *Clin Psychol Rev.* 2006;26(2):162-78. http://doi.org/cmhxt6.
6. **Domingo-Salvany A, Regidor E, Alonso J, Alvarez-Dardet C, Borrell C, Doz, F, *et al.*** Una propuesta de medida de la clase social.. *Aten Primaria.* 2000;25(5):350-63.
7. **Edwards G, Marshall EJ, Cook CCH.** The treatment of drinking problems: A guide for the helping professions. New York: Cambridge University Press; 2003.
8. **Rodríguez-Martos Dauer A, Gual Solé A, Llopis Llácer JJ.** La "unidad de bebida estándar" como registro simplificado del consumo de bebidas alcohólicas y su determinación en España. *Med Clín.* 1999;112(12):446-50.
9. **Gual A, Segura L, Contel M, Heather N, Colom J.** Audit-3 and audit-4: effectiveness of two short forms of the alcohol use disorders identification test. *Alcohol Alcohol.* 2002;37(6):591-6.
10. **Ruiz-Flores Bistuer M.** Consumo de alcohol en población general trabajadora versus pacientes de unidad de salud mental [tesis doctoral]. Ibiza: Universidad de las Islas Baleares; 2016.
11. **Benavides FG, Ruiz-Forès N, Delclós J, Domingo-Salvany A.** Consumo de alcohol y otras drogas en el medio laboral en España. *Gac Sanit.* 2013;27(3):248-53. http://doi.org/f2fpn3.
12. **Morikawa Y, Sakurai M, Nakamura K, Nagasawa SY, Ishizaki M, Kido T, *et al.*** Correlation between shift-work-related sleep problems and heavy drinking in Japanese male factory workers. *Alcohol Alcohol.* 2013;48(2):202-6. http://doi.org/f4mcs6.
13. **Sprague DJ, Vinson DC.** Patient perceptions of risky drinking: knowledge of daily and weekly low-risk guidelines and standard drink sizes. *Subst Abus.* 2015;38(3):253-6. http://doi.org/cjfp.
14. **Halonen JI, Kivimäki M, Pentti J, Virtanen M, Subramanian SV, Kawachi I, *et al.*** Association of the Availability of Beer, Wine, and Liquor Outlets with Beverage-Specific Alcohol Consumption: A Cohort Study. *Alcohol Clin Exp Res.* 2014;38(4):1086-93. http://doi.org/cjfq.
15. **Kerr WC, Greenfield TK, Bond J, Ye Y, Rehm J.** Age, period and cohort influences on beer, wine and spirits consumption trends in the US National Alcohol Surveys. *Addiction.* 2004;99(9):1111-20. http://doi.org/bmk5h4.

16. **Biron M, Bamberger PA, Noyman T.** Work-related risk factors and employee substance use: insights from a sample of Israeli blue-collar workers. *J Occup Health Psychol.* 2011;16(2):247-63. http://doi.org/fr2gjb.

17. **Hwang WJ, Hong O, Kim MJ.** Factors associated with blue-collar workers' risk perception of cardiovascular disease. *J Korean Acad Nurs.* 2012;42(7):1095-104. http://doi.org/cjfr.

18. **Lang JP, Bonnewitz ML, Kusterer M, Lalanne-Tongio L.** Usage d'alcool chez les patients souffrant de troubles psychiatriques : quelles évaluations? Quelle prise en soin? *Encephale*. 2014;40(4):301-7. http://doi.org/cjfs.

19. **Alves H, Kessler F, Ratto LR.** Comorbidity: alcohol use and other psychiatric disorders. *Rev Bras Psiquiatt*. 2004;26(Suppl 1):51-3. http://doi.org/bq5wk6.

20. **Gonzalez VM, Bradizza CM, Vincent PC, Stasiewicz PR, Paas ND.** Do individuals with a severe mental illness experience greater alcohol and drug-related problems? A test of the supersensitivity hypothesis. *Addict Behav.* 2007;32(3):477-90 http://doi.org/bww5hz.

21. **Morris M, Johnson D, Morrison DS.** Opportunities for prevention of alcohol-related death in primary care: results from a population-based cross-sectional study. *Alcohol.* 2012;46(7):703-7. http://doi.org/f37rmg.

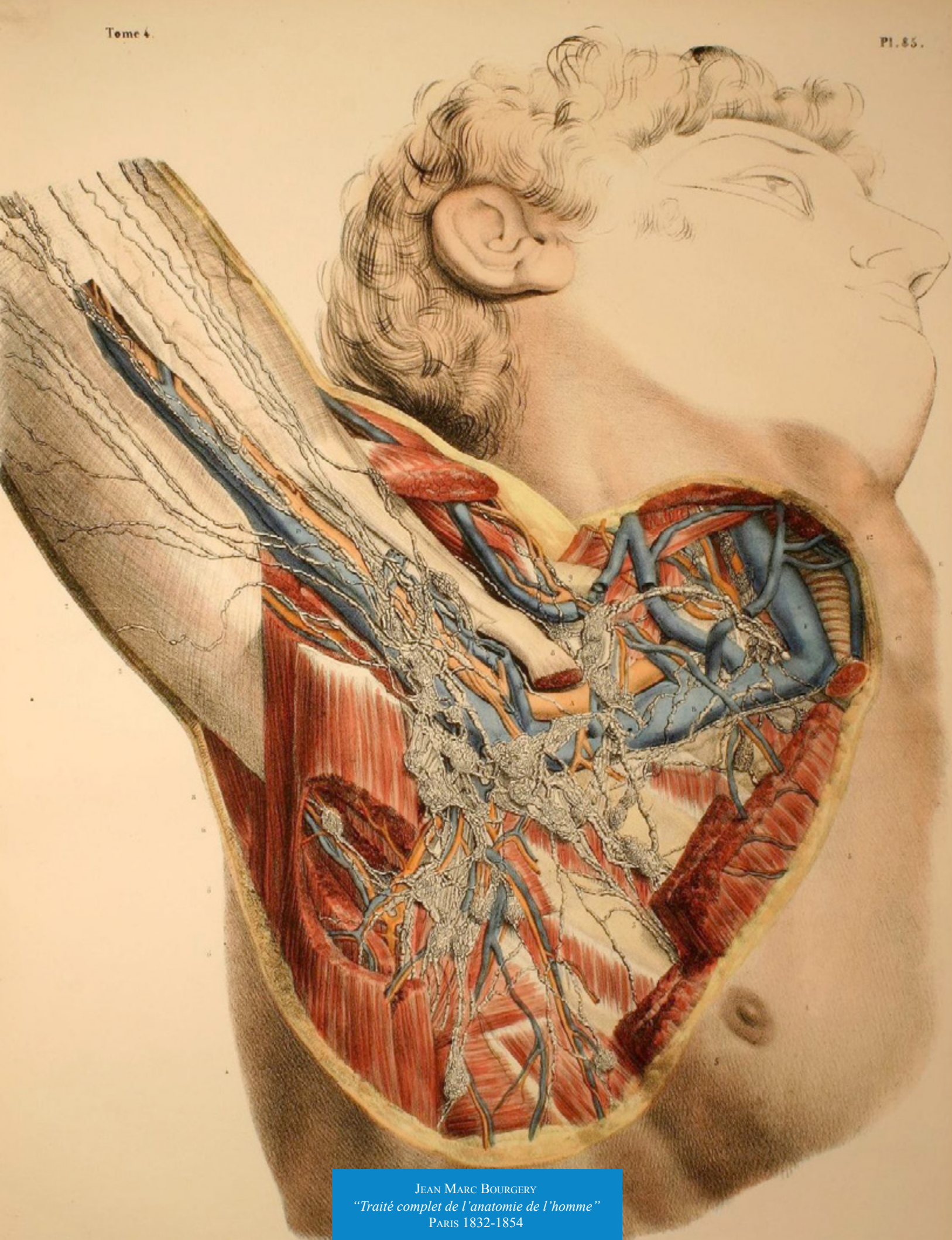
22. **Whitlock EP, Polen MR, Green CA, Orleans T, Klein J.** Behavioral counseling interventions in primary care to reduce risky/harmful alcohol use by adults: a summary of the evidence for the US Preventive Services Task Force. *Ann Intern Med.* 2004;140(7):557-68. http://doi.org/cjft.

23. **Carter MA.** Review: brief multicontact behavioural counselling interventions in primary care reduce risky or harmful alcohol use. *Evid Based Nurs.* 2004;7(4):108. http://doi.org/cm988p.

24. US Preventive Services Task Force. Screening and counseling to reduce alcohol misuse: recommendations from the United States Preventive Services Task Force. *Ann Intern Med.* 2004;140(7):1-64. http://doi.org/cjfv.

25. **Romelsjö A, Diderichsen F.** Changes in alcohol-related inpatient care in Stockholm County in relation to socioeconomic status during a period of decline in alcohol consumption. *Am J Public Health*. 1989;79(1):52-6.

26. **Jones L, Bates G, McCoy E, Bellis MA.** Relationship between alcohol-attributable disease and socioeconomic status, and the role of alcohol consumption in this relationship: a systematic review and meta-analysis. *BMC Public Health.* 2015;15:400. http://doi.org/4d6.



Jean Marc Bourgery
"Traité complet de l'anatomie de l'homme"
Paris 1832-1854

ORIGINAL RESEARCH

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Reference values for spirometric variables for allegedly healthy workers

Valores de referencia de las variables espirométricas en trabajadores cubanos supuestamente sanos

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| Abstract |

Introduction: Spirometry in workers exposed to air pollutants allows for early identification of lung function impairment. Reference values (RV) for spirometric variables (SV) obtained in Cuban workers (CW) are not available.

Objective: To obtain adequate SV-specific RV adequate for supposedly healthy CW.

Materials and methods: Retrospective, analytical study. Forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), FEV_1/FVC ratio and 25-75% forced expiration fraction for FVC (FEF_{25-75}) values were observed in 1 088 allegedly healthy, non-smoker workers from both sexes, aged between 20 - 65 years, assisted at the Instituto Nacional de la Salud de los Trabajadores (INSAT) in Havana (Cuba) between 2009 and 2015. RV were obtained for each sex as solutions of the regression function (RF) $Y=\alpha+\beta$ x age$+\chi$ x height$+\varepsilon$ (Y: FVC, FSV_1, FEV_1/FVC, FEF_{25-75}).

Results: Advanced ages were associated with lower FVC and FEV_1. Taller individuals showed higher FVC and FEV_1. A RF including age and height implied a higher coefficient of determination r^2 and lower estimation of ε error. Behavior of SV values predicted with the locally developed equation was less biased than those obtained with other foreign equations.

Conclusions: Locally developed RV may be more effective for diagnosing lung diseases in CW.

Keywords: Spirometry; Reference Values; Occupational Health (MeSH).

| Resumen |

Introducción. La espirometría permite identificar de forma precoz el deterioro pulmonar en trabajadores expuestos a contaminantes laborales. No se tienen valores de referencia (VR) para variables espirométricas (VE) en trabajadores cubanos (TC).

Objetivo. Obtener VR para VE en TC supuestamente sanos.

Materiales y métodos. Estudio retrospectivo-analítico. Se obtuvo la capacidad vital forzada (CVF), el volumen espiratorio forzado en el primer segundo (VEF_1), el cociente VEF_1/CVF y la fracción de la espiración forzada al 25-75% de la CVF (FEF_{25-75}) de 1 086 TC supuestamente sanos, no fumadores, de ambos sexos, con edades entre 20 y 65 años y atendidos en el Instituto Nacional de la Salud de los Trabajadores de La Habana, Cuba, entre 2009 y 2015. Los VR se obtuvieron para cada sexo de las funciones de regresión $Y=\alpha+\beta$ x Edad$+\chi$ x Talla$+\varepsilon$ (Y=CVF, VEF_1, VEF_1/CVF, FEF_{25-75}).

Resultados. Edades avanzadas se asociaron con CVF y VEF_1 disminuidos; la talla elevada se asoció con mayores CVF y VEF_1; una FR construida se asoció con la edad, y la talla implicó un coeficiente r^2 de determinación superior y un error menor. El comportamiento de la VE predicho con la ecuación desarrollada fue menos sesgado que el observado con otras importadas.

Conclusiones. Los VR construidos localmente pueden ser más efectivos en el diagnóstico de las afecciones pulmonares de los TC.

Palabras clave: Espirometría; Valores de referencia; Trabajador; Salud laboral (DeCS).

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Álvarez-Porbén S, González-Marrero A, Valdivieso-Valdivieso JP, Santana-Porbén S. [Valores de referencia de las variables espirométricas en trabajadores cubanos supuestamente sanos]. Rev. Fac. Med. 2018;66(2):179-85. English. doi: http://dx.doi.org/10.15446/revfacmed.v66n2.63571.

Introduction

In order to be useful, the results of a spirometric test on any person should be contrasted with reference values (RV) that conform to the characteristics of the population of origin. (1-3) However, the assessment of ventilatory function in a particular subject is still done based on RV derived from foreign populations. By way of example, the European Respiratory Society (ERS) proposed using the values reported by Roca *et al.* (4) and Roca *et al.* (5) for diagnosing respiratory diseases in Spanish subjects, although the ethnic and demographic variability of the population of the European Union (in general) and of Spain (in particular) may force to resort to RV derived from Asian and African subjects.

In the USA, Hankinson *et al.* (6) created separate RV for the Caucasian, Afro-American and Mexican-American populations studied in 81 regions of the country based on the Third National Health and Nutrition Survey (NHANES III). Spirometry values found in Caucasian subjects were higher than those reported in 1983 by Knudson *et al.* (7) and in 1981 by Crapo *et al.* (8) Furthermore, the RV of the Caucasian subjects were greater than those observed in African-Americans. (6)

The RV of the spirometric variables (SV) proposed by Roca *et al.* (5), Hankinson *et al.* (6), Knudson *et al.* (7), Crapo *et al.* (8), Quanjer *et al.* (9) and Pérez-Padilla *et al.* (10) are the most used in the Ibero-Latin-American area. According to the PLATINO Study, carried out in 2006 in five cities of Latin America (10), the RV proposed based on Caucasian and Mexican-American subjects examined during NHANES III described better the clinical reality of the countries of the area than the tables elaborated by Knudson *et al.* (7,11-13)

As of the moment in which this work is written, there are no RV for routinely measured SV proper for Cuban workers (CW). This reference gap has been filled with values imported from other populations. However, efforts have been made to document the behavior of SV in healthy, non-smoking CW; Jané-Lara *et al.* (14) obtained RV for spirometry after examining 85 non-smoking workers in the municipality of Cerro, which correlated well with those yielded by Morris *et al.* (15) and Cherniak *et al.* (16). On the other hand, Hechavarría-Miyares *et al.* (17) published RV for SV after studying the healthy workers of the most important economic sectors of the municipality of Puerto Padre in Las Tunas Province. These RV were comparable with those reported by Knudson *et al.* (7), Crapo *et al.* (8) and Morris *et al.* (15)

The RV used for the interpretation of spirometric tests in occupational health have become remarkably relevant in recent years. Many workers are exposed repeatedly and for long periods of time to countless harmful substances that may hinder lung function. The resulting lung disease may cause transient or permanent work disability, thus seriously affecting the quality of life of the workers and posing high costs for local and regional health systems. All these reasons justify the existence and operation of a medical surveillance system in occupational pneumology responsible for diagnosing alterations of lung function caused by exposure to various risk factors in the workplace and, by virtue of this, producing adequate RV to achieve this task. (3)

Considering all these aspects, the present study has been conducted with the purpose of deriving RV for SV used in the diagnosis of pulmonary conditions that may occur in the CW population attended in the National Institute of Workers' Health (INSAT by its Spanish acronym) of Havana, Cuba.

Materials and methods

This is a retrospective and analytical study conducted in the INSAT Spirometry Laboratory in Havana, Cuba.

Study series

This study series was built based on the records of the subjects treated in the laboratory between January 2009 and October 2015, after applying the corresponding inclusion and exclusion criteria. Information regarding age in completed years, sex (male/female), height (centimeters), weight (kilograms), forced vital capacity (FVC) forced expiratory volume in one second (FEV1), FEV% ratio (=FEV1/FVC) and forced expiratory flow25-75 (FEF25-75) was obtained for each subject.

Height and weight were recorded with an accuracy of 0.1 and were obtained during the spirometric examination according to the procedures prescribed by the International Biological Program. (18,19) Body mass index (BMI) was calculated using the current height and weight values of the subject. (20,21)

Inclusion criteria

Subjects of either sex, aged between 20 and 65 years, non-smokers and apparently healthy were included. In the case of workers, it was ensured that the levels of occupational exposure were the permissible according to Cuban standards.

Exclusion criteria

Subjects with the following conditions were excluded from the series: history of chronic respiratory, cardiovascular, neuromuscular diseases (including muscular dystrophy and epilepsy), otorhinolaryngological diseases (such as deviated nasal septum, vasomotor rhinitis and chronic suppurative otitis media) and osteomyoarticular diseases (kyphosis and scoliosis); systemic diseases that could affect ventilatory function such as diabetes mellitus, collagenosis, endocrinopathies, abdominal tumors and ascites; other diaphragmatic conditions; digital clubbing; insufficient weight for height (BMI <18.5kg/m^2); excessive weight for height (BMI ≥25.0kg/m^2); and pregnant women.

The records of individuals with a history of major thoracic and abdominal surgery, active peptic ulcer, occupational exposure above the permissible levels and a history of treatments with bronchodilators, β-blockers, vasodilators, antiarrhythmics and digitalis were also excluded.

Likewise, subjects for whom good morphology as part of the maneuvers performed during spirometry was difficult to obtain due to problems of understanding, cooperation or coordination were excluded, as well as patients with physical deformities of the mouth that prevented proper fitting of the mouthpiece of the spirometer, subjects who presented with a flu-like state at the time of obtaining the flow/volume curve, and subjects who had tracheomalacia or other alterations/deformities of the trachea and the airways.

The identification and registry of respiratory or systemic symptoms found in the subjects were done using the respiratory signs and symptoms questionnaire proposed by the UK Medical Research Council. (22) The spirometric measurements were made with an electronic spirometer DATOSPIR-120D (SIBEL S.A., Spain) standardized and calibrated according to locally valid procedures, and a Fleisch pneumotachometer was used as transducer.

Data processing and statistical-mathematical analysis of the results

The data retrieved from the subjects included in the study were processed using the statistical package SPSS version 19 (SPSS Inc., New York, USA) and were summarized by means of location (mean), dispersion (standard deviation) and aggregation (absolute/relative frequencies, percentages), depending on the type of the variable.

The behavior of the selected SV was modeled according to the age and height of the subject using linear regression techniques based on ordinary least squares (20):

$$\text{Equation 1: } Y = B_0 + B_1 Age + \varepsilon$$
$$\text{Equation 2: } Y = B_0 + B_2\ Height + \varepsilon$$
$$\text{Equation 3: } Y = B_0 + B_1 Age + B_2\ Height + \varepsilon.$$

Where Y: FVC, FEV_1, FEV%, FEF_{25-75}; ε: residual error; and B_0, B_1, B_2: least squares coefficients of the regression line. Separate predictive equations were built according to the sex of the subject.

For each predictive equation of the selected SV, 95% prediction intervals (PI) were obtained to define the possibility of accepting a future observation as a healthy value. (23)

The study also included a comparison of the RV obtained in this research with those used in the daily practice of the authors' laboratory. An exhaustive analysis of the equations that have been proposed for the same purposes in the international literature was not attempted; instead, the formulas of Hankinson *et al.* (6), Knudson *et al.* (7) and Hechavarría-Miyares *et al.* (17) were used as shown in Table 1.

Table 1. Predictive equations of selected spirometric variables.

Author	Variable	Women	Men
Knudson *et al.* (7). 1983	FVC	= -0.0169 x Age + 0.0444 x Height - 3.195	= -0.0298 x Age + 0.0844 x Height - 8.782
	FEV_1	= 0.0332 x Height - 0.019 x Age - 1.821	= 0.0665 x Height - 0.0292 x Age - 6.515
Hankinson *et al.* (6). 1995 *	FVC	= -0.3560 + 0.01870 x Age - 0.000382 x Age^2 + 0.00014815 x $Height^2$	= -0.1933 + 0.00064 x Age - 0.000269 x Age^2 + 0.00018642 x $Height^2$
	FEV_1	= 0.4333 - 0.00361 x Age - 0.000194 x Age^2 + 0.00011496 x $Height^2$	= 0.5536 - 0.01303 x Age - 0.000172 x Age^2 + 0.00014098 x $Height^2$
Hechavarría-Miyares *et al.* (17). 2001	FVC	= -0.020 x Age + 0.045 x Height - 3.283	= -0.021 x Age + 0.05 x Height - 3.545
	FEV_1	= 0.03 x Height - 0.020 x Age - 1.339	= 0.04 x Height - 0.0222 x Age - 2.414

* Only for Caucasian subjects.
Source: Own elaboration based on the data obtained in the study.

Ethical considerations

This research was approved by the institutional ethics committee. Considering the retrospective nature of the study, informed consent from the subjects was not required for inclusion. Data were treated preserving the confidentiality and anonymity of the person from whom they were obtained.

Results

1 370 apparently healthy CW were eligible to be included in the study series. After applying the filters established in the experimental design, the study series was finally made up of 1 086 subjects, who represented 13.5% of the historical records of the Spirometry Laboratory.

Provisions were made to include in the study series subjects with BMI values between 18.5 kg/m^2 and 29.9 kg/m^2 in selected age ranges. The BMI cutoff point was extended to include overweight subjects since the research team was interested in including subjects with a muscular component superior to the rest of the Cuban population.

Men predominated (56.9%) over women (43.1%). Only 6.2% of the subjects studied were aged ≥60 years. It should be noted that the legal age for retirement in Cuba was, until 2009, 60 years for men and 55 for women.

Table 2 shows the state of anthropometric and spirometric variables in the subjects included in the study series. Men were taller and heavier than women, but these differences were not observed in the BMI. Additionally, men had higher FVC and FEV_1 values; however, the FEV% ratio was similar for both sexes. Higher FEF_{25-75} values in men may reflect differences related to sex.

Table 2. Distribution of the anthropometric and spirometric variables of the study series according to the sex of the subject.

Variable	Women	Men
Size *	468	618
Age (years)	41.0±11.0	39.0±12.0
Height (cm)	157.0±6.0	171.0±7.0
Weight (kg)	61.0±8.0	74.0±10.0
Body mass index (kg/m^2)	24.7±2.7	25.3±2.8
FVC	3.22±0.5	4.5±0.7
FEV_1	2.6±0.4	3.7±0.6
FEV%	82.2±4.5	82.8±4.1
FEF_{25-75}	2.9±0.8	4.0±1.0

* The size of the series was of 1 086 subjects.
Source: Own elaboration based on the data obtained in the study.

Table 3 shows the statistics of the regression lines adjusted for each spirometric variable according to sex. Annex 1 shows the predictive equations developed. The values of the spirometric variable examined were inversely proportional to the age of the subject, indicating that ventilatory function naturally decreases with age. It is worth noting that about 800-950 mL of ventilatory function is lost between 20 and 65 years of age, regardless of sex.

On the other hand, the values of the corresponding spirometric variables increased with the height of the subject, which would imply that taller people may show higher ventilatory volumes. The inclusion in the regression equation of both characteristics was evident in higher values of the coefficient of determination r2 and reduced regression errors.

However, it should be noted that height did not influence the FEV% and, perhaps, its behavior is only attributable to the age of the subject. FEV% is a quotient that integrates FVC and FEV1. Although these SV change with age, it is expected that the ratio of both (in short, the FEV%) remains constant for age and independent of height. In response to this behavior, some authors (24,25) have proposed to remove height from the predictive equation for FEV%. However, for homologation purposes, height was included in the FEV% predictive equations developed for each sex in this study.

Figures 1 and 2 show the comparative behavior of the predictive equations examined in this study for FVC and FEV1 when they were evaluated for height in a reference Cuban person (men: 171 cm vs. women: 157 cm). The expected values of the spirometric variable in question were included within the corresponding 95% PI, indicating that they were indistinguishable from those yielded by the equations proposed by the authors of the essay. The average bias included with each equation used for predicting FVC was 0% for the equation presented in this paper, 6.7% for Hankinson *et al.* (6), -1.9% for Knudson *et al.* (7) and -6.9% for Hechavarría-Miyares *et al.* (17). As for FEV1, bias was 0% for the equation presented in this paper, 5.7% for Hankinson *et al.* (6), 0.6% for Knudson *et al.* (7) and -2.5% for Hechavarría-Miyares *et al.* (17).

Table 3. Statistics of the regression models adjusted for each of the spirometric variables examined according to sex, age and height of the subject.

Characteristic	Equation	Men			Women		
		Coefficients	r^2	E	Coefficients	r^2	E
FVC	Age	B1= -0.03	0.23	0.61	B1 = -0.02	0.22	0.41
	Height	B2= 0.06	0.41	0.53	B2 = 0.05	0.36	0.38
	Age ∪ Height	B1= -0.02	0.53	0.48	B1 = -0.02	0.50	0.33
		B2= 0.05			B2 = 0.04		
FEV_1	Age	B1= -0.03	0.32	0.50	B1 = -0.02	0.34	0.32
	Height	B2= 0.05	0.40	0.46	B2 = 0.04	0.32	0.31
	Age ∪ Height	B1= -0.02	0.60	0.39	B1 = -0.02	0.57	0.26
		B2= 0.04			B2 = 0.03		
FEV%	Age	B1= -0.10	0.15	3.8	B1 = -0.2	0.15	4.1
	Height	B2= 0.05	0.01	4.1	B2 = 0.01 *	0.00	4.5
	Age ∪ Height	B1= -0.13	0.15	3.7	B1 = -0.16	0.15	4.2
		B2= -0.00 *			B2 = -0.04		
FEF25-75	Age	B1= -0.04	0.23	0.89	B1 = -0.003	0.24	0.66
	Height	B2= 0.06	0.17	0.93	B2 = 0.04	0.11	0.72
	Age ∪ Height	B1= -0.03	0.33	0.84	B1 = -0.03	0.31	0.63
		B2= 0.05			B2 = 0.03		

∪: operator "AND".
* p <0.05.
Source: Own elaboration based on the data obtained in the study.

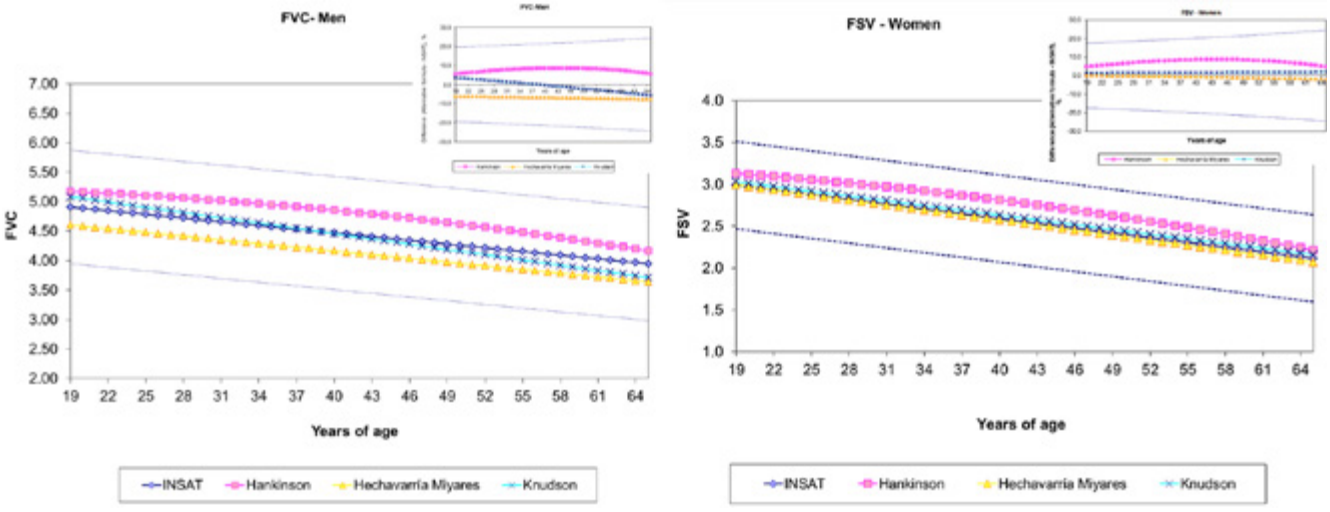

Figure 1. Comparative behavior of different predictive equations of forced vital capacity (FVC).
Dashed lines: 95% prediction intervals for the predicted FVC value. Box: bias in the predicted FVC value caused by the predictive equations.
Source: Own elaboration based on the data obtained in the study.

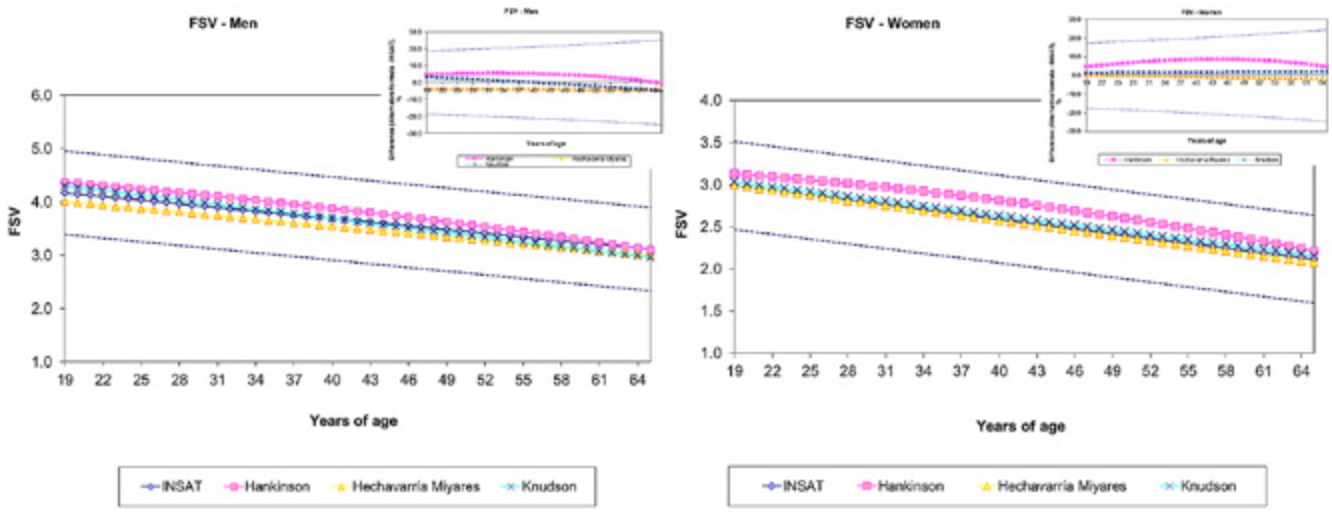

Figure 2. Comparative behavior of different predictive equations of forced expiratory volume in the first second (FEV_1).
Dashed lines: 95% prediction intervals for the predicted FEV_1 value. Box: bias in the predicted FEV_1 value caused by the predictive equations.
Source: Own elaboration based on the data obtained in the study.

Finally, Figure 3 shows the behavior of the FEV% predictive equations according to the sex of the patient; the values estimated by the alternative equations were included within the 95% PI for the INSAT formula. Bias generated by the different examined equations was 0% for the equation presented in this paper, -2.4% for Hankinson *et al.* (6), 1.0% for Knudson *et al.* (7) and 3.3% for Hechavarría-Miyares *et al.* (17).

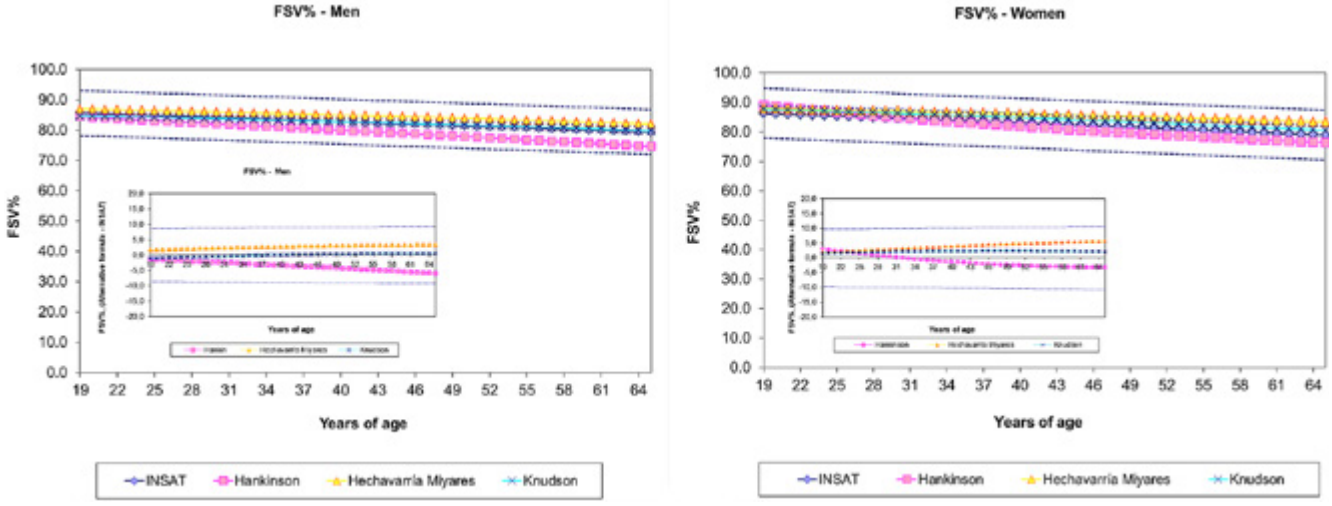

Figure 3. Comparative behavior of different predictive equations for the FEV % ratio.
Dashed lines: 95% prediction intervals for the predicted FEV% value. Box: bias in the predicted FEV% value caused by predictive equations.
Source: Own elaboration based on the data obtained in the study.

Discussion

This work has provided RV and the corresponding predictive equations of the SV assessed in subjects attended in an occupational health institution. In agreement with previous reports, the behavior of the corresponding spirometric variable was dependent on the subject´s sex. With known height values, FVC and FEV_1 values decreased with age, whereas taller subjects showed higher FVC and FEV_1 values when age was set. It was also verified that the RV of the SV predicted using formulas described in the international literature were included within the 95% PI of the equations developed in this work with the subjects treated by the authors. The bias introduced by such formulas was, in any case, <10% of the value obtained with the equations developed locally. In addition, it was verified that the VFE_1/CVF quotient behaved as described above.

All of this points towards the predictive validity of the set of formulas proposed here for the description of the SV of interest, thus making possible its introduction in diagnostic exercises conducted as part of the practice in occupational health in the reference institution.

The construction of RV for a specified biological variable by suitably developed predictive equations has been discussed in the past. (2,26,27) The RV reflect the expected behavior of the variable in a specific subject to enable the possibility of inferring making inferences about the affectation that a disease may cause. (28) Thus, the presence of the disease may be suspected if the value obtained from the biological variable exceeds a critical point placed, for example, two standard deviations to the right of the one yielded by the predictive equation. (29)

In this study, the RV for the SV were obtained from the retrospective analysis of the databases belonging to the authors' laboratory after the

application of the corresponding filters. The existence of computer systems for collecting and storing all kinds of data regarding the patients, and the realization that an important part of this data comes from apparently healthy subjects makes possible the cost-effective construction of predictive equations for observing the behavior of a biological variable that may be quickly transferred to diagnosis. (30-33) Future research should include the assessment of the diagnostic validity of predictive equations developed locally in cases of chronic obstructive pulmonary diseases such as bronchial asthma, asbestosis, silicosis and pulmonary fibrosis, using the ROC methodology. (34,35)

Body weight was excluded from the regression model to prevent distortions due to obesity. A BMI >30 kg/m^2 may have adverse impacts on spirometric function by limiting respiratory excursion. (36,37) Furthermore, skin color was not taken into consideration for the construction of the regression models, since no differences were found between the SV examined when the present study series was distributed according to skin color. A genetic study of national scope revealed a high miscegenation of the Cuban population, making thus unnecessary to stratify it based on ethnic origins, as could be the case of other countries. (38)

Conclusions

The RV derived from the SV used to diagnose ventilatory function in supposedly healthy non-smoking CW depended on the sex and age of the worker, and were comparable with values described in the specialized literature and used in the diagnostic practice of an occupational health institution. A better assessment of the state of ventilatory function in the population of workers assisted in the institution is expected after implementation of the proposed RV.

Conflicts of interest

None stated by the authors.

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References

1. **Guirguis-Blake JM, Senger CA, Webber EM, Mularski RA, Whitlock EP.** Screening for Chronic Obstructive Pulmonary Disease: Evidence Report and systematic review for the US Preventive Services Task Force. *JAMA.* 2016;315(13):1378-93. http://doi.org/cj48.
2. **Stanojevic S, Wade A, Stocks J, Hankinson J, Coates AL, Pan H; *et al.*** Reference ranges for spirometry across all ages: A new approach. *Am J Resp Crit Care Med.* 2008;177(3):253-60. http://doi.org/cj62h6.
3. **Quadrelli S, Roncoroni A, Montiel G.** Assessment of respiratory function: Influence of spirometry reference values and normality criteria selection. *Respir Med.* 1999;93(8):523-35. http://doi.org/c7v5cg.
4. **Roca J, Burgos F, Sunyer J, Saez M, Chinn S, Anto JM, *et al.*** References values for forced spirometry. Group of the European Community Respiratory Health Survey. *Eur Resp J.* 1998;11(6):1354-62.
5. **Roca J, Sanchis J, Agusti-Vidal A, Segarra F, Navajas D Rodriguez-Roisin R, *et al.*** Spirometric reference values from a Mediterranean population. *Bull Eur Physiopathol Respir.* 1986;22(3):217-24.
6. **Hankinson JL, Odencrantz JR, Fedan KB.** Spirometric reference values from a sample of the general US population. *Am J Respir Crit Care Med.* 1999;159(1):179-87. http://doi.org/cj5b.
7. **Knudson RJ, Lebowitz MD, Holberg CJ, Burrows B.** Changes in the normal maximal expiratory flow-volume curve with growth and aging. *Am Rev Resp Dis.* 1983;127(6):725-34.
8. **Crapo RO, Morris AH, Gardner RM.** Reference spirometric values using techniques and equipment that meet ATS recommendations. *Am Rev Resp Dis.* 1981;123(6):659-64.
9. **Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH; *et al.*** Multi-ethnic reference values for spirometry for the 3-95 years age range: the global lung function 2012 equations. *Eur Resp J.* 2012;40(6):1324-43. http://doi.org/f4gqs3.
10. **Pérez-Padilla R, Valdivia G, Muiño A, López MV, Márquez MN, Montes-de Oca MM, *et al.*** Valores de referencia espirométrica en 5 grandes ciudades de Latinoamérica para sujetos de 40 o más años de edad. *Arch Bronconeumol.* 2006;42(7):317-25. http://doi.org/c2btp4.
11. **Lisanti R, Gatica D, Abal J, Delaballe E, Grañana M, Miatello R, *et al.*** Comparación de las pruebas de función pulmonar en población adulta sana de la Provincia de Mendoza, Argentina, con valores de referencia internacionales. *Rev Am Med Resp.* 2014;14(1):10-9.
12. **Torre-Bouscoulet L, Pérez Padilla R.** Ajuste de varias ecuaciones de referencia espirométrica a una muestra poblacional en México. *Salud Pública Méx.* 2006;48(6):466-73.
13. **Rojas MX, Dennis RJ.** Valores de referencia para parámetros de espirometría en la población adulta residente en Bogotá, DC, Colombia. *Biomédica.* 2010 [cited 2016 Dec 12];30(1):82-94. Available from: https://goo.gl/jU7J3a.
14. **Jané-Lara A, Reyes-Hernández D, Clúa-Calderín A, Álvarez-Herrera T, Machado-Molina D, Dalcourt-César A.** Ecuaciones de predicción derivadas de la espirometría en hombres sanos no fumadores. *Rev Cub Med Mil.* 2002 [cited 2016 Mar 3];31(4). Available from: https://goo.gl/CrTP7T.
15. **Morris JF, Koski A, Johnson LC.** Spirometric standards for healthy nonsmoking adults. *Am Rev Respir Dis.* 1971;103(1):57-67.
16. **Cherniak RM, Raber MB.** Normal standards for ventilatory function using an automated wedge spirometer. *Am Rev Respir Dis.* 1972;106(1):38-46. http://doi.org/cj5c.
17. **Hechavarría-Miyares JH, Kuper-Herrera S, Granda-Ibarra A, Rodríguez-García RR, Linares-Fleites G, Sistachs-Vega V, *et al.*** Tablas para la interpretación de los resultados espirométricos en la población laboral del Municipio Puerto Padre, Cuba. *Salud de los Trabajadores.* 2001;9(2):87-99.
18. **Weiner JS, Lourie JA.** Human biology. A guide to field methods. Oxford: International Biological Program; 1969.
19. **Lohman TG, Roche AF, Martorell R.** Anthropometric standardization reference manual. 2nd ed. Champaign: Human Kinetics Books. 1991.
20. **Waterlow JC.** Classification and definition of protein-calorie malnutrition. *Br Med J.* 1972;3(826):566-9.
21. **WHO Working Group.** Use and interpretation of anthropometric indicators of nutritional status. *Bulletin World Health Organ 1986;64(6):929-41.*
22. Standardized questionnaires on respiratory symptoms. *Br Med J.* 1960;2(5213):1665.
23. **Santana-Porbén S, Martínez-Canalejo H.** Manual de procedimientos bioestadísticos. 2nd ed. Madrid: Editorial Académica Española; 2012.
24. **Gutiérrez M.** Comparación de valores espirométricos chilenos con valores de referencia para población mejicano-americana de Estados Unidos. *Rev Chil Enf Respir.* 2001;17:267-74.
25. **Gutiérrez M, del Fiero AM, Vallejo R, Faccilongo C.** Evaluación de diferentes valores de referencia espirométricos para el diagnóstico

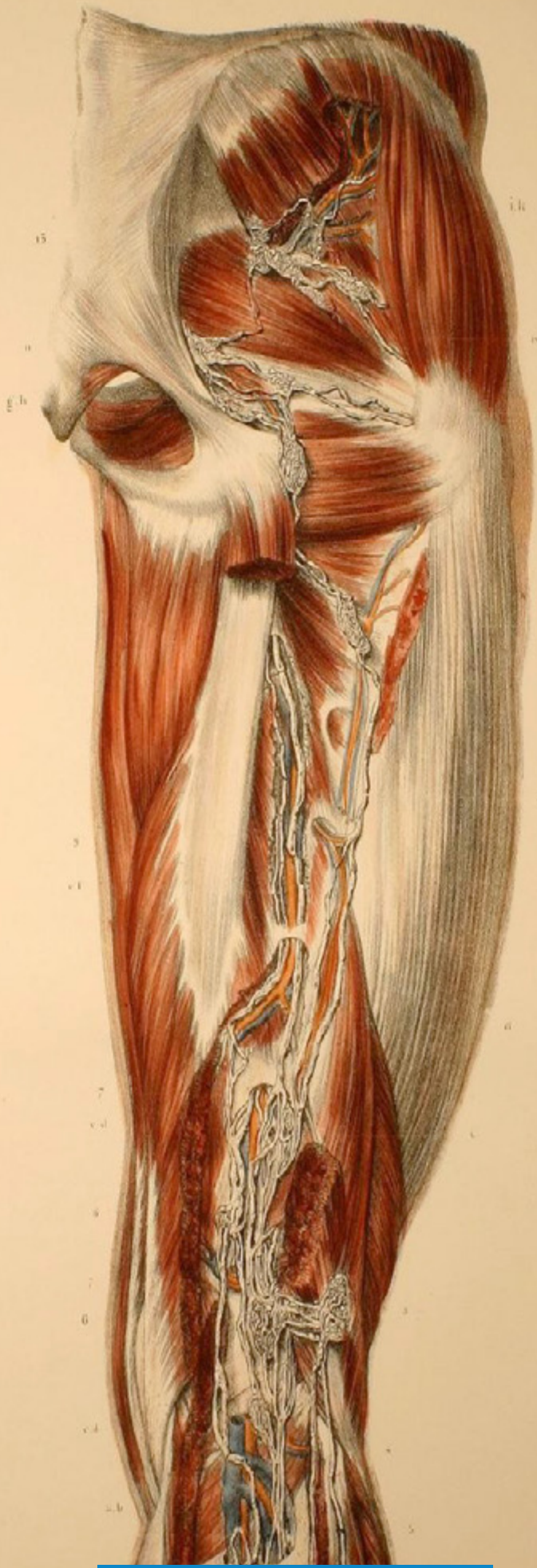
de alteración restrictiva en población chilena. *Rev Chile Enf Resp.* 2006;22(2):86-92. http://doi.org/dqt3rn.

26. **Santana-Porbén S.** Valores locales de referencia para la excreción urinaria de creatinina: Una actualización. *Rev Cubana Aliment Nutr.* 2014;24(2):220-30.
27. **Barreto-Penié J, Santana-Porbén S, Consuegra-Silveiro D.** Intervalos de referencia locales para la excreción urinaria de creatinina en una población adulta. *Nutr Hosp.* 2003;18(2):65-75.
28. **Horn PS, Pesce AJ, Copeland BE.** A robust approach to reference interval estimation and evaluation. *Clin Chem.* 1998;44(3):622-31.
29. **Hoffman RG.** Statistics in the practice of medicine. *JAMA.* 1963;185:864-73. http://doi.org/fthpv3.
30. **Kairisto V, Hänninen KP, Leino A, Pulkki K, Peltola O, Näntö V, *et al.*** Generation of reference values for cardiac enzymes from hospital admission laboratory data. *Eur J Clin Chem Clin Biochem.* 1994;32(10):789-96.
31. **Kouri T, Kairisto V, Virtanen A, Uusipaikka E, Rajamäki A, Finneman H, *et al.*** Reference intervals developed from data for hospitalized patients: Computerized method based on combination of laboratory and diagnostic data. *Clin Chem.* 1994;40(12):2209-15.
32. **Monteagudo-Rodríguez Y, Santana-Porbén S, Salabarría-González JR.** Intervalos locales de referencia para la excreción urinaria de creatinina en niños y adolescentes cubanos. *Rev Cubana Aliment Nutr.* 2015;25(1 Suppl 1):S59-90.
33. **Badell-Moore A, Bacallao-Méndez R, Mañalich-Comas R.** Sobre el establecimiento de valores de referencia de la excreción urinaria de creatinina para la población cubana. *Rev Cubana Aliment Nutr.* 2015;25(1 Suppl 1):S28-58.
34. **Pepe MS.** The statistical evaluation of medical tests for classification and prediction. Oxford: Oxford University Press; 2004.
35. **Zweig MH, Campbell G.** Receiver operating characteristic (ROC) plots: A fundamental evaluation tool in clinical medicine. *Clin Chem.* 1993;39(4):561-77.
36. **Littleton SW.** Impact of obesity on respiratory function. *Respirology.* 2012;17(1):43-9. http://doi.org/bggv2j.
37. **Al Ghobain M.** The effect of obesity on spirometry tests among healthy non-smoking adults. *BMC Pulm Med.* 2012;12:10. http://doi.org/gb3kzg.
38. **Mendizabal I, Sandoval K, Berniell-Lee G, Calafell F, Salas A, Martínez-Fuentes A, *et al.*** Genetic origin, admixture, and asymmetry in maternal and paternal human lineages in Cuba. *BMC Evol Biol.* 2008;8(1):213. http://doi.org/bd6fxd.

Annex 1

Predictive equations for the spirometric variables developed in this study.

Variable	Women	Men
FVC	= 0.040 x Height - 0.016 x Age - 2.451	= 0.053 x Height - 0.021 x Age - 3.753
FEV_1	= 0.031 x Height - 0.019 x Age - 1.517	= 0.044 x Height - 0.023 x Age - 2.916
FEV%	= -0.041 x Height - 0.162 x Age + 95.297	= -0.0002 x Height - 0.135 x Age + 88.151
FEF25-75%	= 0.032 x Height - 0.031 x Age - 0.827	= 0.045 x Height - 0.035 x Age - 2.199



Jean Marc Bourgery
"Traité complet de l'anatomie de l'homme"
Paris 1832-1854

ORIGINAL RESEARCH

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Foot ulcers: perception of patients with Type 2 diabetes

Úlceras de pie: percepción de pacientes con diabetes mellitus tipo 2

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| Abstract |

Introduction: In the past decade, the incidence of diabetes *mellitus* has increased exorbitantly around the world and foot ulcer has become the most serious and costly complication, leading to possible amputation or even death.

Objective: To know the perception of diabetic patients attached to CESFAM BelarminaParedes, Futrono, Chile, regarding the occurrence of diabetic foot ulcers in 2015.

Materials and methods: Qualitative research through intrinsic case study. Non-probabilistic intentional samples of cases based on criteria and convenience (12 patients), who signed an informed consent. Information was obtained through focus groups and analysis was made using data reduction. Validity was endorsed by the Ethics Committee of the Universidad de La Frontera.

Results: Two qualitative domains were obtained out of 495 units of analysis obtained in Level I and their consequent reduction in Level III: "Concepts and experiences lived as a result of illness and healthcare team role" and "Contributions to improve quality of care".

Conclusion: Participants consider that foot ulcer is a wound. Unaware of the risks, they deem amputation as a sequel. However, patients have etiological knowledge, describe signs and symptoms, and reveal pharmacological treatment. Additionally, they state changes in daily life, work absence and degree of dependency.

Keywords: Diabetes *Mellitus* Type 2; Diabetic Foot; Primary Care Nursing (MeSH).

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| Resumen |

Introducción. En la última década, la diabetes *miellitus* ha presentado un aumento exorbitante en el mundo y la úlcera del pie se constituye como la complicación más seria y costosa, con posible amputación e inclusive la muerte.

Objetivo. Conocer la percepción de los pacientes diabéticos pertenecientes al CESFAM Belarmina Paredes en Futrono, Chile, en relación con la aparición de úlceras del pie diabético.

Materiales y métodos. Investigación cualitativa realizada mediante estudio intrínseco de casos. Muestra no probabilística, intencionada de casos por criterios y conveniencia, conformada por 12 pacientes con previa firma del consentimiento informado. La información se obtuvo por medio de grupos focales y el análisis se realizó a través de reducción de datos.

Resultados. De las 495 unidades de significado develadas en el nivel 1 y su consecuente reducción en el nivel 3, se obtuvieron dos dominios cualitativos: "Conceptos y experiencias vividas producto de la enfermedad y rol equipo de salud" y "Aportes para mejorar calidad de atención".

Conclusiones. Los participantes consideran que la úlcera del pie es una herida.Sin consciencia de riesgo, identifican la amputación como secuela; sin embargo, tienen conocimiento etiológico, describen signos, síntomas y develan tratamiento farmacológico. Expresan cambios en la vida diaria, ausencia laboral y grado de dependencia.

Palabras clave: Diabetes *mellitus* tipo 2; Pie diabético; Enfermería de atención primaria (DeCS).

Godoy-Coronao A, Illesca-Pretty M, Cabezas-Gonzáles M, Hernández-Díaz A. [Úlceras de pie: percepción de pacientes con diabetes *mellitus* tipo 2]. Rev. Fac. Med. 2018;66(2):187-94. English.doi: http://dx.doi.org/10.15446/revfacmed.v66n2.65045.

Introduction

Diabetes *mellitus* (DM) is a chronic, non-communicable disease. (1) In 2014, the World Health Organization (WHO) identified it as a pandemic and reported that 422 million people suffer from this disease worldwide. (2,3) According to the International Diabetes Federation (IDF), by 2035, this figure will reach 592 million. (4) As a result of this pathology, there are more than five million deaths per year.

One of the chronic complications of diabetes *mellitus* type 2 (DM2) is diabetic foot (DF) (3), which can result in amputation if it progresses to an ulcer. One of the consequences of such measure is the profound deterioration in patient's self-care, productivity and psychosocial functions, or even death. (2) Therefore, this is a complex disease that causes greater use of health services and requires up to 11% of the total health expenditure of each country. (3) This condition is responsible for 50% of all non-traumatic amputations. In addition, people who have one amputated leg lose the other in less than five years (5); about 20% of patients with DM2 manifest a picture of DF in the course of their life, and about 20% of them undergo amputation. (5) In Chile, in 2014, one in every 200 diabetics underwent and amputation and more than 16 000 received treatment for foot ulcers. During the last decade, the rate of amputations in patients with DM2 has increased by 28%. (6)

The measures taken by the Ministry of Health of Chile and other international organizations to prevent foot ulcers are not effective. This can be seen daily in primary health care (PHC), where patients attend the first consultation due to the presence of a skin disorder on their feet. (7) The most relevant aspect should be the identification of patients at risk, in order to act in a timely manner and prevent the onset of the lesions. The prevention of DF is important for primary care systems, since the expenses generated by the treatment of complications can be reduced —the disease requires around 54.5 billion dollars a year in Latin America only for its management— and also because the quality of life of patients can be improved, given that the disease is a fundamental part of their daily lives and that of their relatives too. (8) From this perspective, a study based on the natural history of this ailment, with prevention at different levels of care, demonstrated a reduction in amputations of up to 85% (2), which proves that DF ulcers are preventable in most cases.

Education is a fundamental tool for prevention; however, for these actions to be successful, psychological, sociocultural, interpersonal and real needs of the individual who suffers from this pathology must be considered. It is essential that this process is based on the reality and experience of patients, since many times the delivery of information does not allow an adequate participation, not forgetting that what they know and what they would like to know should also be considered. (9)

In consequence, it is important to note that inadequate perception of risk, by both the patient and the healthcare team, is a clear cause of the incorrect assessment of danger and, therefore, a human error. (10) It possible to infer that healthcare professionals should know about the perception of their users in relation to the occurrence of signs and symptoms that afflict them. All these factors justify the development of research to learn about the perception of users regarding their health condition and determine how educational and therapeutic intervention should be done at all levels of the disease and its complications. (5)

With this in mind, the personnel of a family health center (CESFAM), in southern Chile has developed multiple strategies to reduce the onset of ulcers in DF patients. However, these measures seem to be insufficient considering that out of 667 diabetic patients, 12 developed wounds to their feet, five of them underwent amputation and the remaining seven are still receiving assistance from nurses. (7)This has an impact on the consumption of human and material resources, which has increased progressively, and has become impossible to maintain.

It is important to note that, despite carrying out the activities suggested in the documents delivered by the Ministry of Health regarding the execution of DF assessments —education about the correct use of footwear, socks, nail cutting, grooming of the feet, proper feeding, and podiatric controls— and the cardiovascular health program, no favorable changes have been observed in terms of the decrease in the incidence of ulcers. For this reason, multiple analyzes have been carried out to determine the causes of this situation, without obtaining results that allow guiding effective improvement plans with patients. (7) Given this situation, research on the perception of the incidence of foot ulcers in DM2 patients who presented with wounds in 2015 is necessary with the purpose of contributing to improve their quality of life.

This study seeks to understand the perception of DM2 patients in relation to the cause to which they attribute the occurrence of ulcers on their feet. The objectives are to discover the meaning of the concept of ulcer in DF and DM2, to understand what it means to live with a DF ulcer and to investigate the role of the health team. This investigation is expected to provide relevant information to design more comprehensive strategies and treatments.

This contribution implies knowing and considering the unmet needs of these patients in care plans, cultural aspects involved and beliefs related to health behaviors and self-care, since these are elements that will act systematically as facilitators of the changes in their behavior to favor improvement.

Materials and methods

Considering the nature of the research object, a qualitative, exploratory, descriptive and interpretative paradigm was applied to an intrinsic case study (11,12), whose purpose is to describe important aspects of a little known phenomenon, document it and explain its causes.

The non-probabilistic, intentional sample of cases, based on criterion and convenience (13), consisted of 12 DM2 patients who developed DF ulcers and were treated at CESFAM in 2015. The inclusion criteria were: age ≥18 years regardless of gender; normal cognitive, oral and auditory abilities to allow an effective communication and understanding of the objective of study, and willingness to participate voluntarily in the study, previously signing an informed consent.

Focus group was selected as the qualitative technique for data collection (two groups of six members each). Testimonies were collected until reaching the point of saturation, that is, repetition of ideas or gathering enough evidence to guarantee the credibility of the investigation. (14) A guideline was used to ensure that all subjects were explored, for example: Can you say what an ulcer is for you? Have you heard of DF ulcer? What do you think was the cause for the occurrence of your ulcers? An audio recorder and field notes were used, with the corresponding authorization, to support the collection of information in an exact way, as narrated by the participants themselves.

The analysis of data followed the constant comparison scheme (15) through a generative and constructive method in which inductive coding of categories was combined with constant comparison. Progressively, information that matched the object of study was reduced in three phases that formed different types of operations: segmentation and coding of units of analysis; identification of the main topics or emerging thematic nuclei, and integration and

interpretation of the results in qualitative domains. (16,17) Information was manually structured in three levels by the researchers:

Level 1: Identification of units of analysis (textual narrations of the participating subjects) and segmentation for grouping into descriptive categories.
Level 2: A system of emerging thematic nuclei or metacategories was built from descriptive categories.
Level 3: As a consequence of the previous level, qualitative domains were identified through a sequential and transversal analysis of metacategories.

It should be noted that under this paradigm, data collection and subsequent analysis were concurrent (12), and that categorization and segmentation were two operations that were executed simultaneously because the used criterion belonged to a certain concept or topic, where the units that made reference to a certain idea were included in the corresponding categories.

Reliability was guaranteed using standards of rigor determined by: truth value or credibility (work over a prolonged period of time, continuous observation, triangulation, verification among participants), applicability or transferability (collection of abundant descriptive data, dense and meticulous descriptions), consistency or dependence (review tracks, including field notebooks, interview notes) and neutrality or confirmability (triangulation).(18)

Ethical considerations were safeguarded since this project was authorized by the Scientific Ethics Committee of the Universidad de La Frontera through Act No. 080/2016. The following ethical principles in research were considered (19,20):

1. Implicit social value since the results will provide probable social and scientific benefits.
2. Scientific validity was assured by a rigorous design, and the products were also triangulated by researchers.
3. The equitable selection of subjects was safeguarded by identifying key informants, that is, those people who contributed to the study because they were directly related to it.
4. A favorable risk-benefit ratio, focused on minimizing potential risks and increasing benefits proportionally, was accomplished following the non-maleficence and beneficence principles, without generating conflicts to the participants.
5. Independent assessment refers to non-distortion of research results, which was endorsed by the Scientific Ethics Committee of the University.
6. The informed consent, authorized by said Committee, included respect for the voluntary and conscious participation of the subjects, offering them the opportunity to raise questions and doubts, and withdraw from the study if they wished.
7. Respect for the subjects enrolled was met by giving them the possibility of changing their mind, ensuring confidentiality of the data and delivering the results of the study.

Results

Level 1

495 units of analysis, relevant to the study, were obtained and grouped into five emerging categories as shown in Table 1.

As a result of this process, five emerging categories were obtained. They are presented in Tables 2, 3, 4, 5 and 6.

Table 1. Percentage distribution of coded emergent categories.

No.	Code	Coded emergent categories	Frequency of units of analysis	
			n	%
1	SUPD	Meaning of diabetic foot ulcers	217	43.8
2	RESA	Role of the healthcare team	183	37.0
3	SVUP	Meaning of living with diabetic foot ulcer	45	9.1
4	SDM	Meaning of diabetes *mellitus* 2	34	6.9
5	SESA	Suggestions for the healthcare team	16	3.2
Total		495	100	

Source:Own elaboration based on the data obtained in the study.

Table 2. Frequency distribution of units of analysis for the category "Meaning of diabetic foot ulcers" (SUPD).

Code	Category	Frequency of units of analysis	
		n	%
Signs and symptoms (SSUP)	Loss of skin integrity	12	5.6
	Pain	9	4.2
	Change of color	7	3.2
	Increase in size	6	2.8
	Alteration of vital signs	6	2.8
	Absence of signs and symptoms	3	1.4
	Burning sensation	2	0.9
	Temperature changes	2	0.9
	Infection	2	0.9
Treatment (TUPD)	Wound care	21	9.7
	Surgical (surgical amputation-grooming)	5	2.3
	Rehabilitation after surgical intervention	5	2.3
	Prosthesis	3	1.4
	Antibiotics	2	0.9
	Special footwear	1	0.5
Cause(CUPD)	Lack of awareness of diabetic foot care	10	4.6
	Lack of awareness of the disease	9	4.2
	Home accidents	5	2.3
	Ignorance of disease	2	0.9
	Non-compliance with the regime	4	1.8
	Interventions by healthcare personnel	5	2.3

Continues.

Code	Category	Frequency of units of analysis	
		n	%
Consequences (COUP)	Amputation	18	8.3
	Psychological damage	8	3.6
	Disability	3	1.4
	Insomnia	2	0.9
	Footwear	8	3.6
Post-diabetic foot ulcer care (CPOS)	Foot care	4	1.8
	Attendance to check ups	3	1.4
	Regimen	2	0.9
	Pause in daily activities	2	0.9
Definition (DUPD)	Ignorance	7	3.2
	Wound	6	2.8
	Disinformation	3	1.4
Risk of suffering fromit (RUPD)	Ignorance	9	4.2
	Awareness of disease	5	2.3
Care before the onset diabetic foot ulcer (CPRE)	Suitable footwear	4	1.8
	Foot care	3	1.4
	Podiatric care	2	0.9
	Attendance to check ups	1	0.5
Recognition of types of ulcers (RTUL)	Gastric	4	1.8
	Leg	1	0.5
	Foot	1	0.5
Total	217	100	

Source: Own elaboration based on the data obtained in the study.

Table 3. Frequency distribution of the units of analysis of the category "Role of the healthcare team" (RESA).

Code	Category	Frequency of units of analysis	
		n	%
Identification of the healthcare team (IESA)	Physician	44	24.0
	Nurse	18	9.9
	Podiatrist	12	6.6
	Nutritionist	6	3.4
	Paramedic	2	1.1
	Surgeon	2	1.1
	Psychologist	1	0.5
	Kinesiologist	1	0.5
	Social assistant	1	0.5
Health control (CSA)	Good service	9	
	Personalized	6	3.4
	Short time for attention	6	3.4
	Different physician in each control	4	2.2
	Short hours for control	3	1.6
	Incomplete	2	1.1
	Lack of punctuality in attention	2	1.1
	Negligent	2	1.1
	Lack of scheduled controls	1	0.5
	Lack of empathy	1	0.5
Education(EDU)	Care and supervision of the feet	13	7.1
	Nail care	4	2.2
	Nutrition	3	1.6
	Footwear	1	0.5
Nutrition controls (CNUT)	Staff does not consider income	8	4.4
	Scarce resources to follow regime	4	2.2
	Lack of willingness to attend controls	3	1.6
	Nutritional education	3	1.6
Consulted services (SCON)	CESFAM	7	3.8
	Hospital	5	2.7
	Rural Health Post	2	1.1
Wound Care (CURA)	Lack of continuity in wound care	4	2.2
	Good	3	1.6
Total		183	100

CESFAM: Family health center.
Source: Own elaboration based on the data obtained in the study.

Table 4. Frequency distribution of the units of analysis of the category "Meaning of living with diabetic foot ulcer" (SVUP).

Code	Category	Frequency of units of analysis	
		n	%
Change of behavior (CACT)	Being aware of the risks of diabetic foot	12	26.7
	Real commitment to caring for diabetic foot	6	13.3
	Sharing experiences with other patients	4	8.9
Changes in daily living (CVDI)	Routine at home	7	15.6
	Dependency	6	13.3
	Labor aspects	3	6.8
Support networks (RAPO)	Family	2	4.4
	Children	2	4.4
	Evangelic church	2	4.4
	Diabetic club	1	2.2
Total		45	100

Source: Own elaboration based on the data obtained in the study.

Table 5. Frequency distribution of the units of analysis of the category "Meaning of diabetes *mellitus* 2" (SDM).

Code	Category	Frequency of units of analysis	
		n	%
Consequences of diabetes *mellitus* 2(CDM)	Diabetic foot ulcers	3	8.9
	Visual	2	5.9
	Renal	2	5.9
	Cardiac	1	2.9
	Ignorance	1	2.9
Careof diabetes *mellitus* 2(CUDM)	Pharmacotherapy	5	14.7
	Hypoglycemic regimen	2	5.9
	Alternative medicine	1	2.9
	Health check ups	1	2.9
Diabetes *mellitus* 2 (DDM)	Knowledge of etiology	4	11.8
	Ignorance	2	5.9
	Characteristics of the disease	2	5.9
Signs and symptoms of diabetes *mellitus* 2 (SSDM)	Polydipsia	4	11.8
	Weight loss	2	5.9
	Myalgia	1	2.9
	Polyuria	1	2.9
Total		34	100

Source: Own elaboration based on the data obtained in the study.

Table 6. Frequency distribution of the units of analysis of the category "Suggestions for the healthcare team" (SESA).

Code	Category	Frequency of units of analysis	
		n	%
Staff attention	Exclusive physician for diabetic patients	6	37.4
	More education	3	18.7
	Involvement of the physician in wound care	1	6.3
Material resources	Availability of prescribed medications	2	12.5
	Availability of equipment for controls	1	6.3
Health check ups	Longer time at controls	2	12.5
	Greater number of controls	1	6.3
Total		16	100

Source: Own elaboration based on the data obtained in the study.

Level 2

Three thematic nuclei or metacategories emerged at this level:

Metacategory 1: Statement regarding concepts associated with the pathology and the role of the healthcare team.
Metacategory 2: Experience of living with a DF ulcer.
Metacategory 3: Suggestions for future consultations.

Level 3

Based on the aforementioned level, two qualitative domains arose as shown in Table 7:

Table 7. Qualitative domains.

	Qualitative domains	Definition
1	Beliefs of diabetic patients associated with their pathology, the healthcare team and the experience of living with the disease.	They correspond to metacategories 1 and 2 and are directly related to specific aspects of the disease, including the concept of diabetic foot ulcer, the definition of diabetes *mellitus*, the healthcare team and what it means to live with diabetic foot ulcer.
2	Contributions from diabetic users to improve the quality of care provided by the healthcare team.	It corresponds to metacategory 3 and is directly related to the contributions made by the interviewees regarding health care for their medical problem.

Source: Own elaboration based on the data obtained in the study.

Examples of domain 1 stories:

"[...] It is a small thing that appears on the foot and gets bigger and bigger. It has to be taken care of because if you don't, it may lead to something severe like an amputation, as was my case [...]"
"[...] Diabetes is the malfunction of the pancreas [...]"
"[...] A doctor told me that the feet are like dead because blood does not circulate, so you could be set on fire and would not feel the toes because blood does not circulate, it does not reach, so you should not get close to the fire [...]"
"[...] One time, a doctor strongly hunted me down, looked at my exams and told me that I could have a stroke at any time and told me to leave. She did not even tell me the result, she only treated me once. So, the point is knowing what is happening, not that they scold you and scare you [...]"
"[...] The podiatrist cut me so deep that I drew blood and everything began at that point [...]"
"[...] The problem is that you are always treated by any physician, and only for like 15 minutes per patient. You don't have time to ask anything [...]"
"[...] The change of physician means the loss of continuity of the indications, because a physician tells you one thing and you already trust him, and then it starts all over again [...]"
"[...] Humanitarianly, I have been treated better by nurses than by physicians [...]"

Examples of domain 2 stories:

"[...] There should be a diabetes doctor, someone who will follow you up and has more specific knowledge of diabetes, someone who feels confident and committed to the issue [...]"
"[...] I would like to receive better information regarding diabetes, what the consequences of this disease are [...]"
"[...] If you are cited for exams, that they are taken early; they call you at eight o'clock and take the sample at eleven o'clock and you have to come on an empty stomach. Just imagine, I use insulin and my sugar levels drop quickly and I cannot inject myself until I eat. There should be priorities [...]"
"[...] That a doctor and a nurse checked the wounds, but there must be a doctor. Another aspect is that sometimes medications are not available and the doctor gives you the prescription so you have to buy them, so I must have money and sometimes

I don't have any. It is also assumed that medicines should not fail us [...]"
"[...] That they take a reasonable length of time for controls and that they are not done so fast. They should be done calmly because some of them just do it in a rush. Also, they should have the drugs available because the government is supposed to provide them for us and I have spent up to 22 000 Chilean pesos in the drug store when the drugs are not available in the pharmacy [...]"

Discussion

Given the specific objective of discovering the meaning of DF ulcer and DM2, some informants reported that it is a wound while others were uninformed. If they are asked about the types of ulcers, it is inferred that they do not recognize the word "ulcer" as an injury to their feet. However, the literature defines it as a "neuropathic-based clinical alteration induced by sustained hyperglycemia, in which injury and/or ulceration of the foot occurs with or without coexisting ischemia and previous traumatic trigger". (21, p1) All of this could be supported by what was expressed as "Suggestions to the healthcare team" in relation to the service provided by the staff, more education on the subject and the frequency of health checkups, since patients ask for longer interventions by the corresponding professionals.

With respect to the risk of developing a DF ulcer, the literature states that "between 40 to 50% of diabetic patients will develop an ulcer on their feet during the course of their illness and, of these, 20% will require amputation". (21, p1) However, the key informants of this study refer ignorance of the occurrence of the ulcer, which may mean that not all of them have been educated on this issue and, therefore, do not know appropriate care measures to prevent a possible injury to their feet. In this regard, it is important to note that for DF prevention, the professional team, in addition to examining the lower limbs, must be able to motivate and educate the patients to check and care for their feet daily, encouraging self-care. (22)

Subjects identified the signs and symptoms experienced when the ulcer appeared on their feet, which correlates to a large extent to the signs exposed by the literature. (23) They recognize, particularly, the lack of awareness of care as a cause associated with the occurrence of ulcers, which coincides with the lack of guidance on how to take care of the feet. (24) In turn, amputation is mentioned as a consequence that can lead to a second amputation, which is compatible with another study carried out in North America stating that 9-20% people with diabetes underwent a second amputation 12 months after the first amputation, and that, within the 5 five years after the initial amputation, 28% to 51% surviving patients would need to undergo a second intervention on the same limb. (25)

Regarding the meaning of DM2, patients stated that they know information related to its etiology and are able identify some signs and symptoms of the disease, which coincides with other studies. (26-28) These findings may arise due to inadequate perception by the healthcare team of the educational needs of the users and reveals the need to rethink a way of working that adapts to local reality and the characteristics of the community. Therefore, education is a fundamental strategy to achieve self-care and promote commitment to health. (29,30)

Regarding the second specific objective "To reveal what it means to live with a DF ulcer", patients expressed undergoing changes in the basic activities of daily life (BADL), which are "universal, related to living conditions and to basic requirements specific to each person, and imply a minimum cognitive effort, so they are acquired early in order to achieve personal independence". (31, p268) They usually included eating, grooming, bathing, dressing, personal mobility, sleep and rest.

The revelations of these discourses are related to other studies on the topic which stress that the loss of mobility, caused by the ulcer or by the treatment received by diabetic people with injuries in their feet, generates considerable restrictions in the performance of daily life activities associated with domestic work, leisure activities and work, and cause different levels of disability that, in turn, have a negative impact on the quality of life, thus generating highly stressful situations. (32,33) This could be attributed to the feeling of threat that puts the well-being of the patient at risk; therefore, the healthcare team should implement strategies that allow patients to cope with the condition, leading to important changes that require previous information and the perception of support. (34)

In relation to the third objective, "to investigate the role of the healthcare team", professionals identified by users were physicians, probably due to their intervention and decision-making at times of decompensation of the pathology, and nurses, because of ministerial protocols (35) and wound care.

Most of the informants reported that protocolized activities carried out by the healthcare team (35), including health checkups, have a good but short personalized attention and that the rotation of physicians implies the lack of follow-up and constant changes in indications. Furthermore, they expressed difficulties for obtaining appointments, lack of punctuality in attention, failure to comply with the appointments and, finally, stressed the lack of empathy of some people who perform the interventions. This may be related to work overload in employees, since the time allocated for consultation (30 minutes) is insufficient to address this type of user. It could be assumed that the aforementioned factors reflect the flaws of knowledge acquired, since not all necessary activities described to prevent the complications of DM2 are fulfilled (29), reflecting again the importance of health education in relation to the needs of users.

With regard to wound care, they are considered adequate; however, lack of continuity was reported, especially in patients who require the procedure at home, probably because of lack of personnel, lack of coordination in case the responsible professional is absent or external factors such as lack of mobility. It has been demonstrated that multidisciplinary work regarding care of DF patients may help to accelerate the healing rate of the ulcer or influence its recurrence and the occurrence of a second amputation in diabetics. (36) This could explain the need for more comprehensive care in the management of patients with DF ulcers.

Likewise, the vast majority of key informants reported that they have received nutritional education, but aspects such as income are not considered, hindering adherence to the regimen due to low family income and the implicit expenses derived from the treatment of DF ulcers. This coincides with a study stating that compliance with dietary recommendations was mostly partial. (36) The findings of this work may be related to the fact that the healthcare team does not know the characteristics and problems of the population and, therefore, care, indications and education have not been adapted to the real context of users to respond accurately to their needs. It should be borne in mind that medical and dietary treatment influence dietary behavior, so health professionals must consider sociocultural determinants when designing and implementing treatment strategies. (36)

Finally, suggestions provided by the users endorse the need for a "multidisciplinary team focused on delivering the necessary knowledge and tools to allow patients to engage in the care of their health". (22, p26) In the last 15 years, care of diabetic patients has been proven to be optimal only when financing and human resources have sufficient quality (2), so it is essential to know and understand the perception and behaviors of DM2 patients, in order to redirect the model of care towards them, incorporating comprehensive care

that includes biological, psychological, social and spiritual well-being dimensions according to the characteristics of the community. (29)

Conclusions

DF ulcer has been described as a wound associated to gastric ulcers in most cases. Without assuming the risk of developing it, users recognize the lack of self-care, home accidents and non-compliance with the diet as the cause of their occurrence. Actually, they understand that the consequence of DF is the amputation of the limb.

With respect to the meaning of DM2, a few users understand its etiology. Others identify signs and symptoms such as polydipsia, weight loss, myalgia and polyuria. In turn, pharmacological treatment has greater adherence compared to hypoglycemic regimen.

Regarding "what it means to live with a diabetic foot ulcer", they stated that they have experienced changes in daily life and in home routines, absence from work and degree of dependency.

Physicians are frequently identified as participants of the healthcare team, followed in order by nurses, podiatrists, nutritionists, paramedics, surgeons, physiotherapists, psychologists and social assistants. Additionally, activities related to the healthcare team are education, taking good care of the feet and nails, diet and appropriate footwear. About health controls, good personalized attention was reported, as well as short periods spent in care, which are insufficient and done by different doctors in each control; an exclusive physician for each patient was suggested.

In conclusion, it was confirmed that health education, based on the perceived needs of users, is one of the most important strategies for self-care and prevention of this disease. It is worth noting that the results of this study are not generalizable and only represent the opinion of the diabetic patients enrolled in the CESFAM Belarmina Paredes of the Futrono borough, who presented foot ulcers in 2015.

Conflicts of interest

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References

1. Chile. Ministerio de Salud. Guíaclínica diabetes *mellitus* tipo 2. Series guías clínicas No. XX. Santiago: Minsal; junio de 2006 [cited 2016 Sep 28]. Available from: https://goo.gl/8Lpy6r.
2. Organización Mundial de la Salud. Informe mundial sobre la diabetes. Resumen de Orientación. [cited 2017 Nov 22]. Available from: https://goo.gl/fusYeJ.
3. Ministerio de Salud. RedCronicas [Internet]. Santiago de Chile: Ministerio de Salud; 2015 [cited2016Jan05]. Available from: https://goo.gl/gMRbxN.
4. Chile. Ministerio de Salud. El desafío de la diabetes en Chile2015. Santiago de Chile: [cited 2016Dec 28]. Available from: https://goo.gl/w7uLtZ.
5. **Tapia-Rangel JC, Ruiz-Mercado H, Ochoa-González FJ, Hernández-Nieto BI.** Proporción de incidencia de amputaciones en pacientes con lesiones de pie del diabético. Revisión de tres años en el Hospital Regional Dr. Valentín Gómez Farías en Zapopan, Jalisco. *Rev. Mex. Angiol.* 2015 [cited 2016 Mar 02];43(1):9-13. Available from: https://goo.gl/tFzChD.
6. **Sapunar J.** Epidemiología de la diabetes *mellitus* en Chile. *Rev. Med. Clin. Condes.* 2016;27(2):146-151. http://doi.org/ch94.
7. Metas sanitarias CESFAM Belarmina Paredes de Futrono. Futrono: ServicioSalud Valdivia; 2015.
8. **Cifuentes-Hoyos V, Giraldo-Hoyos AP.** Factores de riesgo para pie diabético en pacientes con diabetes *mellitus* tipo 2 [tesis de pregrado]. Medellín: Universidad CES; 2010.
9. **Medina J, Sáez S, Font P, Pérez R, Marqués F.** Promoción y educación para la salud: conceptos, metodología, programas. Lleida: Milenio; 2002.
10. **Carbonel-Siam AT, Torres-Valle A.Evaluación de percepción de riesgo ocupacional.** *IngenieríaMecánica.* 2010 [cited 2016 Dec 02];13(3):18-25. Available from: https://goo.gl/nJ3dEV.
11. **Stake RE.** Investigación con estudio de casos. 2nd ed. Madrid: Morata; 1999.
12. **Latorre A.** La investigación-acción: conocer y cambiar la práctica educativa. Barcelona: Graó; 2003.
13. **Polit D, Hungler BP.** Investigación Científica en Ciencias de la Salud. 6th ed. México: McGraw-Hill; 2000.
14. **Martínez-Salgado C.** El muestreo en investigación cualitativa. Principios básicos y algunas controversias. *Ciênc. Saúde Coletiva.* 2012;17(3):613-9. http://doi.org/b9qn.
15. **Glaser BG, Strauss AL.** El método de comparación constante de análisis cualitativo. In: The discovery of Grounded Theory: strategies for qualitative research. New York: Aldine, 1967. p. 45-77.
16. **Gil-Flores J, Perera-Rodríguez VH.** Análisis informatizado de datos cualitativos. Sevilla: Kronos; 2001.
17. **Miles MB, Huberman AM.** Qualitative data analysis: a sourcebook of new methods. Beverly Hill: Sage; 1984.
18. **Guba EG, Lincoln YS.** Naturalist Inquiry. London: Sage; 1985.
19. **Lolas F, Quezada A, editors.** Pautas éticas de investigación en sujetos humanos: nuevas perspectivas. Chile: Programa Regional de Bioética OPS/OMS; 2003.
20. **González-Avila M.** Aspectos éticos de la investigación cualitativa. *Revista Iberoamericana de Educación.* 2002 [cited 2016 Nov 10];(29):85-103. Available from: https://goo.gl/zczZxk.
21. **Sánchez-Hernández A.** Guía clínica del manejo del pie diabético. Murúa-Barbenza A, editor. Servicio de cirugíaadultodel Hospital Regional Valdivia; 2007.
22. **Álvarez-Barcia J.** Eficacia de la prevención en pie diabético [tesis]. La Coruña: Universidad de La Coruña; 2014.
23. **Del Castillo-Tirado RA, Fernández-López JA, del Castillo-Tirado FJ.** Guía de práctica clínica en el pie diabético. *Archivos de Medicina.* 2014 [cited 2016 May 05];10(2:1):1-17. Available from: https://goo.gl/gsEBMZ.
24. **Ramos-Vieira-Santos IC, Freese de Carvalho E, Vieira de Souza W, Cavalcanti de Albuquerque E.** Factors associated with diabetic foot amputations. *J. Vasc. Bras.* 2015;14(1):37-45. http://doi.org/cjbf.
25. **Reiber GE.** The epidemiology of diabetic foot problems. *Diabet Med.* 1996;13(Suppl 1):S6-11.
26. **Zafra JA, Méndez JC, Failde I.** Nivel de conocimientos y autocuidados de los pacientes diabéticos atendidos en un centro de salud de El Puerto de Santa María (Cádiz). *Endocrinol. Nutr.* 2001;48:187-92. http://doi.org/f2kjnz.
27. **Valdés-Ramos E, Castillo-Oliva Y, Cedeño-Ramírez Y.** Intervención educativa en personas con diabetes *mellitus* en la provincia Granma. *Rev. Cubana Med. Gen. Integr.* 2012 [cited 2016 Feb 28];28(4):658-67. Available from: https://goo.gl/EfLENU.
28. **Siqueira-Péres D, dos Santos MA, Zanetti ML, Ferronato AA.** Dificultades de los pacientes diabéticos para el control de la enfermedad: sen-

timientos y comportamientos. *Rev. Latinoam Enfermagem.* 2007;15(6). http://doi.org/djtkm6.

29. **Pérez-Rodríguez M, Godoy S, Mazzo A, Nogueira PC, Trevizan M, Mendes I.** Cuidado en los pies diabéticos antes y después de intervención educativa. *Enferm. glob.* 2013;12(29):63-72.

30. **Castillo-Arriaga A, Delgado-Sánchez V, Carmona-Suazo JA.** Percepción de riesgo familiar a desarrollar diabetes *mellitus*. *Rev. Med. Inst. Mex. Seguro Soc.* 2006 [cited 2016 Apr 30];44(6):505-510. Available from: https://goo.gl/CrmNqP.

31. **Romero-Ayuso DM.** Actividades de la vida diaria. *Anales de psicología.* 2007 [2016 Mar 10];23(2):264-271. Available from: https://goo.gl/PsJ7xK.

32. **Boulton AJ, Kirsner RS, Vileykite L.** Clinical practice. Neuropathic diabetic foot ulcers. *N Engl J Med.* 2004;351(1):48-55.http://doi.org/dj6p77.

33. **Urzúa A, Chirino A, Valladares G.** Autoreporte de la calidad de vida relacionada con la salud en diabetes *mellitus* tipo 2. *Rev méd. Chile.* 2011;139(3):313-320. http://doi.org/ch7v8z.

34. **SepúlvedaVildósolaAC, Romero-Guerra AL, Jaramillo-Villanueva L.** Estrategias de afrontamiento y su relación con depresión y ansiedad en residentes de pediatría en un hospital de tercer nivel. *Bol. Med. Hosp. Infant. Mex.* 2012;69(5):347-354.

35. Chile. Ministerio de Salud. Guíaclínica diabetes *mellitus* tipo 2. Series guías clínicas Minsal. Santiago: Minsal; enero de 2010 [cited 2016 Mar 28]. Available from: https://goo.gl/8Lpy6r.

36. **Chávez-Courtois M, Graham C, Romero-Pérez I, Sánchez-Miranda G, Sánchez-Jiménez B, Perichart-Perera O.** Experiencia y percepciones de la diabetes gestacional y su automanejo en un grupo de mujeres multíparas con sobrepeso. *Ciênc. Saúdecoletiva.* 2014;19(6):1643-52.http://doi.org/cjbt.

ORIGINAL RESEARCH

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Effectiveness of nursing intervention to control fear in patients scheduled for surgery

Eficacia de una intervención de enfermería para control del temor en pacientes programados para cirugía

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| Abstract |

Introduction: Fear before surgery has multiple consequences that can be handled by means of nursing interventions.

Objective: To determine the effectiveness of two nursing interventions to control fear in patients scheduled for surgery.

Materials and methods: Controlled clinical trial carried out in Bucaramanga on 45 people, 15 in the intervention group (preoperative teaching and reduction of anxiety) and 30 in the control group (usual management). Sample size considered power of 0.90, alpha error of 0.05 and intervention ratio of 1:2 in the control group. Block-randomized double-blind clinical trial. Internal consistency of the evaluation format of both result labels of the Nursing Outcomes Classification (NOC) was measured using Chronbach's alpha. The reproducibility of the formats was determined using Bland-Altman plots. The effects of nursing interventions on fear were established through covariance analysis (ANCOVA).

Results: The intervention group presented a coefficient of changes in the "fear control" label, controlled by initial NOC, age and sex of 1.09 (p=0.000). The coefficient of changes in the "knowledge on therapeutic scheme" label was 1.33 (p=0.000).

Conclusion: People who received nursing interventions showed a significant decrease in fear compared to those who received usual care (control group).

Keywords: Fear; Anxiety; Surgery; Perioperative Nursing (MeSH).

| Resumen |

Introducción. El temor prequirúrgico tiene múltiples consecuencias. Este se puede controlar mediante intervenciones de enfermería.

Objetivo. Determinar la eficacia de dos intervenciones de enfermería en el control del temor en pacientes programados para cirugía.

Materiales y métodos. Ensayo clínico controlado. Grupo intervención de 15 participantes y grupo control de 30. Se consideró un poder de 0.90, un error alfa de 0.05 y una razón de intervenido a control de 1:2. La asignación aleatoria utilizó el sistema de bloques. Se usó enmascaramiento tipo doble ciego. Se midió la consistencia interna del formato de evaluación de las dos etiquetas de resultados de la Clasificación de resultados de enfermería (NOC) mediante el alfa de Chronbach. Se determinó la reproducibilidad de los formatos usando los límites de acuerdo de Bland y Altman. Los efectos de las intervenciones de enfermería en el temor fueron establecidos mediante análisis de covarianza (ANCOVA).

Resultados. El grupo intervención tuvo un coeficiente de cambios en la etiqueta "Control del temor", controlado por NOC inicial, edad y género de 1.09 (p=0.000) y su coeficiente de cambios en la etiqueta "Conocimientos: régimen terapéutico" fue de 1.33 (p=0.000).

Conclusión. Las personas que recibieron las intervenciones de enfermería presentaron una disminución significativa del temor respecto a las que recibieron la atención usual.

Palabras clave: Temor; Ansiedad; Cirugía; Enfermería perioperatoria (DeCS).

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Introduction

Surgical procedures are individual, separate and systematic manipulations on or inside the body, which may be complete, and are performed by a physician or other qualified health professional, with or without instruments, to restore torn or deficient body parts, remove diseased or injured tissue, remove foreign bodies, assist deliveries or facilitate diagnosis. (1) In consequence, surgical trauma causes a series of physiological and psychological responses that, taken to the extreme, can alter the functions of the main organ systems. (2)

Studying fear related to surgical interventions is relevant considering the usual reaction that this state generates in people who will be operated, and also because of the multiple consequences it can have during the postoperative period. Fear is a feeling that can trigger negative impacts in social, family, affective and work environments.

Several factors, which can be classified as external or internal, may cause fear before surgery. External factors include the type of surgery, the quality of medical care (3), strange environments, lack of privacy in the rooms and surgical environments, undergoing anesthesia and lack of social support. On the other hand, internal factors include age, sex, socioeconomic status, occupation, physical condition, fear of hospital environment (3), personality type, internal locus of control, poor tolerance of ambiguity and emotion-focused coping. (4)

Patient care, defined as an activity that requires personal and professional value aimed at the conservation, restoration and self-care of life, is based on the nurse-patient therapeutic relationship and is the essence of the nursing profession. (5) This activity puts into practice knowledge in standard nursing language to generate high quality care.

Nursing diagnosis defines fear as the response to perceived threats that are consciously recognized as dangerous. (6) In this way, fear experienced by patients before a surgical intervention is caused by the psychological stress to which they are exposed. (7,8) Preoperative education involves any verbal, written or audiovisual information that seeks to provide emotional support and complete information about the procedure and its complications to patients, to help them understand that the surgical procedure is safe. (9-11)

Previous studies have shown that preoperative teaching can be applied to control fear in patients, establish a better therapeutic relationship with them and their relatives, develop self-control and self-care behaviors and provide information about the surgical procedure through communication and humanization. (12-14) The information and education offered to patients through nursing interventions can reduce preoperative fear and increase the degree of satisfaction and well-being in patients and, therefore, the quality of care provided to them. (15)

The aim of this study is to evaluate the efficacy of nursing interventions in preoperative teaching and reduction of anxiety to control fear in patients scheduled for surgery, compared with usual preoperative care.

Materials and methods

Design and participants

A randomized controlled clinical trial was carried out in people scheduled for surgery in a private tertiary hospital located in the city of Bucaramanga. This hospital has two endoscopy rooms, a delivery room, and six operating rooms where 400 surgeries are performed per month on average.

This study included patients of different specialties scheduled for surgery aged >15 years, with a nursing diagnosis of fear established based on at least two defining characteristics: identification of the object of fear and a score of ≤4.0 in the "Fear control" result label. Patients who presented alterations in mental status or limitations to provide relevant information were excluded from the study.

Two evaluation labels of the *Nursing Outcomes Classification* (NOC) were used: "Fear Control", which consists of 18 indicators —five were selected—, and "Knowledge: Therapeutic Procedures", which consists of 14 indicators —six were selected. The labels evaluated through operationalization of the selected indicators are presented in Tables 1 and 2.

The improvement of the NOC score was observed through two intervention labels from the *Nursing Interventions Classification* (NIC): "Decrease in anxiety", which has 22 activities that were applied in their entirety during the first educational session, and "Preoperative teaching", which has 26 activities that were applied in their entirety during the second educational session.

Table 1. Operationalization of the fear evaluation scale.

Indicator	Never manifested	Rarely manifested	Sometimes manifested	Frequently manifested	Constantly manifested
	1	2	3	4	5
Use of effective coping strategies	No	Inquired but not used	One used without favorable outcome	Several used without favorable outcome	One used with favorable outcome
Reference to decrease in the duration of episodes	Fear 24/7	Fear six times a day	Fear four times a day	Fear twice a day	Fear once a day
Maintaining realization role	None realized	Difficulty in realizing most of them	Difficulty for realizing two	Difficulty for realizing one	All maintained
Maintaining social relations	Isolated from others	Relationships with relatives only	Relationships with relatives and friends	Relationships with relatives, friends and colleagues	Relationship with the environment
Control of fear response	Crying, aggression, logorrhea, choked voice, silence, insomnia, etc.	7-8 manifestations	5-6 manifestations	2-4 manifestations	One manifestation

Source: Own elaboration based on the data obtained in the study.

A sample size of 45 people was estimated taking into account a power of 0.90, an alpha error of 0.05, a ratio of intervened to not intervened of 1:2, an average of 3.5 in the final NOC of the control group and an average of 4.0 in the final NOC of the intervention group regarding the "fear control" outcome label, and a standard deviation of 0.5 for both groups. Randomization of the intervention was made using the block system. (16) After identifying the participants who met the inclusion criteria and prior acceptance of enrollment in the study, a nurse from the surgery department performed the randomization.

Table 2. Operationalization of the "Knowledge: therapeutic procedures" evaluation scale.

Indicator	None	Low	Moderate	High	Significant
	1	2	3	4	5
Description of the therapeutic procedure	No response	Response to one question	Response to two or three questions	Response to four questions	Response to five questions
Explanation of the purpose of the procedure	No knowledge on why the procedure is performed	Knowledge of the purpose but no comprehension	Knowledge of the purpose and request for clarification	Explanation and understanding of the purpose	Explanation and understanding of the purpose acknowledging advantages
Description of the steps of the procedure	None described	One described	Two or three described	Four described	Five described
Description of activity precautions	None described	One described	Two or three described	Four described	All precautions described
Description of restrictions related to the procedure	None described	One described	Two described	More than two described	All restrictions described
Description of possible undesirable effects	None described	Some symptom described	Two symptoms described	Three symptoms described	All side effects described

Source: Own elaboration based on the data obtained in the study.

Instruments and procedures

The researchers and evaluators of the study did not know the randomization sequence. The evaluators of the outcome of interest did not participate in the nursing intervention sessions nor did they have knowledge of the group to which each study participant was assigned.

Before the information collection phase, a pilot test was carried out in 10 participants to test instruments, interviewers' training and execution of interventions. For data collection, three formats were applied: one of focused assessment that contained basic data about the patients, preoperative information and defining characteristics for the identification of fear diagnosis; one for the evaluation of initial and final results of the "fear control" label, and one for the evaluation of initial and final results of the "Knowledge: therapeutic procedures" label.

Interventions

Participants assigned to the intervention group received two individual sessions the day before the scheduled surgery. During the sessions, two interventions proposed in the NIC (17) were used: "Reduction of anxiety" with 22 activities, and "Preoperative education" with 26 activities.

During the first session, preoperative teaching was performed to provide structured preoperative information to the patient who was going to be operated. The information was provided by means of pictures, posters, diagrams and brochures. In addition, patients had direct contact with some elements used during surgeries such as masks, anesthesia bags, venoclysis equipment, catheters, probes, cystoflo bag, oxygen therapy equipment and surgical clothing.

During the second session, activities were carried out to know the response of patients to fear, its impact on their daily lives, its characteristics, the strategies used in previous experiences and the perception regarding the situation that triggers fear. Participants were instructed on some behavioral, cognitive and sensory coping techniques. Additionally, a guided imagery protocol, a relaxation music CD and a sheet with daily affirmations were delivered to patients, while the visual analog scale was applied to measure fear. Both sessions were held the day before surgery by last-year nursing students who were trained and had experience in this type of intervention.

In contrast, the control group received the usual care provided by the health personnel of the outpatient surgery service of the hospital where the study was conducted. This care consisted in verifying compliance with the authorization and the supplies required (orthopedics material, meshes, ear valves), complete clinical history, pre-anesthetic sheet completion, additional surgery requirements (blood reservation, freeze biopsy), oral information on general instructions according to the surgical procedure, delivery of instructions, taking vital signs and weight control. The usual care ended with the pre-anesthetic assessment.

Evaluation of results

Nursing intervention for "Reduction of anxiety" was evaluated through the "Fear Control" label and the "Preoperative teaching" nursing intervention with the label "Knowledge: therapeutic procedures". Both labels coincide with the NOC. (18)

The scales of the aforementioned labels were evaluated taking into account the operationalization of the formulated indicators, which was validated and used in a previous research. (19) Said operationalization consists in transforming the question into each indicator to allow its quantification and help the patient and the evaluator to understand them easily.

Variables

The dependent variable of this study was fear control. Five indicators were considered for the "Fear control" label to determine the patient's condition and evaluate the effectiveness of the intervention. Said indicators were measured through a Likert scale, with a range from 1 to 5, going from never manifested (6) to constantly manifested. (4,18) The five indicators are: use of effective coping strategies, referring reduction of the duration of episodes, maintaining role performance, maintaining social relationships and controlling fear response.

People in both intervention and control groups were evaluated at two moments: the day before the surgery during the pre-anesthetic assessment, where the nursing diagnosis of fear was established using the focused assessment form (initial NOC), and the day of the surgical procedure before being transferred to the surgery service (final NOC). The evaluation was applied by two people so that each participant in the study was evaluated twice, at both moments. Evaluators did not know to which group the participants were assigned. The assigned score corresponded to the average of the two values given by the evaluators. In addition, variables of age, sex, marital status, socioeconomic status, schooling, weight, companion at the time of surgery, type of anesthesia, type of surgical procedure, previous surgeries, number of dependents, occupation, religion, and medical diagnosis were analyzed.

Data analysis

Once the information was collected, a database was created in the EpiInfo 6.04b program. Information was entered twice and compared with the Validate subprogram to correct errors.

Student's t-test and X2 test were performed to determine if there were statistically significant differences in the study variables between the intervention and control groups. Parametric tests were used with previous assumption of normality and equality of variances. Chronbach's alpha was used to measure the internal consistency of the evaluation format for both result labels: "Fear control" and "Knowledge: therapeutic procedures".

To determine the reproducibility of the evaluation forms, the limits were calculated according to the Bland-Altman method, which allowed comparing the scores given by both evaluators. The analysis of covariance (ANCOVA) was used to calculate the effects of nursing interventions (final NOC), controlled by the initial NOC score, age and sex. The analysis was carried out by intention of treatment.

Ethical considerations

The project was approved by the directives of the hospital where the participants of the study were recruited. It was adjusted to the guidelines provided by Resolution 8430 of 1993 of the Ministry of Health of Colombia for research on human subjects. (20) Compliance with the principles and ethical standards of the Declaration of Helsinki was guaranteed at all times. (21) The participants signed an informed consent.

Results

A total of 437 people with scheduled surgeries were evaluated, of which 227 (52%) did not meet the inclusion criteria and 165 (38%) refused to participate in the research. The remaining 45 people made up the analytical sample: 15 were assigned randomly to the intervention group and 30 to the control group as shown in Figure 1.

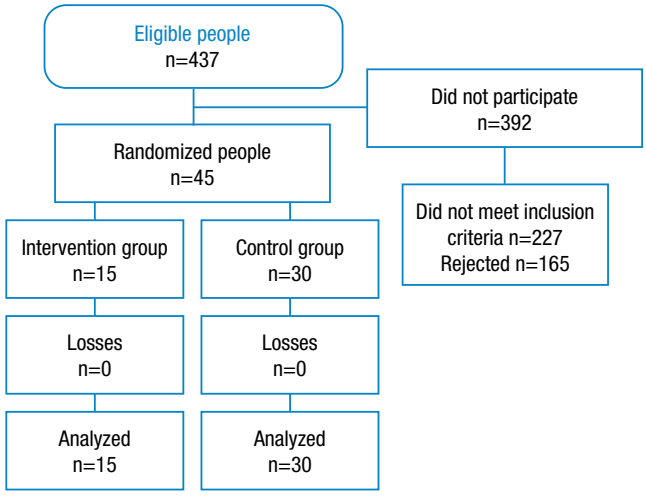

Figure 1. Flowchart of study participants.
Source. Own elaboration based on the data obtained in the study.

Table 3 shows the baseline characteristics of the participants. No statistically significant differences were found ($p < 0.05$) in any of the study variables between the intervention group and the control group.

Table 3. General characteristics of the study population.

Variable		Intervened (n=15)	Not intervened (n=30)
		Average (σ) (%)	Average (σ) (%)
Age (years)		45(17)	36(17)
Weight (kg)		63(7)	63(13)
Years of school		9(5)	10(4)
Sex: female (yes)		11(73)	16(53)
Number of dependents	≤2	8(53)	21(70)
	>2	7(47)	9(30)
Previous surgeries (yes)		8(53)	16(53)
Social stratification	1	2(13)	2(7)
	2	6(40)	8(27)
	3	1(7)	11(36)
	4 and 5	6(40)	9(30)
Occupation	Home	5(33)	9(30)
	Teaching	3(20)	5(17)
	Other	7(47)	16(53)
Marital status	Married-domestic partnership	11(73)	16(53)
	Single-divorced-widower	4(27)	14(47)
Specialty	Orthopedics	6(40)	9(30)
	General Surgery	5(33)	7(24)
	Other	4(27)	14(47)
Anesthesia	General	13(87)	27(90)
	Regional	2(13)	3(10)
	Companion (yes)	11(73)	26(87)
Object of fear	Anesthesia	12(80)	21(70)
	Needles	2(13)	3(10)
	Surgery outcome	3(20)	8(27)
	Pain	4(27)	5(17)

σ: standard deviation; %: percentage.
Source. Own elaboration based on the data obtained in the study.

Both internal consistency and reproducibility of the evaluation forms are shown in Tables 4 and 5. It should be noted that internal consistency was lower for the initial labels. In addition, data of both initial and final NOC were similar among the evaluators.

Table 4. Internal consistency of initial and final nursing result labels.

Result		Evaluator No. 1	Evaluator No. 2
Initial NOC	"Knowledge: therapeutic procedures"	0.64	0.65
	"Fear control"	0.62	0.65
Final NOC	"Knowledge: therapeutic procedures"	0.90	0.91
	"Fear control"	0.80	0.79

NOC: Nursing Outcomes Classification.
Source. Own elaboration based on the data obtained in the study.

Table 5. Limits according to the evaluation instruments.

Instrument	Initial		Final	
	Average	Limits	Average	Limits
NOC "Knowledge: therapeutic procedures"	-0.085	-0.540-0.369	-0.044	-0.453-0.364
NOC "Fear control"	-0.067	-0.50-0.372	-0.006	-0.153-0.142

NOC: Nursing Outcomes Classification.
Source. Own elaboration based on the data obtained in the study.

ANCOVA can be seen in Table 6.

Table 6. Changes in the labels *Classification of final nursing results* for "Fear control" and *Classification of final nursing results* for "Knowledge: therapeutic procedures".

Changes in the final NOC of "Fear control" label			
Variable	Coefficient	p	CI95%
Intervention	1.09	0.000	0.82-1.36
Initial NOC	0.41	0.001	0.18-0.64
Sex	0.01	0.949	-0.24-0.26
Age	0.01	0.036	0.00-0.02
Changes in the final NOC of "Knowledge: therapeutic procedures" label			
Variable	Coefficient	p	IC95%
Intervention	1.33	0.000	1.00-1.66
Initial NOC	0.12	0.404	-0.17-0.42
Sex	0.08	0.609	-0.22-0.38
Age	0.00	0.031	0.00-0.02

p: p value; CI95%: 95% confidence interval; NOC: Nursing Outcomes Classification.
Source. Own elaboration based on the data obtained in the study.

Discussion

Several studies have evaluated the effectiveness of nursing interventions to reduce anxiety and fear in patients who will undergo different types of surgeries. These intervention strategies range from clinical hypnosis (22) to guided visits to health centers. (23) Some of these studies have demonstrated the efficacy of preoperative nursing interventions on postsurgical recovery and on the control of anxiety in surgical patients. (24-26)

This study demonstrated that nursing interventions in preoperative education and anxiety reduction are effective to control fear in people scheduled for surgery. A good level of internal consistency and reproducibility of the evaluation forms was observed. In the same way, agreement limits using the Bland-Altman method indicate that the agreement of the measurements between evaluators is acceptable.

The analysis of covariance showed changes in both the "Fear control" result label (1.09) and the "Knowledge: therapeutic procedures" label (1.33), which were statistically significant after adjustment by sex and age.

The results of this study corroborate the findings found in a controlled clinical trial conducted in Bucaramanga, Colombia, in which the effectiveness of nursing interventions for the diagnosis of fear was also evaluated. (19) In said study, the group received four nursing interventions (anxiety reduction, preoperative education, preparatory sensory information and increased coping, while this study provided the group with two interventions (reduction of anxiety and preoperative education) and obtained more significant results.

The need for preoperative interventions has been acknowledged in other studies, such as the one carried out in Malaga, Spain, on the emotional impact of medical information offered to preoperative patients. (12) In that study, 87.7% of the participants preferred to be informed about their pathology and its surgical management. In turn, providing the right information did not increase anxiety.

Díez *et al.* (25) reported that the patients who received a nursing visit showed a favorable result in the study performed regarding the effect of structured and individualized nursing visits on anxiety (a term used in that study as a synonym of fear) in surgical patients.

On the other hand, Alorda *et al.* (13) state that there are statistically significant differences between the group that receives structured nursing information and that which does not receive it, according to the study they conducted on the effectiveness of information in the postoperative emotional state of patients undergoing cardiac surgery.

One of the strengths of this study was the equitable distribution of the baseline characteristics observed between both comparison groups. In addition, the evaluators involved were trained and had experience in this type of intervention, which helped obtaining more precise measurements.

The main limitation of this study was the difficulty for getting patients to attend several appointments before surgery. The reason is that surgical schedules are not planned well in advance in most cases. Therefore, the intervention sessions had to be done the day before surgery, taking advantage of the pre-anesthetic assessment appointment, and on the same day of surgery during the final evaluation.

Nursing professionals are a team of health workers with great potential to implement and evaluate interventions that facilitate the prevention and reduction of adverse outcomes such as pre-surgical fear.

Conclusions

The analysis of the results obtained in this study allow to confirm that nursing interventions in preoperative education and reduction of anxiety, suggested to control fear in patients scheduled for surgery, have a high applicability in the surgical area. The study showed that patients who received these interventions achieved a significant increase in fear control compared to patients who did not receive them.

It is necessary to further study this topic considering that nursing interventions generate a tangible impact on the population, physically and emotionally, improving their conditions during the surgical process. In this way, it is possible to justify to health promoting entities (EPS by its acronym in Spanish) and health service delivery institutions (IPS by its acronym in Spanish) the benefits that implementing these interventions represents for the patients and for the quality of the care provided.

Future research should include a cost analysis in order to demonstrate convincingly the cost-benefit of nursing interventions and to evaluate more objective outcomes such as complications, surgical times and even mortality.

The individuality of each patient makes their responses to fear vary significantly, hence the advantage of having the nursing process as a tool that allows personalized care.

The results and conclusions of this study have been validated externally to the extent that they can be extrapolated to populations >15 years, scheduled for surgery with a nursing diagnosis of fear.

Conflicts of interest

None stated by the authors.

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References

1. **Medina-Dávalos DM, Pons-Armenteros M, Coba-Coronel MG, Tigsilema-Duque MDR, Patuña-Dolcela RH.** Procedimientos de enfermería en el área quirúrgica. Ecuador: EDIMEC; 2015. [cited 2017 May 2]. Available from: https://goo.gl/GWFZaW.
2. **Carpenito LJ.** Planes de cuidados y documentación en enfermería. 2nd ed. Madrid: Interamericana; 1994. p. 36-49.
3. **Ruiz-López E, Muñoz-Cuevas JH, Olivero-Vásquz YI, Islas-Saucillo M.** Ansiedad preoperatoria en el Hospital General de México. *Rev. Med. Hosp. Gen. Mex.* 2000;63(4):231-236.
4. **Nigussie S, Belachew T, Wolancho W.** Predictors of preoperative anxiety among surgical patients in Jimma University Specialized Teaching Hospital, South Western Ethiopia. *BMC Surg.* 2014;14:67. http://doi.org/gb3p97.
5. **Juárez-Rodríguez PA, García-Campos MDL.** La importancia del cuidado de enfermería. *Rev. Enferm. Inst. Mex. Seguro Soc.* 2009;17(2):109-111.
6. **Asociación Norteamericana para el Desarrollo de Diagnósticos de Enfermería (NANDA).** Diagnósticos Enfermeros: Definiciones y clasificación. Madrid: Harcourt; 2001-2002.
7. **Shafer A, Fish MP, Gregg KM, Seavello J, Kosek P.** Preoperative anxiety and fear: a comparison of assessments by patients and anesthesia and surgery residents. *Anesth. Analg.* 1996;83(6):1285-91.
8. **Pritchard MJ.** Managing anxiety in the elective surgical patient. *Br. J. Nurs.* 2009;18(7):416-9.
9. **McDonald S, Page MJ, Beringe K, Wasiak J, Sprowson A.** Pre-operative education for hip or knee replacement. *Cochrane Database Syst. Rev.* 2014;13(5):CD003526. http://doi.org/f543gp.
10. **Laguado-Jaimes E, Yaruro-Bacca KY, Hernández-Calderón EJ.** El cuidado de enfermería ante los procesos quirúrgicos estéticos. *Enfermería global.* 2015;14(4):362-374. http://doi.org/cfx5.
11. **Díez-Álvarez E, Arrospide A, Mar J, Alvarez U, Belaustegi A, Lizaur B, *et al.*** Efectividad de una intervención preoperatoria de enfermería sobre el control de la ansiedad de los pacientes quirúrgicos. *Enferm. Clin.* 2012;22(1):18-26. http://doi.org/fg868n.
12. **Rodríguez-Navarro JC, Gómez-Gracia E, Fernández-Crehuet-Navajas J.** El Impacto emocional de la información médica en pacientes quirúrgicos. *Cuadernos de Bioética.* 2001;12:367-78.
13. **Alorda C, Gili M, González D, Pomar A, Prieto J, Aloy C.** Eficacia de la información sobre el estado emocional postoperatorio en pacientes sometidos a cirugía cardiaca. *Enferm Clín.* 1999;9(3):109-14.
14. **Sánchez-Alonso RI, Prieto de Lamo G.** Visita preoperatoria de enfermería: evaluación de la efectividad de la intervención enfermera y percepción del paciente. *Enferm. Clin.* 2011;21(4):230-1. http://doi.org/dvfv6j.
15. **Aparcero-Bernet L, Núñez-García A, Ramos-Fernández M, Zahino-Ruiz R, Olcina-Santoja R, Romero-Sánchez M, *et al.*** La visita entrevista prequirúrgica: Intervención de enfermera e instrumento para la calidad. *Enfuro.* 2003;88:9-13.
16. **Gordis L.** Epidemiology. Philadelphia: Saunders Company; 1996.
17. **McCloskey-Dochterman J, Bulechek GM.** Clasificación de Intervenciones de Enfermería (CIE). 2nd ed. España: Síntesis S.A.
18. **Johnson M, Maas M, Moorhead S.** Clasificación de Resultados de Enfermería. 2nd Ed. Madrid: Harcourt; 2001.
19. **Orozco LC, Rangel R, López LE Rueda E, Ortíz AF.** Eficacia de las Intervenciones de Enfermería en el control del temor prequirúrgico: ensayo clínico controlado. *Actual. Enferm.* 2005;8(1):8-13.
20. **Colombia.** Ministerio de Salud. Resolución 8430 de 1993 (octubre 4): Por la cual se establecen las normas científicas, técnicas y administrativas para la investigación en salud. Bogotá D.C.; octubre 4 de 1993 [cited 14 Nov 2017]. Available from: https://goo.gl/GokC65.
21. **Asociación Médica Mundial.** Declaración de Helsinki de la Asociación Médica Mundial. Principios éticos para las investigaciones médicas en seres humanos. Fortaleza: 64.ª. Asamblea General de la AMM; 2013 [cited 2015 Feb 14]. Available from: https://goo.gl/hvf7l1.
22. **Ghoneim MM, Block RI, Sarasin DS, Davis CS, Marchman JN.** Tape-recorded hypnosis instructions as adjuvant in the care of patients scheduled for third molar surgery. *Anaesth Analg.* 2000;90(1):64-8.
23. **Lynn-Mchale D, Corsetti A, Brady-Avis E, Shaffer R, McGrory J, Rothenberg C.** Preoperative ICU tours: are they helpful? *Am J Crit Care.* 1997;6(2):106-15.
24. **Fernández MD, Luciano C, Valdivia-Salas S.** Impact of acceptance-based nursing intervention on postsurgical recovery: preliminary findings. *Span J Psychol.* 2012;15(3):1361-70.
25. **Díez-Álvarez E, Arrospide A, Mar J, Alvarez U Belaustegi A, Lizau B, *et al.*** Efectividad de una intervención preoperatoria de enfermería obre el control de la ansiedad de los pacientes quirúrgicos. *Enferm Clin.* 2012;22(1):18-26. http://doi.org/fg868n.
26. **Cuñado A, Legarre MJ, Ruíz J, Silveira de la Torre J, Caballero L, García F.** Efecto de una visita enfermera estructurada e individualizada en la ansiedad de los pacientes quirúrgicos. *Enferm Clín.* 1999;9(3):98-104.

ORIGINAL RESEARCH

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Morphometric variations of two populations of *Anopheles albitarsis* F (Diptera: Culicidae) in the Orinoquia region, Colombia

Variaciones morfométricas de poblaciones de Anopheles albitarsis F *(Diptera: Culicidae) en la Orinoquía colombiana*

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| Abstract |

Introduction: *Anopheles albitarsis* F has been reported with natural infection by *Plasmodium falciparum.* In the Orinoquía, this species is in sympatry with *Anopheles darlingi*, a major malaria vector.

Objective: To determine morphometric variations in diagnostic characters of wings and hind legs in adult mosquitoes of two populations of the Orinoquia region, where malaria is a major public health issue.

Materials and methods: Using linear and geometric morphometry approaches, wing patterns of Costa veins from wild females, females obtained from entomological series and isofamilies were analyzed. Shape and wing size were estimated. The second hindtarsomere was analyzed by means of linear morphometry.

Results: Two patterns of spots on the Costa vein of the wings were observed. Significant statistical differences ($p<0.05$) were found in wing size and shape between wild females and females obtained under laboratory conditions. In the populations studied, a PHD/HP ratio of 1.17-1.19 in the Costa vein and a 0.38-0.54 for the $DSIII_2/TaIII_2$ ratio in the second posterior tarsomere of the hind legs, proposed as diagnostic characters.

Conclusion. The studied populations of *An. albitarsis* F showed significant differences between wild females and those obtained under laboratory conditions, not only in wing size, but also in shape. New ranges presented for the diagnostic characters of the species.

Keywords: *Anopheles*; Body Size; Malaria (MeSH).

| Resumen |

Introducción. *Anopheles albitarsis* F ha sido registrada con infección natural por *Plasmodium falciparum.* En la Orinoquía, se encuentra en simpatría con *Anopheles darlingi*, un vector primario de malaria.

Objetivo. Determinar variaciones morfométricas en caracteres diagnósticos de ala y pata posterior de mosquitos adultos procedentes de dos poblaciones naturales de la Orinoquía, donde la malaria constituye un problema de salud pública.

Materiales y métodos. Se analizaron, mediante morfometría lineal y geométrica, los patrones de manchas de la vena Costa del ala de hembras silvestres, de hembras obtenidas de series entomológicas y de isofamilias. Se estimó la forma y el tamaño alar. El segundo tarsómero posterior se analizó por morfometría lineal.

Resultados. Se observaron dos patrones de manchas de la vena Costa; se encontraron diferencias estadísticamente significativas en el tamaño y forma alar ($p<0.05$) entre las hembras silvestres y las obtenidas en condiciones de laboratorio. Para las poblaciones estudiadas, se proponen como caracteres diagnósticos la proporción PHD/HP de 1.17-1.19 en la vena Costa y 0.38-0.54 para la proporción $DSIII_2/TaIII_2$ del segundo tarsómero posterior de la pata posterior.

Conclusión. Las poblaciones estudiadas de *An. albitarsis* F presentaron diferencias significativas entre las hembras silvestres y las obtenidas en condiciones de laboratorio, no solo en el tamaño de las alas, sino también en la forma. Se presentan nuevos rangos para los caracteres diagnósticos de la especie.

Palabras clave: *Anopheles*; Tamaño corporal; Malaria (DeCS).

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Introduction

Anopheles albitarsis F is a lineage characterized by sequences in the barcode region of mitochondrial DNA (1), ribosomal DNA ITS2 and fragments of the white gene (2). This species, together with *Anopheles albitarsis* I, are the only members of the *Anopheles albitarsis* Complex, found in the north of the natural barrier of the Amazon River. (2,3)

In Colombia and Venezuela, *An. albitarsis* F has been registered as *Anopheles marajoara* (4-6) because it has morphological characters similar to those of other members of the *albitarsis* Complex (7-9) and, because its molecular recognition is based on DNA fragments this has not allowed a clear separation between these species. (1,2,10) In the Colombian Orinoquia, *An. albitarsis* F is considered as an opportunistic species, with a wide distribution in urban and rural areas (11), behavioral resistance to insecticides (12), experimental infection by *Plasmodium vivax* (13) and entomological inoculation rates of up to 5.1 of natural infection by *Plasmodium falciparum.* (14,15) In this context, *An. albitarsis* F, in sympatry with *Anopheles darlingi*, may contribute to maintaining endemicity of malaria in the Orinoquia throughout the year. (16)

The *argyritarsis* section of the subgenus *Nyssorhynchus* of *Anopheles*, that include all members of the *albitarsis* complex, is recognized by adults with hindtarsomere 5 entirely white, presence of two rows of white scales on first abdominal sternum, dark caudolateral scale tufts of abdomen, dark basal band of hindtarsomere 2; absence of sector pale spot (SP) in the Costa vein, and radial vein 3 (R3) with 1 to 3 dark spots. (17) The proportion of the basal dark band in hindtarsomere 2 ($DS\text{-}III_2$) with respect to the total length of tarsomere ($TaIII_2$) allows distinguishing two groups: one represented by *Anopheles albitarsis s.s.* and *Anopheles deaneorum* —characterized by having a range of 0.51-0.90—, and another conformed by *Anopheles oryzalimnetes, An. marajoara* and *Anopheles janconnae,* with a range of 0.28-0.63. (5) It appears that the ratio of $DS\text{-}III_2/Ta\text{-}III_2$ indirectly incorporates differences in body size from individuals in natural populations. (8) The proportion between prehumeral dark spot (PHD) and humeral pale spot (HP) in the Costa vein, with a range of 0.22-1.00, is a diagnostic character, considering that the fusion or not of the distal dark sectorial spots (DSD), subcostal pale spot (SCP) and dark preapical spot (PD) allows to recognize two different wing patterns. (6,18)

In Colombia, although *An. albitarsis* I has been registered in the Atlantic Coast (2,19) and *An. albitarsis* F in the Orinoquia (2), studies of geometric morphometry and ITS2 (rDNA) question the separation of these two lineages (10). Since these species have not been described morphologically, entomological surveillance is complex, as it is based on the taxonomic determination of eggs, larvae, pupae or genitals of males from entomological series and isofamilies obtained from wild females that, due to their geographical distribution, can be related to each lineage or with mtDNA barcode sequences (1)

In this context, morphometry of diagnostic characters in mosquitoes allows to infer biological information for natural populations, and geometric morphometric analysis, based on wing shape and size (individual wing conformation and population variation) (20,21), contributes to the taxonomic identification of the species and, therefore, to the accurate association of biological and ecological aspects. In anophelines, body size is relevant because it defines characteristics that determine its status as a malaria vector. It has been reported, for example, that males usually select females of larger body size for copulation (22, 23) and that there is a positive correlation between wing size with respect to fecundity (24), daily survival rate (25), response to *Plasmodium* infection (26) and sensitivity to insecticides. (27)

The objective of this study was to determine morphometric variations in the diagnostic characters of the wing and hind leg of *An. albitarsis* F females from two natural populations of the Colombian Orinoquía. The research was carried out using the characterization of the standardized nomenclature for the Costa wing scale spots; determination of morphometric variations in wings and, the proportion of basal dark spot of the hindtarsomere 2 with respect to total length hindtarsomere 2, by means of linear morphometry. Additionally, differences in body size by analysis of shape and wing size using geometric morphometric analysis were estimated.

Materials and methods

Entomological material

Specimens of *An. albitarsis* F from Puerto Carreño - Vichada and San José del Guaviare - Guaviare were included (Table 1).

Table 1. Geographical location of larvae and adults of *Anopheles albitarsis* F collected in two towns of the Colombian Orinoquia.

Department	Municipality	Geographical coordinates	Altitude masl	Average annual temperature *	Average annual relative humidity*	Average annual rainfall*	Year of collection	Specimens analyzed
Guaviare	San José del Guaviare (SJG)	2°34′26″N 72°38′32″O	189	25.7°C	85%	2 498mm	2009-2012	Wild (9)
								Series (2)
								Isofamilies (0)
Vichada	Puerto Carreño(VPC)	6°11′09″N 67°28′52″O	51	28.2°C	70%	2 166mm	2010	Wild (17)
								Series (11)
								Isofamilies (11)

* Environmental information consulted in the Diccionario Geográfico de Colombia (Geographic Dictionary of Colombia) (28).
Source: Own elaboration based on the data obtained in the study.

Human landing catches were conducted indoors and outdoors of dwellings with malaria cases reported, for three consecutive nights each month, for nine months, between 18:00 and 06:00 hours, 50 minutes each hour. (29) Larvae and pupae were collected from larval habitats located close to the sites were adult females were caught. (30) Live wild-females were placed in plastic bottles labeled with collection information, provided with a 10% sugar solution, and transported in thermal boxes to laboratory conditions, where they were kept alive at a temperature of 26°±1°C, relative humidity of 75-80% and a photoperiod of 12L:12D. Isofamilies were obtained by forced mating as result of one leg and wing removed from each wild-female to obtain F1 offspring. Exuviae or larva IV and pupae

were preserved in 70% ethanol labeled with the same code assigned to their wild adult parent. (31) Entomological series corresponded to the adults obtained from each immature form collected. Immature forms were placed in a five-ounce plastic cup with water from the same larval habitat; III and IV larvae were individualized to collect the emerged adult. (31) Larvae feeding was based on powdered light food for dogs (Purina® Dog Chow® Light), adding the same amount in milligrams for each series and isofamily. Wild females and males and females retrieved from immature forms maintained under controlled conditions were kept dry in Eppendorf tubes with a hole in the lid, arranged in plastic bags with silica gel.

All analyzes were carried out at the area of Insect Genetics of Economic Interest, at the Laboratory of Entomology, Faculty of Agricultural Sciences, Universidad Nacional de Colombia, Bogotá.

Protocols for mosquitoes collection procedures were approved by the Ethics Committee of the Faculty of Medicine of the Universidad Nacional de Colombia and by the protocol number 02-028 of the Institutional Review Board of the Wadsworth Center, NY State Department of Health, Albany, NY, USA. Mosquitoes sampling was supported by U.S. National Institutes of Health Grant (AI) R01 54139 "Malaria Vectors Biology in Brazil: Ecology & Genetics" and Universidad Nacional de Colombia, Bogotá, Faculty of Agricultural Sciences, Quipu code 201010012197.

Taxonomic identification was based on morphological characters (7,8), and, mtDNA-COI Barcode Region sequences. (1) gDNA was extracted from abdomens and the COI gene region was amplified using the LCO and HCO universal primers. PCR products were subjected to bidirectional sequencing and similarities with publicly available sequences on GenBank and Bold System (The Barcode of Life database) were assessed using BLAST (Basic Local Alignment Search Tool (http://blast.ncbi.nlm.nih.gov/Blast.cgi). (1)

Measurements were made on 50 specimens (Table 1) of *An. albitarsis* F. The wings and legs taken from the right side of the body of each female were carefully removed and placed dry on microscope slides under a coverslip sealed with a transparent nail polish.

Linear morphometry analysis

The dorsal side of each wing was measured without scales, in millimeters, and based on the standard nomenclature for the Costal wing spots of the genus *Anopheles* as follows: basal pale + prehumeral pale (BP+PHP), prehumeral dark (PHD), humeral pale (HP), humeral dark (HD), presector pale (PSP), presector dark (PSD), sector pale (SP), proximal sector dark (PRSD), accessory sector pale (ASP), distal sector dark (DSD), subcostal pale (SCP), preapical dark (PD), preapical pale (PP), apical dark (AD) (6,18,32) (Figure 1A). The length (L) of each wing (at 30X) was measured from the *alulae* to the R3 intersection including the wing margin (Figure 1A). Ta-III$_2$ and DS-III$_2$ (Figure 1B) were measured for each hind leg and the DS-III$_2$/TaIII$_2$ proportion was estimated. All measurements were made using a Nikon® 5MZ 800 stereomicroscope with a ocular micrometer calibrated with a glass ruler to 0.01mm

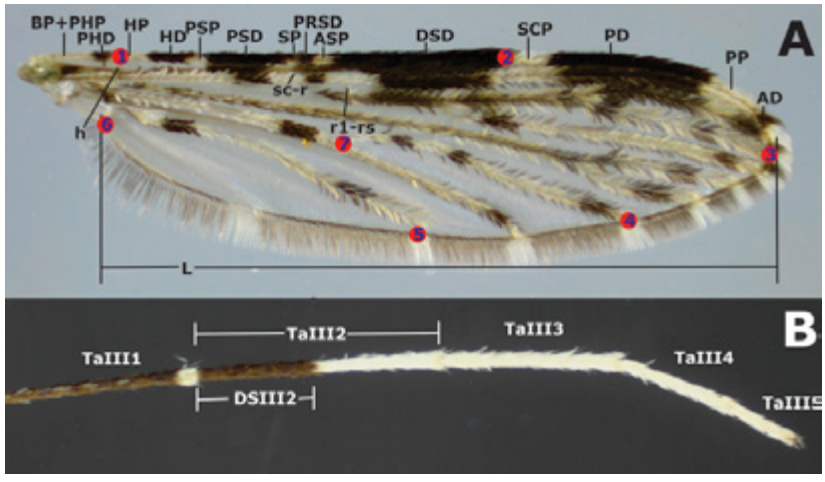

Figure 1. *Anopheles (Nyssorhynchus) albitarsis* F. A) Wing with pattern I (no mergers) of Costa vein spots *; B) Tarsomeres of hind leg†.
* The red marks indicate the location of landmarks (LM) analyzed: LM1 intersection of the Humeral vein with Costa vein; LM2 intersection Subcosta vein with Costa vein; LM3 Radial 3 vein intersection with wing margin; LM4 intersection M_{3+4} vein with wing margin; LM5 Anal vein and wing margin intersection; LM6 *alulae*; LM7 anterior Cubital vein intersection with transverse mcu.
† DS-III$_2$/TaIII proportion is specified.
Source: Own elaboration based on the data obtained in the study.

Costa vein spots measurements with respect to the wing length of each female (33) were standardized using equation [1] (34):

$$P = \sqrt{\text{Arcsin}\left[\sqrt{X/(L+1)}\right] + \text{Arcsin}\left[\sqrt{(X+1)/(L+1)}\right]} \quad [1]$$

Where *P* is the transformed proportion of the length of the Costa vein spots with respect to the total length of the wing; X is the length of each Costa vein spot and L is the total wing length.

Statistical analysis was made based on the transformed values, taking the PHD/HP proportion of the wing spots, the total length of each wing and the DSIII$_2$/TaIII$_2$ proportion of the hind leg. Several Costa vein spot patterns have been recognized in *Anopheles* (6), then, to unify the number of variables for statistical analysis, PSD, SP and PRSD spots (pattern I) measurements per female were added because they are fused in the pattern VI.

Normality tests were used (35), a multivariate analysis of variance and a test of Hotelling were performed for measuring the normalized spots. An analysis of variance for wing length was also carried out to establish possible significant differences between populations regarding

the size of the specimens. According to source of specimens, three groups were established, one consisting of wild-females and another two, formed by females from entomological series and isofamilies. To describe the relationships between two or more compared groups in an algebraic way, a canonical discriminant analysis was carried out. (36) The statistical analyzes were made using the statistical programs InfoStat (37) and RWizard v.2.3. (38)

Geometric morphometry analysis

Each wing evaluated by linear morphometry was photographed at 30X using a Nikon® DS-2Mv digital camera coupled to a Nikon® 5MZ 800 stereomicroscope. Seven anatomical landmarks at wing vein intersections, representing a polygon, covering the total area of the wing, were digitized in duplicate with TpsDig version 2.16 (39) (Figure 1A). Since the wing did not have scales, all reference points corresponded to type I landmark. (40) Repeatability of landmark digitization was estimated by calculating the R_n index and both sets of digitized reference points were averaged to minimize the error associated with each specimen. (41)

Wing shape was defined from two Procrustean coordinates for each landmark, while wing size corresponded to the size of the centroid expressed as the square root of the sum of the squared distances of each landmark to the centroid of the polygon. Landmarks of each specimen were scaled, translated and rotated by superposition with respect to the consensus configuration, using a Procrustes analysis. (42) This analysis allows to center each landmark configuration at the origin that is aligning all the landmarks configurations to their centroid in a way to eliminate the effect of position. Each landmark configuration is scaled to unit centroid size to eliminate the effect of size; and then they are rotated around the origin to minimize the summed square distance between homologous landmarks, in order to remove the effect of orientation.

Statistical analyzes were carried out using the MorphoJ program. (43) For this, the file generated in TpsDig2 version 2.16 (39) was imported with landmark coordinates and a graph was obtained using the RWizard software. (38) The normality of the data was verified (35), differences of size and wing shape were evaluated by means of an analysis of variance (44,45) and a discriminant analysis was performed with 10 000 permutations using Mahalanobis distances between groups as criteria for discrimination to determine possible differences in wing shape in each group studied. (46) The allometric effects, understood as the effects of size on the wing shape, were evaluated with a multivariate regression analysis of shape variables onto size, using the coordinates of each landmark with respect to the centroid. The statistical significance was estimated by non-parametric testing using 10 000 permutations. (47)

Results

Linear morphometry analysis

The pattern VI of the Costa vein spots was the most predominant (74%, n=37), followed by the pattern I without merger of Costa vein spots (26%, n=13) (Figure 2).

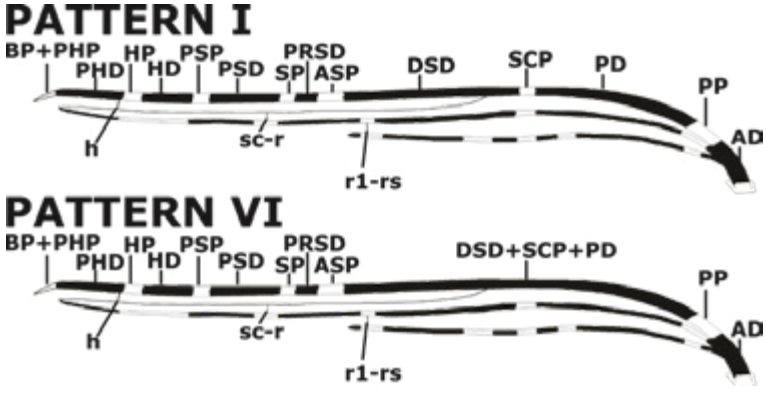

Figure 2. Ideogram of the two patterns of the Costa vein spots found in natural populations of *Anopheles albitarsis* F in two towns of the Colombian Orinoquía.
Source: Own elaboration based on the data obtained in the study.

The typical PHD/HP proportion for *An. albitarsis* s.l was represented by a 0.4-0.6 range in 29 specimens (58%) (5,8) However, a range of 1.17-1.19 was obtained for 49 specimens (98%) after standardizing the data by the equation [1], considering the length of each wing length and analyzing the mean (1.18) ± three times the standard deviation of the data distribution (3σ=0.0105),$DSIII_2/TaIII_2$ proportion registered a range of 0.5-0.9 for 24% (n=12) of females (5,8), but when the mean (2σ=0.54) ± two times the standard deviation (0.08) of its distribution was estimated, 98% (n=49) of the specimens were represented by the 0.38-0.54 range.

Largest females (2.96 mm) corresponded to wild-females, followed by those obtained from entomological series (2.74 mm) and isofamilies (2.50 mm). Those three groups were significantly different (F=29.67, gl=2, p<0.001). Wild-females from Puerto Carreño (2.96 mm) had a greater wing size (F=5.00, gl=1, p=0.04) than wild-females of San José del Guaviare (2.79mm).

Not significant differences between populations (F=1.23, gl=14, p=0.43) were found when the lengths of the Costa vein spots and the proportions between them, considered as diagnostic, were evaluated. However, when each group was analyzed separately (wild females, series and isofamilies), *An. albitarsis* F population from Puerto Carreño showed significant differences (F=3.60, gl=26, p=0.001) in the Costa vein spots length and in the diagnostic proportions used for taxonomic identification.

Discriminant analysis of principal components for the wing length variables and the PSD, SP, PRSD and PD spots, allowed correct identification of 100% of females for each group analyzed (Figure 3).

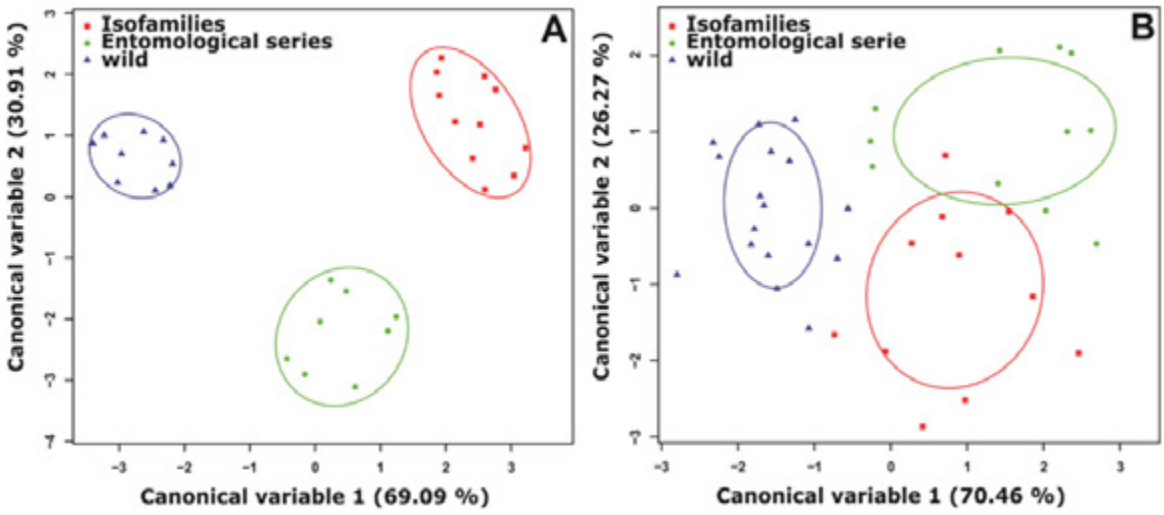

Figure 3. Discriminant analysis for *Anopheles albitarsis* F females from Puerto Carreño, Vichada. Each dot represents each female analyzed while the ellipses indicate groups according to the source of specimens. A) Linear morphometry. B) Geometric morphometry.
Source: Own elaboration based on the data obtained in the study.
Software RWizard 2.3. (38)

Geometric morphometry

Repeatability values for landmarks digitization were found for both, the Procrustes coordinates (R_n=0.98) and the centroid size (R_n=0.99). The analysis of variance did not show significant differences either in size (F=0.03, gl=1, p=0.87) nor in wing shape (F=1.04, gL=10, p=0.18) for wild-females according to their geographical origin. However, as in the case of wing length, wing size of *An. albitarsis* F from Puerto Carreño (2.64mm) was larger than wing size of the population from San José del Guaviare (2.63mm).

According to the source of each group analyzed (wild-females, series, and isofamilies), Puerto Carreño groups (n=39) showed significant differences, both in size (F=3.65, gl=2, p=0.036), and wing shape (F=7.02, gl=20, p<0.0001) where wild-females were larger (2.64mm) than those obtained from entomological series (2.52mm) and isofamilies (2.43mm). Discriminant analysis allows identifying correctly 86% (n=43) of the females from Puerto Carreño based on landmarks 2, 4, 6 and 7, particularly (Figure 4). Wing shape registered differences in the axillary, anal, cubital and radial wing regions of wild-females and those obtained by series and isofamilies. In addition, a comparison between consensus configurations was observed for all three groups (Figure 4).

Regression analysis of the variables associated with shape and wing size showed evidence of allometric effects (p <0.0001) with a prediction of 33.7%. Since almost identical results were found when regression residuals were used in a new discriminant analysis to correct allometric effects, the first analysis was considered.

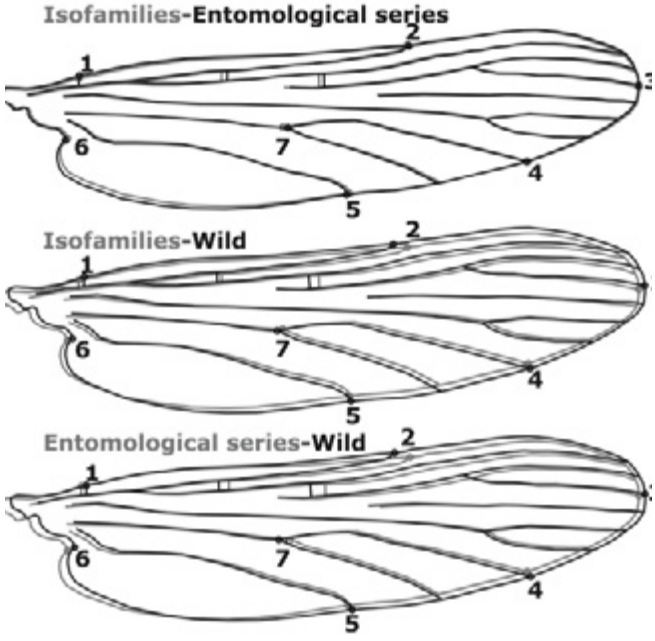

Figure 4. Graphic representation of paired groups showing the variation of wing shape in *Anopheless albitarsis* F of Puerto Carreño, Vichada.
Source: Own elaboration based on the data obtained in the study.
Software MorphoJ (43).

Discussion

An. albitarsis F from the Colombian Orinoquia showed slight phenotypic variation in wings, represented by two of the Costa vein spot patterns like 12 Venezuelan populations of *An. marajoara* (6) as *An. albitarsis* F or *An. albitarsis* I (6), two lineages only reported in the north of the Amazon River.

Differences in the length of the Costa vein spots, wing shape and centroid size could be influenced by breeding conditions. Under controlled conditions, a nutritional imbalance derived from artificial diets (27,48), population density, natural lighting and changes in water temperature are aspects that define the fitness of entomological series and isofamilies (49). In natural conditions, wild females develop under different conditions. The Colombian Orinoquia has a monomodal rainfall regime (50) in which important rivers such as the Orinoco, the Meta, and the Guaviare rivers generate runoff that provides nutrients to all mosquito larval habitats. These habitats are permanently exposed to the sun (51), so natural light determines the conversion of essential fatty acids and contributes to the quality and quantity of essential micronutrients for the development of immature forms of anophelines. (52,53) In consequence, in natural populations, the genetic background together with abiotic factors, defined by latitude and ecological characteristics, may play a fundamental role in the phenotypic expression of these traits for the species.

Wing length in mosquitoes of the genus *Anopheles* constitutes an indirect estimator of body size (20), a characteristic associated with their status as malaria vector. This study revealed that wild females from Puerto Carreño, Vichada have larger relative body size than the wild females from San José del Guaviare, Guaviare. This is interesting since Puerto Carreño populations have been found to be naturally infected by *P. falciparum*, reaching entomological inoculation rates of up to 5.1 (54), while no natural infection by human malaria parasites has been found in populations of *An. albitarsis* F from San José del Guaviare. (55)

As in other mosquito species, the ratio of wing size may be involved in fitness through the preference for copulation (21,22), increased fecundity (24) and, the ability to search for a good quality blood source. (25) In general, for anophelines, larger females have a higher rate of bite in humans and a higher rate of survival, which favors infection with *Plasmodium spp.* (52,56). In this context, in the Orinoquia Region of Colombia, *An. albitarsis* F may act as an auxiliary or regional vector, contributing to maintaining malaria endemicity, even when populations of the primary vector *An. darlingi* are very low. (11)

It is clear that body size influences the vectorial capacity of mosquitoes of the genus *Anopheles*; for this reason, it is very important to analyze the wing length as an indirect estimator of body size for taxonomic identification of the lineage of *An. albitarsis* F, and associated bionomic aspects of natural populations. Based on linear and geometric morphometric analyzes, this study proposes the main diagnostic characters for *An. albitarsis* F, a range of 1.17-1.19 for the PHD/HP proportion of the Costa vein spots and, the range of 0.38-0.54 for the proportion of $DSIII_2/TaIII_2$ of hindtarsomere 2 (Table 2). Analyzing these range values, in the *Argyritarsis* Section, *An. albitarsis* F would be closer to *An. oryzalimnetes* and *An. janconnae* than *An. marajoara*, as this lineage has been denominated in previous studies with specimens from Venezuela and Colombia. (5) However, more studies for these diagnostic characters with a greater sample size and that include samples of both lineages, *An. albitarsis* F and *An. albitarsis* I, are required.

Table 2. Diagnostic character ranges for natural populations of *Anopheles albitarsis* F for Colombia, Brazil and Venezuela.

Character	Range *	Author	Species Name
PHD/HP	0.22-1.00	Rubio-Palis *et al.* (6)	*An. marajoara*
PHD/HP	1.17-1.19 †	This study	*An. albitarsis* F
$DSIII_2/TaIII_2$	0.30-0.62	Rubio-Palis *et al.* (6)	*An. marajoara*
$DSIII_2/TaIII_2$	0.40-0.63	Motoki *et al.* (5)	*An. marajoara*
$DSIII_2/TaIII_2$	0.38-0.54	This study	*An. albitarsis* F

* Range obtained by using equation [1].
† *An. albitarsis* F has been denominated as *An. marajoara* in other studies.
Source: Own elaboration based on the data obtained in the study.

For members of *An. albitarsis* Complex, it is important to normalize [equation 1] the measurements of each Costal vein spots with respect to the wing length (body size) of each specimen analyzed for morphometry studies. This allows a better association between taxonomic identification status and biological and ecological characteristics based on their geographical location and epidemiological scenarios. Ranges for $DSIII_2/TaIII_2$ proportion found in this study overlap with ranges for this proportion reported in natural populations of *An. marajoara* (4-6) without molecular confirmation (1,2,10), so it is likely that, in fact, this means a synonymy and the ranges observed for *An. marajoara* are actually ranges for *An. albitarsis* F, which would support the range proposed in this study (Table 2).

The study of diagnostic characters based on linear and geometric morphometry helps to define the identity of lineages that do not yet have a morphological description, as is the case of *An. albitarsis* F, and offers indirect information on some aspects of its biology, which are fundamental for understanding their role as malaria vectors. The sample size for this study was limited by molecular confirmation, so evaluating the same parameters with a greater number of individuals, whose sample size shall be representative for wild populations of *An. albitarsis* F and other members of the *An. albitarsis* Complex, is suggested. Since latitude and abiotic factors determine wing size and shape in mosquitoes (57), populations from other locations should be included throughout their geographical distributions and in different collection years that include El Niño-Southern Oscillation (ENSO) for linear and geometric morphological analysis of diagnostic characters used for taxonomic identification.

Conclusion

In natural populations, females of *An. albitarsis* F can vary in size according to their geographical and ecological origin. Biotic and abiotic factors associated with obtaining entomological series and isofamilies under controlled conditions, as a strategy for taxonomic determination based on the morphological characters of their associated stages, define the differences in body size and wing shape with respect to wild -females. This study presents new ranges for diagnostic characters used for the taxonomic identification of *An. albitarsis* F in Colombia.

Conflict of interests

None stated by the authors.

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References

1. **Ruíz-Lopez F, Wilkerson RC, Conn JE, McKeon SN, Levin DM, Quiñones ML, *et al.*** DNA barcoding reveals both known and novel taxa in the Albitarsis Group (*Anopheles: Nyssorhynchus*) of Neotropical malaria vectors. *Parasit Vectors.* 2012;5:44. http://doi.org/cg4d.
2. **Brochero HH, Li C, Wilkerson RC.** A newly recognized species in the *Anopheles (Nyssorhynchus)* Albitarsis Complex (Diptera: Culicidae) from Puerto Carreno, Colombia. *Am. J. Trop. Med. Hyg.* 2007;76(6):1113-7.
3. **Foley DH, Linton YM, Ruiz-Lopez JF, Conn JE, Sallum MA, Póvoa MM, *et al.*** Geographic distribution, evolution, and disease importance of species within the Neotropical *Anopheles* Albitarsis Group (Diptera, Culicidae). *J. Vector Ecol.* 2014;39(1):168-81. http://doi.org/f54xf2.
4. **Rubio-Palis Y, Ruiz-Lopez F, Guzmán H, Sánchez V, Moreno JE, Estrada Y, *et al.*** Primer registro de *Anopheles (Nyssorhynchus) oswaldoi* B y *Anopheles (Nys.) albitarsis* F en la cuenca del río Caura, Estado Bolívar, Venezuela. *Bol. Mal. Salud Amb.* 2013;53(1):68-72.
5. **Motoki MT, Wilkerson RC, Sallum MA.** The *Anopheles* albitarsis complex with the recognition of *Anopheles oryzalimnete*s Wilkerson and Motoki, n. *sp.* and *Anopheles janconnae* Wilkerson and Sallum, n. sp. (Diptera: Culicidae). *Mem. Inst. Oswaldo Cruz.* 2009;104(6):823-50.
6. **Rubio-Palis Y, Wilkerson R, Guzmán H.** Morphological characters of adult *Anopheles (Nyssorhynchus) marajoara* in Venezuela. *J. Am. Mosq. Control Assoc.* 2003;19(2):107-14.
7. **Faran ME, Linthicum KJ.** A handbook of the Amazonian species of *Anopheles (Nyssorhynchus)* (Diptera: Culicidae). *Mosq. Syst.* 1981;13(1):1-81.
8. **Linthicum KJ.** A revision of the Argyritarsis section of the subgenus *Nyssorhynchus* of *Anopheles* (Diptera: Culicidae). *Mosq.* Syst. 1988;20(2):98-271.
9. **Brochero H, Quiñones ML.** Challenges of the medical entomology for the surveillance in public health in Colombia: reflections on the state of malaria. *Biomédica.* 2008;28(1):18-24.
10. **Gómez G, Jaramillo L, Correa MM.** Wing geometric morphometrics and molecular assessment of members in the Albitarsis Complex from Colombia. *Mol. Ecol. Resour.* 2013;13(6):1082-92. http://doi.org/gbdxfx.
11. **Brochero HL, Rey G, Buitrago LS, Olano VA.** Biting activity and breeding sites of *Anopheles* species in the municipality Villavicencio, Meta, Colombia. *J. Am. Mosq. Control Assoc.* 2005;21(2):182-6. http://doi.org/btxpmr.
12. **Quiñones ML, Suarez MF.** Indoor resting heights of some anophelines in Colombia. *J. Am. Mosq. Control Assoc.* 1990;6(4):602-4.
13. **Collins WE, Warren M, Skinner JC, Sutton BB.** Infectivity of two strains of *Plasmodium vivax* to *Anopheles albitarsis* mosquitoes from Colombia. *J. Parasitol.* 1985;71(6):771-3.
14. **Jiménez P, Conn JE, Wirtz R, Brochero H.** *Anopheles* (Diptera: Culicidae) vectors of malaria in Puerto Carreno municipality, Vichada, Colombia. *Biomédica.* 2012;32(Suppl 1):13-21.
15. **Herrera SV, Suárez MF, Sanchez GI, Quiñones ML, de Herrera M.** Uso de la técnica inmuno-radiométrica (IRMA) en *Anopheles* de Colombia para la identificación de esporozoitos de *Plasmodium*. *Colombia Med.* 1987;18:2-6.
16. **Brochero H, Li C, Wilkerson R, Conn JE, Ruiz-García M.** Genetic structure of *Anopheles (Nyssorhynchus) marajoara* (Diptera: Culicidae) in Colombia. *Am. J. Trop. Med. Hyg.* 2010;83(3):585-95. http://doi.org/fr9wh3.
17. **González R, Carrejo NS.** Introducción al estudio taxonómico de *Anopheles* de Colombia: claves y notas de distribución. 2nd ed. Cali: Universidad del Valle; 2009.
18. **Rosa-Freitas MG, Deane LM.** The neotype of *Anopheles albitarsis* (Diptera: culicidae). *Mem. Inst. Oswaldo Cruz.* 1989;84(3):289-302. http://doi.org/bbmmxz.
19. **Gutiérrez LA, Orrego LM, Gómez GF, López A, Luckhart S, Conn JE, *et al.*** A new mtDNA COI gene lineage closely related to *Anopheles janconnae* of the Albitarsis complex in the Caribbean region of Colombia. *Mem. Inst. Oswaldo Cruz.* 2010;105(8):1019-25.
20. **Dujardin JP.** Modern morphometrics of medically important insects. In: Tibayrenc M, editor. Genetics and Evolution of Infectious Disease. Londres: Elsevier; 2011.
21. **Garros C, Dujardin JP.** Genetic and phenetic approaches to *Anopheles* systematics. In: Manguin S, editor. *Anopheles* mosquitoes - New insights into malaria vectors: InTech; 2013.
22. **Bonduriansky R.** The evolution of male mate choice in insects: a synthesis of ideas and evidence. *Biol. Rev. Camb. Philos. Soc.* 2001;76(3):305-39.
23. **Okanda FM, Dao A, Njiru BN, Arija J, Akelo HA, Touré Y, *et al.*** Behavioural determinants of gene flow in malaria vector populations: *Anopheles gambiae* males select large females as mates. *Malar. J.* 2002;1(1):10.
24. **Lyimo EO, Takken W.** Effects of adult body size on fecundity and the pre-gravid rate of *Anopheles gambiae* females in Tanzania. *Med. Vet. Entomol.* 1993;7(4):328-32. http://doi.org/bw39mk.
25. **Takken W, Klowden MJ, Chambers GM.** Effect of body size on host seeking and blood meal utilization in *Anopheles gambiae* sensu stricto (diptera: culicidae): the disadvantage of being small. *J. Med. Entomol.* 1998;35(5):639-45.
26. **Suwanchaichinda C, Paskewitz SM.** Effects of larval nutrition, adult body size, and adult temperature on the ability of *Anopheles gambiae* (Diptera: Culicidae) to melanize sephadex beads. *J. Med. Entomol.* 1998;35(2):157-61.
27. **Oliver SV, Brooke BD.** The effect of larval nutritional deprivation on the life history and DDT resistance phenotype in laboratory strains of the malaria vector *Anopheles arabiensis*. *Malar. J.* 2013;12:44. http://doi.org/cg4n.
28. Diccionario Geográfico de Colombia [Internet]. Colombia: Instituto Geográfico Agustín Codazzi; 2017. [cited 2016 Apr 20]. Available from: https://goo.gl/sqJjYU.

29. World Health Organization. Manual of practical entomology in malaria. Methods and techniques. Geneva: WHO; 1975.

30. World Health Organization. Manual of practical entomology in malaria Vol II. Methods and techniques. Geneva: WHO; 1975.

31. **Estrada DA, Quiñoes ML, Sierra DM, Calle DA, Ruiz F, Erazo HF, *et al.*** Utilidad de la morfología de los huevos como un método indirecto para identificar *Anopheles benarrochi* Gabaldón, Cova García & López, *Anopheles oswaldoi* (Peryassu) y *Anopheles rangeli* Gabaldón, Cova García & López, (Diptera: Culicidae) en Putumayo, Colombia. *Biomédica.* 2003;23(4):388-95. http://doi.org/cg4p.

32. **Wilkerson RC, Peyton EL.** Standardized nomenclature for the costal wing spots of the genus *Anopheles* and other spotted-wing mosquitoes (Diptera: Culicidae). *J. Med. Entomol.* 1990;27(2):207-24.

33. **Hribar LJ.** Costal wing spot variation within and among progeny of single female *Anopheles nuneztovari* (Diptera: Culicidae). *Mosq.* Syst. 1995;27:1-15.

34. **Freeman MF, Tukey JW.** Transformations related to the Angular and Square Root. *Ann. Math. Statist.* 1950;21(4):607-11.

35. **Shapiro SS, Wilk MB.** An Analysis of Variance Test for Normality (Complete Samples). *Biometrika.* 1965;52(3):591-611. http://doi.org/c2jspz.

36. **Fisher RA.** The Use of Multiple Measurements in Taxonomy Problems. *Ann.* Eugen. 1936;7:179-188. http://doi.org/b6bjbc.

37. **Di Rienzo JA, Casanoves F, Balzarini MG, Gonzalez L, Tablada M, Robledo CW.** InfoStat, version 2014. [Software]. Córdoba: Universidad Nacional de Córdoba; 2011.

38. **Guisande C, Heine J, González-DaCosta J, García-Roselló E.** RWizard, version 2.3. *[Software]*. Vigo: University of Vigo; 2014.

39. **Rohlf JF.** TPSDig2, version 2.18. [Software]. New York: State University of New York at Stony Brook; 2015.

40. **Toro-Ibacache MV, Manriquez-Soto G, Suazo-Galdames I.** Morfometría Geométrica y el Estudio de las Formas Biológicas: De la Morfología Descriptiva a la Morfología Cuantitativa. *Int. J. Morphol.* 2010;28(4):977-90. http://doi.org/cg4q.

41. **Arnqvist G, Mårtensson T.** Measurement error in geometric morphometrics: empirical strategies to assess and reduce its impact on measures of shape. *Acta Zool. Hung.* 1998;44(1):73-96.

42. **James-Rohlf F, Marcus LF.** A revolution morphometrics. *Trends Ecol.* Evol. 1993;8(4):129-32. http://doi.org/dt6pzz.

43. **Klingenberg CP.** MorphoJ: an integrated software package for geometric morphometrics. *Mol. Ecol. Resour.* 2011;11(2):353-7. http://doi.org/b4m8ct.

44. **Klingenberg CP.** Analyzing fluctuating asymmetry with geometric morphometrics: concepts, methods, and applications. *Symmetry.* 2015;7(2):843-934. http://doi.org/cg4r.

45. **Klingenberg CP, Barluenga M, Meyer A.** Shape analysis of symmetric structures: quantifying variation among individuals and asymmetry. *Evolution.* 2002;56(10):1909-20.

46. **Klingenberg CP, Monteiro LR.** Distances and directions in multidimensional shape spaces: implications for morphometric applications. *Syst. Biol.* 2005;54(4):678-88. http://doi.org/cd7tp5.

47. **Klingenberg CP.** Size, shape, and form: concepts of allometry in geometric morphometrics. *Dev. Genes Evol.* 2016;226(3):113-37. http://doi.org/f8q23c.

48. **Grech K, Maung LA, Read AF.** The effect of parental rearing conditions on offspring life history in *Anopheles stephensi*. *Malar. J.* 2007;6:130. http://doi.org/b3cdfv.

49. **Phasomkusolsil S, Soonwera M.** Potential larvicidal and pupacidal activities of herbal essential oils against Culex quinquefasciatus Say and *Anopheles minimus* (Theobald). *Southeast Asian J. Trop. Med. Public Health.* 2010;41(6):1342-51.

50. **Correa HD, Ruiz SL, Árevalo LM.** editors. Plan de acción en biodiversidad de la cuenca del Orinoco-Colombia 2005-2015 Propuesta técnica. Bogotá D.C.: Corporinoquia, Cormacarena, I.A.v.H, Unitrópico, Fundación Omacha, Fundación Horizonte Verde, Universidad Javeriana, Unillanos, WWF-Colombia, GTZ-Colombia; 2005.

51. **Jiménez IP, Conn JE, Brochero H.** Preliminary biological studies on larvae and adult *Anopheles* mosquitoes (Diptera: Culicidae) in Miraflores, a malaria endemic locality in Guaviare Department, Amazonian Colombia. *J. Med. Entomol.* 2014;51(5):1002-9.

52. **Araújo Md, Gil LH, e-Silva Ad.** Larval food quantity affects development time, survival and adult biological traits that influence the vectorial capacity of *Anopheles darlingi* under laboratory conditions. *Malar. J.* 2012;11:261. http://doi.org/gbbzk9.

53. **Rejmánková E, Grieco J, Achee N, Roberts DR.** Ecology of Larval Habitats. *In: Manguin S, editor. Anopheles* mosquitoes-New insights into malaria vectors: InTech; 2013.

54. **Jiménez P, Conn JE, Wirtz R, Brochero H.** *Anopheles* (Diptera: Culicidae) vectores de malaria en el municipio de Puerto Carreño, Vichada, Colombia. *Biomédica.* 2012;32(Suppl 1):13-21.

55. **Jiménez IP, Conn JE, Brochero H.** Malaria vectors in San José del Guaviare, Orinoquia, Colombia. *J. Am. Mosq. Control Assoc.* 2014;30(2):91-8. http://doi.org/f57ppx.

56. **Rodríguez-Zabala J, González R, Correa MM, Gómez GF.** Análisis morfométrico de dos poblaciones de *Anopheles (Anopheles) calderoni* (Diptera: Culicidae) del suroccidente colombiano. *Revista Mexicana de Biodiversidad.* 2016;87(3):966-71. http://doi.org/cg4t.

57. **Pacheco MA, González R, Brochero HL.** *Anopheles darlingi* Root 1926 (Diptera: Culicidae): variaciones morfométricas en alas y patas de poblaciones de Colombia. *Biomédica.* 2017;37(Suppl 2):124-34.

ORIGINAL RESEARCH

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After-school leisure time: physical activity and estimated caloric expenditure in schoolchildren from southeast Spain

El periodo de ocio extraescolar: actividad física y gasto energético estimado en escolares del sureste español

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| Abstract |

Introduction: The after-school period is commonly used by schoolchildren to do physical activities; however, the level of moderate-to-vigorous physical activity (MVPA) and caloric expenditure achieved during that period of time is unknown.

Objective: To analyze the physical activity levels and the estimated caloric expenditure during the after-school period.

Materials and methods: 408 schoolchildren enrolled in the Spanish education system and aged between 11 and 12 years were included in the study, of whom 205 were females (11,21±0,41) and 203 males (11,20±0,40). This is a descriptive, relational and cross-sectional study. Schoolchildren reported their physical activity by means of the Previous Day Physical Activity Recall (PDPAR) instrument. Physical activity was analyzed through the average minutes involved in MVPA (>3METs) and the caloric expenditure taken from the MET levels.

Results: The results showed a higher average of MVPA ($p<0.05$) and caloric expenditure ($p<0.001$) in males than in females.

Conclusions: The average MVPA minutes estimated by schoolchildren meet the recommendations of daily physical activity established by the World Health Organization (WHO). Special attention is required for the female gender and the beginning of adolescence.

Keywords: Physical Activity; Health; Children (MeSH).

| Resumen |

Introducción. Por lo general, el periodo de ocio extraescolar es empleado por los escolares para realizar actividades físicas; sin embargo, se desconoce el nivel de actividad física de moderada a vigorosa intensidad (AFMV) y de gasto calórico registrados en ese periodo.

Objetivo. Analizar los niveles de actividad física y gasto energético estimado durante el periodo de ocio extraescolar.

Materiales y métodos. Participaron 408 escolares, con un rango de edad entre 11 y 12 años, siendo 205 niñas (11.21±0.41) y 203 niños (11.20±0.40) del sistema educativo español. Se siguió un diseño de tipo descriptivo relacional y de carácter transversal. Los escolares registraron la actividad física con el instrumento Previous Day Physical Activity Recall y su análisis se hizo a través del promedio de minutos realizando AFMV (>3 MET) y el gasto calórico extraído de los niveles de MET.

Resultados. Se encontraron medias superiores para los hombres respecto a las mujeres, tanto en los minutos de AFMV ($p<0.05$) como en el gasto calórico ($p<0.001$) registrado.

Conclusiones. El promedio de minutos de AFMV estimada por los escolares estudiados cumple con los valores diarios recomendados por la Organización Mundial de la Salud. Se debe prestar especial atención al género femenino y a la entrada a la adolescencia.

Palabras clave: Actividad física; Salud; Consumo de energía; Niños (DeCS).

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Introduction

The World Health Organization (WHO) recommends that all young people aged between 5 and 17 perform minimum 60 minutes of moderate-to-vigorous physical activity (MVPA) per day, that is, above three MET. (1) A subjective way to estimate physical activity intensity is the metabolic equivalent of task (MET), which is defined as the ratio of energy expenditure to a resting rate.

A study conducted to find which are the appropriate recommendations to avoid adiposity in Spanish schoolchildren revealed that 60 minutes of MVPA are adequate for the Spanish context; however, a high dose of vigorous physical activity is also necessary for a more optimal health condition. (2)

During the International Conference on Physical Activity and Obesity in Children, it was stated that a low level of physical activity translates into a higher risk of developing obesity, while a high level of physical activity leads to a lower risk. (3) In young Europeans aged between 10 and 12 years, De Bourdeaudhuij *et al.* (4) found that those who spent more time in MVPA and less time in sedentary activities had a better body weight status. (4)

An increase in weekly energy expenditure through physical activity in the after-school leisure period is essential to prevent overweight and the risk of childhood obesity. (5) In this sense, special attention should be paid to the level of physical activity after the school day is over, since some authors suggest that, during this period, young people carry out most of their activities. (6-8)

A study with European schoolchildren aged 10 to 12 years indicated that the level of physical activity inside schools was scarce and was mainly focused on sedentary activities. (9) Similarly, other studies on physical activity have reported that the level of activity in schoolchildren is higher during the week compared to the weekend. (10-12)

On the other hand, the international literature states that physical activity levels notably decrease when children go from primary education to high school. (13-15) In studies with primary school children (aged 6 to 12 years), physical activity levels seem to be acceptable and, in some cases, comply with the established recommendations. (8,16-18); however, in studies with schoolchildren aged 12 years and older, physical activity levels are lower than recommended, especially in the female gender. (17,19,20) In all the studies reviewed on young people, physical activity is significantly higher in men than in women. (21,22)

In epidemiological studies related to physical activity level in the subjects, MVPA episodes have been observed in numerous occasions, since it is considered that movement below 3 MET is of little relevance. MET, as unit of measurement of energy expenditure, has been used by several studies in Spanish adolescents, obtaining different results depending on the instrument and the population studied. (23-25) This article is part of a more extensive research where an international instrument for the valuation of physical activity and caloric expenditure in MET was validated in a self-reported way by the subjects. (26)

With this in mind, the objectives of this study are to assess the level of physical activity after school and the estimated caloric expenditure using MET, and to determine compliance with WHO guidelines in sixth grade students.

Materials and methods

Design and participants

The sample consisted of 408 sixth grade students, aged between 11 and 12 years, 205 girls (11.21±0.41 years) and 203 boys (11.20±0.40 years), from eight schools (public and state-subsidized private schools) of the Region of Murcia in the Spanish southeast. Sampling was non-probabilistic and chosen non-randomly for convenience. Students with cardiovascular diseases were excluded. The design of this study was descriptive, relational and cross-sectional.

Instruments

The Previous Day Physical Activity Recall (PDPAR), adapted to the Spanish culture, was used for measuring after-school physical activity. (26) For this version, semantic, idiomatic and conceptual patterns of the different items were adapted, obtaining a content validity index (CVI) between 0.8 and 1 for all items. The instrument consists of 19 periods of 30 minutes between 2:00 pm and 11:00 pm; the subject had to remember and mark the main activity performed the day before during each time interval. Once the questionnaires were completed, the responses of the participants regarding MET intensities were compared with the MET activity-intensity sheet. (27,28) This form translates the responses of the subjects into a MET number according to the studies carried out by the authors and the compendium of intensities in physical activities.

The results obtained in this study after applying the instrument are presented in three ways: first, as the average daily time used for MVPA; second, as the MET average resulting from physical activity; and third, as the estimation of the caloric expenditure resulting from the MET level established in kcal/day, in relation to the average obtained from the three weekly measurements of after-school leisure period. To calculate daily calories, regarding each activity indicated by the participant, the standardized formula number of MET in the activity x 3.5 x weight (kg)/200 was applied. With this, the estimated daily kilocalories of the after-school leisure period were obtained. (29)

Process

An action protocol was established in the schools to take measurements for three consecutive days during the week (Tuesday, Wednesday and Thursday). During those three days, the students had to answer a physical activity questionnaire (PDPAR) every day.

The evaluators received training before starting with the process to get acquainted with the instrument; then, the study was carried out. The PDPAR was explained in the first session by the evaluator, using the application tool and a digital presentation to expose the characteristics of the questionnaire prior to the beginning of the implementation by schoolchildren; during the remaining sessions, once the exercise was understood, the tool was applied autonomously.

The research was carried out in accordance with the ethical standards of the Declaration of Helsinki (revision of 2008) (30) and following the recommendations of Good Clinical Practice Directive of the EEC. (31) In turn, the management team of the schools and the legal guardians of the participants authorized their participation in the study.

Statistical analysis

Frequency tables were made with basic descriptive statistics to estimate the mean, dispersion and distribution of the data to find the characteristics of the sample. In addition, an inferential statistical analysis was performed using the chi-square statistical association test to observe physical activity levels per time intervals. Similarly, a t-Student test was carried out to estimate differences by sex in the average of minutes of daily physical activity in the after-school leisure period. The statistical analyzes were performed using the SPSS program version 19.0 (Chicago, USA) and the level of significance was set at p=0.05.

Results

Table 1 shows the average minutes invested in MVPA by the subjects studied. It can be seen how boys had a higher average [84 minutes, standard error (SE): 3.47] than girls (63 minutes, SE: 3.01). Moreover, the daily average MET shows higher levels in boys than in girls (48 MET, SE: 0.79 vs. 41 MET, SE: 0.65). Regarding the estimated average of calories during the after-school period, the same trend can be observed with respect to boys (981 kcal/day, SE: 0.79) and girls (766 kcal/ day, SE: 0.65).

Table 2 shows significant differences between the results obtained from both sexes for the MVPA and MET ($p<0.05$) and in the total calories obtained ($p<0.001$). Thus, the t-Student test indicates differences of 20.82 minutes of MVPA, 6.73 MET and 215 kcal/day in favor of the male gender.

Table 1. Average minutes of moderate-to-vigorous physical activity, MET and estimated calories by sex.

Sex	MVPA *			MET			Calories †		
	Mean	SD	SE	Mean	SD	SE	Mean	SD	SE
Male	84.67	49.49	3.47	48.42	11.39	0.79	981.43	643.28	45.14
Female	63.85	43.16	3.01	41.68	9.39	0.65	766.19	370.52	25.87

MVPA: moderate-to-vigorous physical activity; MET: metabolic equivalent of task; SE: standard error; SD: standard deviation.
* Average of minutes obtained from three measurements and representative of the after-school period in a day.
† Average of calories obtained from three measurements and representative of the after-school period in a day expressed in kcal/day.
Source: Own elaboration based on the data obtained in the study.

Table 2. T-Student and Levene's test for independent samples correlating the minutes of moderate-to-vigorous physical activity, MET and the estimated calories by sex.

Correlation of variables	Levene's test for equality of variances		Student's t-test for equality of means						
	f	sig	t	df	Sig. (bil)	Dif. means	Dif. SE	CI95%	
								Lo	Up
MVPA *	3.60	0.050	4.52	397.55	0.000	20.82	4.59	11.78	29.86
MET	4.11	0.43	6.51	390.38	0.000	6.73	1.03	4.70	8.77
Calories †	21.25	0.000	4.13	322.10	0.000	215.23	52.04	112.85	317.62

f: F-test; sig: significance; t: t-test; df: degree of freedom; Sig (bil): bilateral significance; Dif. means: difference of means; Dif. SE: difference in standard error; CI: confidence interval; Lo: lower limit; Up: upper limit.
* MVPA: mean MVPA minutes obtained from the three measurements and representative of after-school period in a day.
† Mean calories obtained from the three measurements and representative of the after-school period in a day expressed in kcal/day.
Source: Own elaboration based on the data obtained in the study.

The chi-square test detected significant differences in the MVPA level ($\chi2=19.276$; $p<0.005$) of the participants analyzed. The classification (Table 3) shows that 8.1% of the subjects lack this type of activity. The girls perform more physical activity in the interval from 0 to 30 minutes (63.6% vs. 36.4%) and 30 to 60 minutes (61.6% vs. 38.4%), while boys perform more physical activity of over 60 minutes compared to girls (59.7% vs. 40.3%).

Table 3. Classification in minutes of moderate-to-vigorous physical activity performed by sex.

Classification according to the MVPA		Sex		Total
		Male	Female	
No MVPA	Count	13	20	33
	% of Classification	39.4	60.6	100.0
	% Total	3.2	4.9	8.1
	Corrected residuals	-1.2	1.2	
0-30 minutes	Count	20	35	55
	% of Classification	36.4	63.6	100.0
	% Total	4.9	8.6	13.5
	Corrected residuals	-2.1	2.1	
30-60 minutes	Count	38	61	99
	% of Classification	38.4	61.6	100.0
	% Total	9.3	15.0	24.3
	Corrected residuals	-2.6	2.6	

Continues.

Classification according to the MVPA		Sex		Total
		Male	Female	
>60 minutes	Count	132	89	221
	% of Classification	59.7	40.3	100.0
	% Total	32.4	21.8	54.2
	Corrected residuals	4.4	-4.4	
Total	Count	203	205	408
	% of Classification	49.8	50.2	100.0
	% Total	49.8	50.2	100.0
$\chi 2$= 19,276; p< 0.005				

MVPA: moderate-to-vigorous physical activity; $\chi 2$: chi-square distribution.
Source: Own elaboration based on the data obtained in the study.

Discussion

This study analyzed the level of physical activity, MET and estimated calories in schoolchildren from the region of Murcia during the after-school leisure period. The average results point that both boys and girls reach the levels of physical activity recommended by the WHO. Likewise, the estimated caloric expenditure seems to have a relative agreement in the maintenance of an adequate energy balance in the studied sample.

The mean MVPA minutes were 84 minutes for males and 64 minutes for females, exceeding 60 minutes per day. (1) The findings of the study coincide with a longitudinal study with a sample of 2 185 young people from Denmark, Portugal, Estonia and Norway, followed since age 9 until age 15. In this population, 97.4% of the boys and 97.6% of the girls complied with the minimum recommendations of the WHO at the age of 9. However, when the data were analyzed for the age of 15, a decrease in these compliance percentages was found, with 81.9% of men and 62% of women. (17)

In another cross-sectional study carried out with 503 Portuguese young people aged between 6 and 18 years, the level of habitual physical activity was analyzed to establish if they met the WHO recommendations. The oldest participants had a lower number of MVPA episodes than younger participants: until age 14, the average of daily physical activity minutes was 79 minutes for girls and 144 minutes for boys; after that age, there was a decrease to 44 and 56 minutes, respectively. The authors concluded that participants aged 6 to 15 years complied with the WHO recommendations. (20) The results of this study coincide with those findings, since both boys and girls with those interval ages achieved the daily physical activity recommendations.

It is necessary to remember that the average values of this study comprise the whole sample in a global way, without making a classification by time intervals. When doing this classification, it was found that 8% of the participants did not perform any type of MVPA in the after-school leisure period, while 13.5% performed between 0 and 30 minutes, 24% between 30 and 60 minutes and 54% 60 minutes or more. The latter accumulated plenty of minutes of physical activity, which makes the averages for the entire sample higher.

In the European study IDEFICS (16), 7 684 young people aged between 2 and 11 years were evaluated in Cyprus, Italy, Hungary, Belgium, Spain, Estonia, Germany and Sweden. Regarding the sample of Spanish people selected for the study, and following the recommendations of the WHO, 30.4% of boys and 12.3% of girls complied with these guidelines. Girls outnumbered boys in the 0 to 30 minutes interval (38.2% vs. 21.5%) and in the 30 to 60 minutes interval (49.5% vs. 48.2%). These results are similar to those found in our study, in the sense that girls outnumber boys in the 0 to 30 minutes (26.8% vs. 16.2%) and 30 to 60 minutes intervals (29.7% vs. 18.7%), with boys outnumbering girls (65% vs. 43.4%) in the MVPA performed over 60 minutes, as recommended by the WHO. However, the percentages of this study are substantially higher, especially in the category of more than 60 minutes (65% and 43.4% vs. 30.4% and 12.3%). This may be caused by multiple factors, mainly because in the IDEFICS study the averages include all subjects aged between 2 and 11 years; this study included a sample with an average age of 11.21 years and, as described by the authors of the study themselves, physical activity increased with age within the ranges studied.

Going back to the study carried out in Spain, it was found that only 35% of a sample of 438 schoolchildren aged 9 fulfilled the recommendations of physical activity in the community of Madrid. (32) After analyzing the results of this study, from that perspective, 54% of the total of the sample comply with the recommendations of the WHO, which is similar to the findings of other authors (18) and is above the data of the community of Madrid.

In another study recently conducted in the Region of Murcia (21), 1 055 young people between 3 and 18 years of age were analyzed, finding that they did not comply with the minimum MVPA recommendations and that 77% of them were inactive according to the Physician-based Assessment and Counseling for Exercise (PACE) questionnaire implemented in that study. These data differ from our findings, perhaps because of the wide range of age and the type of instrument used.

Regarding MET levels and kcal/day found in the present investigation, 48 MET and 981 kcal/day were observed in boys and 41 MET and 766 kcal/day in girls. In a sample of 323 adolescents between 12 and 16 years of age from the Valencian community who used MET as reference value and were assessed through a self-report physical activity questionnaire, mean daily values of 44.68 MET for men and 38.77 MET for women were observed. (24)

Another study conducted in adolescents aged between 12 and 18 years from the province of Teruel found an average energy expenditure of 40.1 MET in males and 37.2 MET in females. (23) A different study with Aragonese adolescents found an average of 39.70 MET in males and 37.51 MET in females. (25)

As it can be seen, the results of MET levels in the study are higher than what other studies have described, which may be caused by several reasons; first, the measuring instruments are different, although they were equated in terms of energy expenditure, and second, the way of quantifying was different in terms of questions asked and time intervals. Another reason may be that the populations of most studies reviewed were older than 12 years, whereas our sample is younger. At this point, it is necessary to remember what has been described about the decrease in energy expenditure as age increases. (24)

When the means of caloric expenditure are analyzed for the after-school leisure period, males show higher values because their level of physical activity is higher than in females. In the average classification established by the consensus document on energy requirement (33), it is observed that the total daily energy expenditure in males is around 2 316 kcal/day. Considering that the established basal metabolic rate of energy expenditure is 1 321 kcal/day plus the average caloric expenditure of the children included in this study (981 kcal/day), and that the possible physical activity carried out during the school day was not included, the average values of the sample seem to coincide with the physical activity necessary to satisfy the requirements in said classification.

With regard to women, the document of the Food and Agriculture Organization of the United Nations (33) establishes an average total energy expenditure of 2 123 kcal/day for the age group between 11 and 12 years, the basal metabolic expenditure being 1 217 kcal/day. Thus, observing the values shown by the girls in the present study (766 kcal/day) and knowing that they are limited to the after-school leisure period, the figures seem to be slightly lower than the estimates proposed in said classification.

This study has some limitations. On the one hand, physical activity has been measured with a self-report instrument, which can cause an overestimation of physical activity (34); however, this type of instruments are useful for evaluating activity type and mode and its determinants, which may be more complex to evaluate objectively. (35) On the other hand, it must be borne in mind that the school hours (9:00-14:00 h) were not considered in the present study, and more schoolchildren may comply with the WHO recommendations; however, some studies indicate that physical activity is considerably lower inside the school than outside. (11)

Conclusions

The findings of this study suggest that schoolchildren in the Region of Murcia perform physical after-school activities on a regular basis during the last year of the primary stage, which seems to be combined with an adequate energy balance, based on the estimated energy expenditure extracted from the physical activities they perform. The values in MVPA minutes established by the WHO are met in the total average of subjects; however, only 54% of the sample exceeds 60 minutes per day. Policies to promote physical activity should focus on maintaining physical activity levels during the transition to secondary education, where a more noticeable decrease in physical activity levels has been described, especially in the female gender.

Conflicts of interest

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References

1. Organización Mundial de la Salud. Recomendaciones mundiales sobre actividad física para la salud. Ginebra: OMS; 2010 [cited 2018 Jan 19]. Available from: https://goo.gl/NVTaHW.
2. **Laguna M, Ruiz JR, Lara MT, Aznar S.** Recommended levels of physical activity to avoid adiposity in Spanish children. *Pediatr Obes.* 2013;8(1):62-9. http://doi.org/f25mp8.
3. **Katzmarzyk P, Baur LA, Blair SN, Lambert EV, Oppert JM, Riddoch C, *et al.*** International conference on physical activity and obesity in children: summary statement and recommendations. *Int J Pediatr Obes.* 2008;3(1):3-21. http://doi.org/dwjwp2.
4. **De Bourdeaudhuij I, Verloigne M, Maes L, Van Lippevelde W, Chinapaw MJ, Te Velde SJ, *et al.*** Associations of physical activity and sedentary time with weight and weight status among 10- to 12-year-old boys and girls in Europe: A cluster analysis within the ENERGY project. *Pediatr Obes.* 2013;8(5):367-75. http://doi.org/cjvh.
5. **Cordova A, Villa G, Sureda A, Rodriguez-Marroyo JA, Martínez-Castañeda R, Sánchez-Collado MP.** Energy Consumption, Body Composition and Physical Activity Levels in 11- to 13-Year-Old Spanish Children. *Ann Nutr Metab.* 2013;63(3):223-8. http://doi.org/f5nr32.
6. **Arundell L, Hinkley T, Veitch J, Salmon J.** Contribution of the After-School Period to Children's Daily Participation in Physical Activity and Sedentary Behaviors. *PLoS One.* 2015;10(10):e0140132. http://doi.org/f78mjx.
7. **Arundell L, Ridgers ND, Veitch J, Salmon J, Hinkley T, Timperio A.** 5-year changes in afterschool physical activity and sedentary behavior. *Am J Prev Med.* 2013;44(6):605-11. http://doi.org/f4zt23.
8. **García-Cantó E, Rodríguez-García PL, Sánchez-López C, López-Miñarro PA.** Tiempo de ocio y práctica físico-deportiva en escolares (10-12 años) de la región de Murcia (España): diferencias en función del género. *Rev estud exp educ.* 2012;11(22):155-68.
9. **Van Stralen MM, Yildirim M, Wulp A, te Velde SJ, Verloigne M, Doessegger A, *et al.*** Measured sedentary time and physical activity during the school day of European 10- to 12-year-old children: The ENERGY project. *J Sci Med Sports.* 2014;17(2):201-6. http://doi.org/f5xvpp.
10. **Baskin ML, Thind H, Affuso O, Gary LC, LaGory M, Hwang SS.** Predictors of Moderate-to-Vigorous Physical Activity (MVPA) in African American Young Adolescents. *Ann Behav Med.* 2013;45(Suppl 1):S142-50. http://doi.org/cjvk.
11. **Brooke HL, Corder K, Atkin AJ, van Sluijs EM.** A systematic literature review with meta-analyses of within-and between-day differences in objectively measured physical activity in school-aged children. *Sports Med.* 2014;44(10):1427-38. http://doi.org/f6qjtt.
12. **Comte M, Hobin E, Majumdar SR, Plotnikoff RC, Ball GD, McGavock J, *et al.*** Patterns of weekday and weekend physical activity in youth in 2 Canadian provinces. *Appl Physiol Nutr Metab.* 2013;38(2):115-9. http://doi.org/f4nvs3.
13. **Middelbeek L, Breda J.** Obesity and Sedentarism: Reviewing the Current Situation Within the WHO European Region. *Curr Obes Rep.* 2013;2(1):42-9. http://doi.org/cjvm.
14. **Sallis J, Prochaska JJ, Taylor WC.** A review of correlates of physical activity of children and adolescents. *Med Sci in Sports Exerc.* 2000;32(5), 963-75.
15. **Van der Horst K, Paw MJ, Twisk JW, Van Mechelen W.** A brief review on correlates of physical activity and sedentariness in youth. *Med Sci Sports Exerc.* 2007;39(8):1241-50. http://doi.org/ct82d6.
16. **Konstabel K, Veidebaum T, Verbestel V, Moreno LA, Bammann K, Tornaritis M, *et al.*** Objectively measured physical activity in European children: the IDEFICS study. *Int J Obes.* 2014;38(Suppl 2):S135-43. http://doi.org/cjvn.
17. **Riddoch CJ, Bo Andersen L, Wedderkopp N, Harro M, Klasson-Heggebø L, Sardinha LB, *et al.*** Physical activity levels and patterns of 9- and 15-yr-old European children. *Med Sci in Sports Exerc.* 2004;36(1):86-92. http://doi.org/bqsxnr.
18. **Román B, Serra-Majem L, Ribas-Barba L, Pérez-Rodrigo C, Aranceta J.** How many children and adolescents in Spain comply with

the recommendations on physical activity? *J Sports Med Phys Fitness.* 2008;48(3):380-7.

19. **Aibar A, Bois JE, Generelo E, Zaragoza-Casterad J, Paillard T.** A cross-cultural study of adolescents' physical activity levels in France and Spain. *Eur J Sport Sci.* 2013;13(5):551-8. http://doi.org/cjvp.
20. **Lopes VP, Vasques CM, Maia JA, Ferreira JC.** Habitual physical activity levels in childhood and adolescence assessed with accelerometry. *J sports med phys fitness.* 2007;47(2):217-22.
21. **Gil P, Cuevas R, Contreras OR, Díaz A.** Educación física y hábitos de vida activa: percepciones de los adolescentes y relación con el abandono deportivo. *Aula Abierta.* 2012;40(3):115-24.
22. **López-Sánchez GF, González-Víllora S, Díaz-Suárez A.** Level of habitual physical activity in children and adolescents from the Region of Murcia (Spain). *SpringerPlus.* 2016;5:386. http://doi.org/chpv.
23. **Cantera-Garde MA, Devís-Devís J.** Physical activity levels of secondary school Spanish adolescents. *Eur J Phys Educ.* 2000;25(1):28-44. http://doi.org/b4b79g.
24. **Peiró-Velert C, Devís-Devís J, Beltrán-Carrillo VJ, Fox KR.** Variability of Spanish adolescent's physical activity patterns by seasonality, day of the week and demographic factors. *Eur J Sport Sci.* 2008;8(3):163-71. http://doi.org/frn4bh.
25. **Serra-Puyal JR, Zaragoza-Casterad J, Generelo-Lanaspa E.** Influencias de "otros significativos" para la práctica de actividad física en adolescentes. *Rev Int Med Cienc Act Fís Deporte.* 2014;14(56):735-53.
26. **Rodríguez-García PL, Pérez-Soto JJ, García-Cantó E, Rosa-Guillamón A.** Cross-cultural adaptation of a questionnaire that evaluates physical activity among children aged 10 and 11. *Arch argent pediatr.* 2015;113(3):198-204. http://doi.org/cjvq.
27. **Trost S, Ward D, Mcgraw B, Pate RR.** Validity of the Previous Day Physical Activity Recall (PDPAR) in Fifth-Grade Children. *Pediatr Exerc Sci.* 1999;11(4):341-8.
28. **Weston AT, Petosa R, Pate RR.** Validity of an instrument for measurement of physical activity in youth. *Med Sci Sports Exerc.* 1997;29(1):138-43.
29. American College of Sports Medicine. ACSM's Complete Guide to Fitness and Health. 4th ed. Champaign: Human Kinetics; 2011.
30. Asociacion Medica Mundial. Declaracion de Helsinki de la Asociacion Medica Mundial Principios éticos para las investigaciones médicas en seres humanos. Seúl: 59ª Asamblea General de la AMM; 2008.
31. Recomendaciones de Buena Práctica Clínica de la CEE. Comunidad Europea; 1990.
32. **Laguna-Nieto M, Lara-Herández MT, Aznar-Laín S.** Patrones de Actividad Física en función del género y los niveles de obesidad en población infantil española. Estudio EYHS. *Rev Psicol Deport.* 2011;20(2):621-36.
33. Food and Agriculture Organization of the United Nations, World Health Organization, United Nations University. Human energy requirements. Report of a Joint FAO/WHO/UNU Expert Consultation. Rome: FAO; 2001 [cited 2018 Jan 26]. Available from: https://goo.gl/ocwqYg.
34. **Shephard R, A Vuillemin.** Limits to the measurement of habitual physical activity by questionnaires. *Br J Sports Med.* 2003;37(3):197-206.
35. **Corder K, Ekelund U, Steele RM, Wareham NJ, Brage S.** Assessment of physical activity in youth. *J Appl Physiol.* 2008;105(3):977-87. http://doi.org/dpzxwt.

ORIGINAL RESEARCH

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English proficiency level in Colombian undergraduate students of medical programs

Nivel de inglés de los futuros egresados de los programas de pregrado de medicina en Colombia

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| Abstract |

Introduction: The government intends to position Colombia as a health and welfare tourism destination. To achieve this goal, it is necessary to increase the levels of English proficiency in health professionals, which is in line with the goal set by the Colombian Ministry of National Education for 2014: 20% of medical graduates should score at intermediate or advanced English proficiency levels.

Objectives: To determine if the bilingualism goal set for 2014 was achieved by students of undergraduate medical programs in Colombia.

Materials and methods: Descriptive and statistical approach (parametric and nonparametric tests) based on data from the Saber Pro test (2011-2015) for medical programs offered in universities of academic nature.

Results: The overall percentage of students who met the goal countrywide (28.6%) was satisfactory; however, only 16 medical programs out of 43 (37.2%) achieved the goal.

Conclusions: In general, the English proficiency level of potential medical graduates is aligned with the government's goal. However, there is much to be improved considering that about 70% of future medical graduates do not have an intermediate or advanced level in this skill.

Keywords: Language Test; Colombia; Education, Medical; Medical Tourism (MeSH).

| Resumen |

Introducción. El gobierno propuso posicionar a Colombia como un destino turístico de salud y bienestar, siendo uno de los objetivos aumentar los niveles de competencia del inglés en los profesionales de la salud. Esto se relaciona con la meta, para 2014, del Ministerio de Educación Nacional (MEN) de que 20% de los graduados deberían clasificar en nivel intermedio o superior en inglés.

Objetivos. Analizar el cumplimiento de la meta establecida por el MEN para los graduandos de los programas de medicina.

Materiales y métodos. Aproximación descriptiva y estadística (pruebas de proporciones paramétricas y no paramétricas) que empleó datos de la prueba Saber Pro (2011-2015) para los programas de medicina de las instituciones de educación superior de carácter académico universitario.

Resultados. El porcentaje global de estudiantes que cumplió la meta (28.6%) fue satisfactorio; sin embargo, solo 18 de 43 (37.2%) programas de medicina la cumplieron.

Conclusiones. El nivel de inglés de los potenciales graduados de los programas de medicina está alineado con la meta del gobierno. No obstante, hay mucho por mejorar si se tiene en cuenta que cerca del 70% de los futuros graduados de los programas de medicina no alcanza un nivel intermedio o superior en esta competencia.

Palabras clave: Lenguaje; Educación de pregrado en medicina; Colombia; Turismo médico (DeCS).

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Introduction

A good command of English language is fundamental for the professional development and the growth of the country. (1) Some health sciences areas in which learning English is necessary include academic research and development (2), handling instruction manuals for medical devices and instruments, using computer programs and interacting with English-speaking patients and their caregivers. (3)

Similarly, in a globalized world, medical services have begun to be outsourced. Thus, it is possible to find that in areas such as radiology or interpretation of specialized medical examinations, foreign medical professionals, coming from countries where these examinations are practiced, are hired if they live in countries that can provide the service in different time zones. For example, if an x-ray is taken during the day in the USA, a doctor in India (during his daytime working hours) can review it at night. This makes assistance more efficient and allows lower costs for users.

In Colombia, that health personnel is able to master a second language is even more important considering that the government has adopted a strategy to position the country as a destination for health and wellness tourism and hopes to reach a share between 20% and 30% of the medical tourism market by 2032. (4) This type of tourism targets at those people who enter a country looking for specialized medical, dental or surgical care, which can be preventive, cosmetic, curative or wellness treatments. (4)

To achieve this goal, one of the proposed objectives is to increase the English language proficiency levels in health professionals. (5) This objective was established after identifying that the level of English in health professionals was one of the deficiencies of the sector according to the consultancy firm McKinsey & Company, which conducted a baseline study of this public policy embodied in the Conpes 3678 of 2010. (6)

Specifically, it is crucial for physicians to master English for the health tourism sector and thus be able to have contact with patients (who mostly come from English-speaking countries or use English as a lingua franca), prescribe medications and medical orders, and understand assertively their needs and symptoms, among others. (7) Moreover, these reasons are even more important considering that the lack of understanding between doctors and patients for not sharing a common language can prevent the former from correctly identifying symptoms, which increases the probability of diagnosis errors and incorrect treatment. (8)

In order to assess the challenge for achieving this goal and to take advantage of the health tourism boom that the country is experiencing, it is necessary to establish the level of English in Colombian doctors. (9) Determining this information is possible and there are tools to calculate the proficiency level of medical graduates. Therefore, the first objective of this article is to present an analysis of the results of the English component of the Examen de Estado de Calidad de la Educación Superior - Saber Pro (Higher Education Quality State Exam) taken by potential graduates of different medical programs offered by universities between 2011 and 2015.

In addition, prior to the adoption of the strategy to position the Colombian health sector as an option for health and well-being tourism, in 2005, the Ministry of National Education (MEN by its acronym in Spanish) created the National Bilingualism Program Colombia 2004-2019 within the framework of an educational revolution. (10) With this program, the MEN established the Program for Strengthening the Development of Foreign Language Skills (PFDCLE by its acronym in Spanish) and set as a goal that 20% of graduates should be classified at intermediate or higher level in English by 2014. (1) It is worth noting that Colombia is not the only country that has a bilingualism policy in Latin America: Chile proposed the National English Strategy 2014-2030 (11) with the program English Opens Doors (PIAP by its acronym in Spanish); Peru created the policy English, The Door to the World (2015-2021) (12), and Uruguay developed the Ceibal Plan. In these three countries, the policy focuses on improving performance in English language in students at initial educational levels (primary and secondary education).

The second objective of this article is to assess whether the goal (20% of graduates classified at intermediate or higher level according to the Saber Pro test) proposed by MEN for 2014 was met or not by medical programs in Colombia.

This document is organized in four sections. The first presents the justification and objectives, the second describes the database and the methodology used to establish whether different medical programs met or not the goal established by the MEN for 2014, the third presents the results and the fourth offers some final comments.

Materials and methods

In order to determine the proportion of future medical graduates that reached an intermediate level of English language proficiency or higher, the database developed by the Colombian Institute for the Evaluation of Education (ICFES by its acronym in Spanish) for the Saber Pro tests conducted between 2011 and 2015 was used. This is a standardized and mandatory test to obtain the degree in all higher education programs. The exam is given once a year, in two sessions for two days and may last between 4 hours and 40 minutes and 8 hours depending on the program, because not all students have to take the second section. In the morning, generic skills (including English) are evaluated and in the afternoon the specific skills of the study program are evaluated. The English section provides results comparable over time, as they are aligned with international reference frameworks, and assesses reading and language use skills; this is a written test with multiple-choice questions.

The ICFES database contains the performance level achieved by each student in the English component. This level coincides with the adjustments made by the Colombian government of the conceptual framework and measurement of language proficiency of the Common European Framework of Reference for Languages for the country (Table 1).

Table 1. Equivalences between the reference levels of the Common European Framework of Reference for Languages, the reference levels of the country and of the classification of the Saber Pro test.

User classification	CEFR level	Equivalence in Colombia	Saber Pro Level
Not applicable	Not applicable	Does not meet the minimum requirements to be a beginner	A-
Basic user	A1	Beginner	A1
	A2	Basic	A2
Independent user	B1	Pre-intermediate	B1
	B2	Intermediate	B+
Competent user	C1	Early Advanced	
	C2	Advanced	

CEFR: Common European Framework of Reference for Languages.
Source: Own elaboration based on Alonso *et al.* (10)

Table 2 describes the total number of students evaluated and the percentage of those who were classified as B+ in each of the years studied. The percentage of students of medical programs is around 3% of the total potential of university graduates. The number of medical students evaluated was 3 722 in 2011. The students of medical programs evaluated had a relatively steady growth between 2011 and 2013, then, it decreased in 2014 and increased again in 2015. The average number of medical graduates from 2011 to 2015 is 4 457 per year.

The results of the English test are available for all professional and technical programs in the country and they allow comparisons between programs of different types. Table 2 presents the population of medical students and, to contextualize the results of the medical programs, presents the results of administrative science programs, software engineering and other future graduates.

As described in Table 3, the universities that registered their medical students in the Saber Pro test went from 40 in 2011 to 44 in 2015. The average number of students per program increased from 93 in 2011 to 111 in 2015. The past year, the Universidad Metropolitana de Barranquilla registered 342 medical students in the Saber Pro test, while the Universidad de Nariño registered 22 students. The increase, of about 30% in the minimum and maximum number of students per university, partially explains the 20% growth in the average number of medical students per program.

Table 2. Percentage of students in intermediate or higher level (B+) according to the Saber Pro test per type of program 2011-2015.

Programs	2011		2012		2013		2014		2015	
	n	% in B+	n	% in B+	n	% in B+	n	% in B+	n	% in B+
Administration and related	27 890	7.8%	29 677	9.7%	38 305	9.7%	32 780	10.7%	30 666	11.9%
Medicine	3 722	20.3%	4 151	26.5%	5 167	24.5%	4 340	28.6%	4 905	31.8%
Software	4 669	10.8%	4 545	14.1%	6 348	13.2%	5 019	15.4%	4 360	19.1%
Others	101 898	9.5%	100 549	11.9%	122 130	13.1%	108 243	14.5%	111 450	15.6%

n: number of students evaluated.
Source: Own elaboration based on the data obtained in the study.

Table 3. Descriptive statistics of the Saber Pro test according to the medical program. 2011-2015.

Category	2011	2012	2013	2014	2015
Programs that registered students in the Saber Pro test	40	41	42	43	44
Average number of students per program	93	101.2	123	100.9	111.5
Standard deviation of the number of students per program	57.7	55.7	75.2	59.5	70.8
Maximum number of students per program	261	262	354	323	342
Minimum number of students per program	16	12	30	20	22

Source: Own elaboration based on the data obtained in the study.

A descriptive approximation was carried out using this database. First, the percentage of students from the 44 medical programs classified in each of the five categories of English language proficiency level was estimated according to Table 1. In addition, in order to infer about the achievement or not of the policy goal, parametric (Z test) and nonparametric tests were carried out (χ^2 test) to determine if the proportions found are statistically higher than the 20% goal; both tests were performed for each program with the medical students that presented the test in 2014.

The statistics of the parametric test (and the corresponding correction) that was used was:

$$Z = \frac{\hat{p} - 0.2}{\sqrt{\frac{0.2(1-0.2)}{n-1}}} \quad (1)$$

Where $\hat{p}$ is the observed proportion of medical students classified in B+. This statistics allows refuting the null hypothesis that the observed proportion of students classified in B+ is ≤0.2 (20%). The alternative hypothesis is that said proportion is >0.2.

The trial statistics of the first equation follows a standard normal distribution, if a single comparison is made; so, to reject the null hypothesis, different corrections were used taking into account the number of comparisons made. In addition, the nonparametric test that was used involved the following trial statistics:

$$\chi^2 = \sum_i \frac{(O_i - E_i)^2}{E_i} \quad (2)$$

Where O_i is the observed value of individuals that are classified in B+ and E_i is the expected number of individuals in B+ if the 20% goal was met. Said trial statistics allows verifying the same hypothesis obtained with the parametric test described above and follows a χ^2 distribution with 1 degree of freedom, if only one test is made.

For this exercise, it was necessary to perform these tests on all the programs that registered students in the Saber Pro test. In other words, it seeks to determine simultaneously if each of the 42 programs that registered students in the test in 2014 met the goal or not. To avoid the bias generated when drawing a joint conclusion from joining individual test results, it is necessary to make an adjustment that takes into account the number of comparisons. This adjustment is made on the p-value and not on the statistics; for this purpose, the methods of Holm (13), Hochberg (14), Hommel (15), Benjamini & Hochberg (16) and Yekutieli & Benjamini were used. (17)

Microdata and statistical tests processing was carried out using the statistical software R (18). The confidence level used for the conclusions was 95%.

Results

Before analyzing the results per program, it is important to note that once the results have been evaluated by category for Administration and related programs, Software and Medicine, the proportion of medical students classified in B+ was found to be higher than in the other programs (Table 2). In 2011, while Administration and related programs classified 7.8% of their students and software 10.8% in B+, Medicine had 20.3%. Likewise, for the year 2014, 10.7% of the students of Administration and related programs, 15.4% of software students and 28.6% of medical students were classified as B+. For 2015, 31.8% of medical students, 11.9% of students of Administration and related programs, and 19.1% of software students were classified as B+. It should be noted that medical students had a higher number of students classified in B+ during the study period than the other areas; furthermore, this number increased by 40.6% from 2011 to 2014 and by 11.8% in the past two years.

Figure 1 represents with a dot the proportion of medical students classified in B+ and with colors, public institutions (in black) and private institutions (in gray). This graph allows identifying six interesting results:

1) Most Colombian universities exceeded the goal established by the PFDCLE for 2014, specifically, 23 programs (it is important to note that the corresponding statistical tests will be presented later on).
2) The number of universities that have a proportion >20% of students classified in B+ increased during the study period: it went from 17 programs in 2011 to 27 in 2015.
3) Programs offered by public universities do not reach relatively high percentages of students in B+ level, but a large part of them is located above the goal, especially in 2014.
4) There is no medical program in Colombia for which all of its students are classified as B+ in English language proficiency.
5) The number of programs with over 70% of students classified in B+ is relatively low; no public university was found in this group.
6) The dispersion in the proportion is very high: there is a relatively large number of universities that do not have 10% of their students classified in B+; the dispersion in private universities is higher, while for public universities is lower.

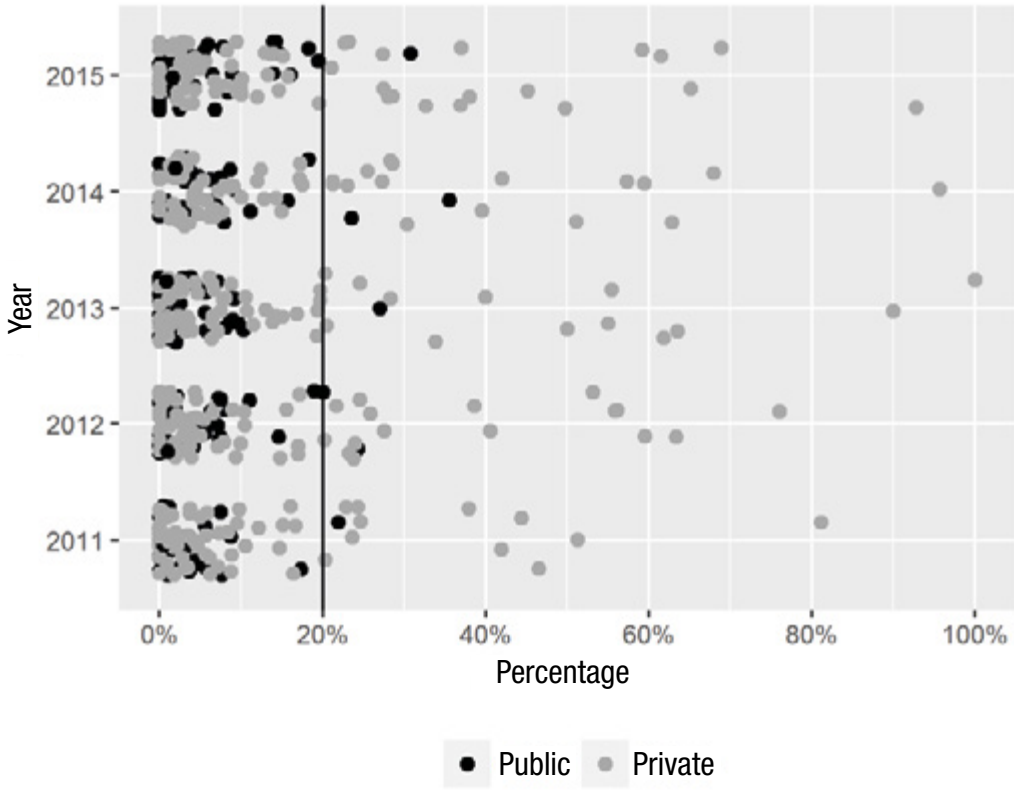

Figure 1. Percentage of medical students in intermediate or higher level (B+) according to the Saber Pro test. 2011-2015.
Source: Own elaboration based on the data obtained in the study.

To go into the detail of each of the programs and the fulfillment of the goal established for 2014, it was necessary to determine if the proportions calculated were statistically greater than the goal (Tables 4 and 5). It was found that the null hypothesis could be rejected for 16 medical programs only by applying either the parametric or nonparametric test; that is, the proportion of medical students who achieved B+ was >20%. Said programs are offered by the Universidad de los Andes, the Universidad Icesi, the Universidad Javeriana - Bogotá Campus, and the Universidad Nacional de Colombia.

If the fact that multiple comparisons were made is not considered and if p-values were adjusted, two more universities (Universidad Militar Nueva Granada and Universidad del Tolima) would have met the goal in 2014. It is worth noting that although the p values for most universities were different in magnitude among the criteria used —Holm (13), Hochberg (14), Hommel (15), Benjamini & Hochberg (16) and Yekutieli & Benjamini (17)—, the decision was always directed in the same direction: rejecting the null hypothesis. However, for the Universidad Militar Nueva Granada, when the parametric test was used only under the Yekutieli & Benjamini criterion, the null hypothesis was rejected, which did not occur in other cases. Given that under the nonparametric test the null hypothesis was rejected when using any of the criteria, it is concluded that, for this year, the university did not meet the goal.

Table 4. Results of nonparametric test regarding the difference of proportions in students with B+ classification according to the medical program. 2014.

University *	X^2	Criteria for adjusting the p-value						
		None	Holm	Hochberg	Hommel	Bonferroni	Benjamini & Hochberg	Yekutieli & Benjamini
Colegio Mayor de Nuestra Señora del Rosario	213.55	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Instituto de Ciencias de la Salud	210.26	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Pontificia Universidad Javeriana, Bogotá Campus	307.66	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Universidad Antonio Nariño	5.72	0.99	1.00	1.00	1.00	1.00	1.00	1.00
Universidad Autónoma de Bucaramanga	24.76	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Universidad Cooperativa de Colombia, Bogotá Campus	14.78	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Universidad Cooperativa de Colombia, Medellín Campus	4.6	0.98	1.00	1.00	1.00	1.00	1.00	1.00
Universidad Cooperativa de Colombia, Santa Marta Campus	33.73	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Universidad de Antioquia	80.58	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Universidad de Boyacá	6.12	0.99	1.00	1.00	1.00	1.00	1.00	1.00
Universidad de Caldas	24.12	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Universidad de Cartagena	0.75	0.19	1.00	1.00	1.00	1.00	1.00	1.00
Universidad de Ciencias Aplicadas y Ambientales	8.1	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Universidad de La Sabana	70.57	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Universidad de los Andes	165.02	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Universidad de Manizales	5.94	0.99	1.00	1.00	1.00	1.00	1.00	1.00
Universidad de Nariño	0	0.50	1.00	1.00	1.00	1.00	1.00	1.00
Universidad de Pamplona	4.8	0.99	1.00	1.00	1.00	1.00	1.00	1.00
Universidad de Santander	4.66	0.98	1.00	1.00	1.00	1.00	1.00	1.00
Universidad de Sucre	5.88	0.99	1.00	1.00	1.00	1.00	1.00	1.00
Universidad del Atlántico	4.76	0.99	1.00	1.00	1.00	1.00	1.00	1.00
Universidad del Cauca	1.18	0.86	1.00	1.00	1.00	1.00	1.00	1.00
Universidad del Magdalena	0.17	0.66	1.00	1.00	1.00	1.00	1.00	1.00
Universidad del Norte	47.3	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Universidad del Quindío	1.89	0.08	1.00	1.00	1.00	1.00	1.00	1.00
Universidad del Sinú Elias Bechara Zainum, Cartagena Campus	3.42	0.97	1.00	1.00	1.00	1.00	1.00	1.00
Universidad del Sinú Elias Bechara Zainum, Montería Campus	10.94	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Universidad del Tolima	2.88	0.04	1.00	1.00	1.00	1.00	1.00	1.00
Universidad del Valle	59.61	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Universidad El Bosque	12.42	0.00	0.01	0.01	0.01	0.01	0.01	0.04
Universidad Icesi	35	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Universidad Industrial de Santander	70.74	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Universidad Libre	0.57	0.77	1.00	1.00	1.00	1.00	1.00	1.00
Universidad Metropolitana	60.9	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Universidad Militar Nueva Granada	8.72	0.00	0.07	0.07	0.07	0.07	0.07	0.29
Universidad Nacional de Colombia	91.78	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Universidad Pedagógica y Tecnológica de Colombia	0.44	0.25	1.00	1.00	1.00	1.00	1.00	1.00
Universidad Pontificia Bolivariana	51.14	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Universidad Santiago de Cali	8.47	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Universidad Simón Bolívar	17.42	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Universidad Surcolombiana	0.01	0.47	1.00	1.00	1.00	1.00	1.00	1.00
Universidad Tecnológica de Pereira	26.21	0.00	0.00	0.00	0.00	0.00	0.00	0.00

* The universities are listed alphabetically.
Source: Own elaboration based on the data obtained in the study.

Table 5. Results of parametric test regarding the difference of proportions in students with B+ classification according to the medical program. 2014.

University *	Z	Criteria for adjusting the p-value						
		None	Holm	Hochberg	Hommel	Bonferroni	Benjamini & Hochberg	Yekutieli & Benjamini
Colegio Mayor de Nuestra Señora del Rosario	14.67	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Instituto de Ciencias de la Salud	14.55	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Pontificia Universidad Javeriana, sede Bogotá	17.58	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Universidad Antonio Nariño	-2.54	0.99	1.00	1.00	1.00	1.00	1.00	1.00
Universidad Autónoma de Bucaramanga	5.07	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Universidad Cooperativa de Colombia, Bogotá Campus	-3.95	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Universidad Cooperativa de Colombia, Medellín Campus	-2.29	0.99	1.00	1.00	1.00	1.00	1.00	1.00
Universidad Cooperativa de Colombia, Santa Marta Campus	-5.88	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Universidad de Antioquia	9.04	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Universidad de Boyacá	-2.64	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Universidad de Caldas	5	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Universidad de Cartagena	0.98	0.16	1.00	1.00	1.00	1.00	1.00	1.00
Universidad de Ciencias Aplicadas y Ambientales	-2.95	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Universidad de La Sabana	8.48	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Universidad de los Andes	12.9	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Universidad de Manizales	-2.55	0.99	1.00	1.00	1.00	1.00	1.00	1.00
Universidad de Nariño	0	0.50	1.00	1.00	1.00	1.00	1.00	1.00
Universidad de Pamplona	-2.33	0.99	1.00	1.00	1.00	1.00	1.00	1.00
Universidad de Santander	-2.28	0.99	1.00	1.00	1.00	1.00	1.00	1.00
Universidad de Sucre	-2.59	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Universidad del Atlántico	-2.26	0.99	1.00	1.00	1.00	1.00	1.00	1.00
Universidad del Cauca	-1.23	0.89	1.00	1.00	1.00	1.00	1.00	1.00
Universidad del Magdalena	-0.56	0.71	1.00	1.00	1.00	1.00	1.00	1.00
Universidad del Norte	6.96	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Universidad del Quindío	1.56	0.06	1.00	1.00	1.00	1.00	1.00	1.00
Universidad del Sinú Elias Bechara Zainum, Cartagena Campus	-1.94	0.97	1.00	1.00	1.00	1.00	1.00	1.00
Universidad del Sinú Elias Bechara Zainum, Montería Campus	-3.42	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Universidad del Tolima	1.89	0.03	1.00	1.00	1.00	1.00	1.00	1.00
Universidad del Valle	7.81	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Universidad El Bosque	3.62	0.00	0.01	0.01	0.01	0.01	0.01	0.03
Universidad Icesi	6.04	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Universidad Industrial de Santander	8.49	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Universidad Libre	-0.85	0.80	1.00	1.00	1.00	1.00	1.00	1.00
Universidad Metropolitana	-7.86	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Universidad Militar Nueva Granada	3.1	0.00	0.04	0.04	0.04	0.04	0.04	0.17
Universidad Nacional de Colombia	9.65	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Universidad Pedagógica y Tecnológica de Colombia	0.8	0.21	1.00	1.00	1.00	1.00	1.00	1.00
Universidad Pontificia Bolivariana	7.25	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Universidad Santiago de Cali	-3.02	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Universidad Simón Bolívar	-4.28	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Universidad Surcolombiana	0.23	0.41	1.00	1.00	1.00	1.00	1.00	1.00
Universidad Tecnológica de Pereira	5.22	0.00	0.00	0.00	0.00	0.00	0.00	0.00

* The universities are listed alphabetically.
Source: Own elaboration based on the data obtained in the study.

The results of applying the statistical tests on the results of the English component of the Saber Pro 2011-2013 and 2015 were not included due to space limitations, but are available upon request.

Table 6 shows that of the 44 programs analyzed, only 9 met the goal in each of the years of the study period. Likewise, it was found that five universities improved: Universidad Autónoma de Bucaramanga, Universidad El Bosque and Universidad Tecnológica de Pereira met the goal for 2014, while Universidad de La Sabana and Universidad Pontificia Bolivariana have met the goal since 2012. On the contrary, Universidad Militar Nueva Granada did not have a clear trend, since it did not meet the goal in 2011, 2012 and 2014. The medical programs of Universidad Icesi and Universidad Javeriana, Cali Campus, met the goal of the government since the first cohort of graduates who presented the Saber Pro test, that is, since 2014 and 2015, respectively.

Table 6. Summary of target compliance (20% of graduates in B+ per medical program). 2011-2015.

University *	2011	2012	2013	2014	2015
Colegio Mayor de Nuestra Señora del Rosario	✓	✓	✓	✓	✓
Instituto de Ciencias de la Salud	✓	✓	✓	✓	✓
Pontificia Universidad Javeriana, Bogotá Campus	✓	✓	✓	✓	✓
Pontificia Universidad Javeriana, Cali Campus	NA	NA	NA	NA	✓
Universidad Antonio Nariño	NA	NA	*x*	*x*	*x*
Universidad del Atlántico	*x*	*x*	*x*	*x*	*x*
Universidad Autónoma de Bucaramanga	*x*	*x*	*x*	✓	✓
Universidad Cooperativa de Colombia, Bogotá Campus	*x*	*x*	*x*	*x*	*x*
Universidad Cooperativa de Colombia, Medellín Campus	NA	NA	*x*	*x*	*x*
Universidad Cooperativa de Colombia, Santa Marta Campus	*x*	*x*	*x*	*x*	*x*
Universidad de Antioquia	✓	✓	✓	✓	✓
Universidad de Boyacá	NA	NA	*x*	*x*	*x*
Universidad de Caldas	*x*	*x*	*x*	✓	*x*
Universidad de Cartagena	*x*	*x*	*x*	*x*	✓
Universidad de Ciencias Aplicadas y Ambientales.	*x*	*x*	*x*	*x*	*x*
Universidad de La Sabana	*x*	✓	✓	✓	✓
Universidad de los Andes	✓	✓	✓	✓	✓
Universidad de Manizales	*x*	*x*	*x*	*x*	*x*
Universidad de Nariño	*x*	*x*	*x*	*x*	*x*
Universidad de Pamplona	NA	NA	*x*	*x*	*x*
Universidad de Santander	*x*	*x*	*x*	*x*	*x*
Universidad de Sucre	NA	*x*	*x*	*x*	*x*
Universidad del Cauca	*x*	*x*	*x*	*x*	*x*
Universidad del Norte	✓	✓	✓	✓	✓
Universidad del Quindío	*x*	*x*	*x*	*x*	*x*
Universidad del Sinú Elias Bechara Zainum, sede Cartagena	*x*	*x*	*x*	*x*	*x*
Universidad del Sinú Elias Bechara Zainum, sede Montería	*x*	*x*	*x*	*x*	*x*
Universidad del Tolima	*x*	*x*	*x*	*x*	*x*
Universidad del Valle	✓	✓	✓	✓	✓
Universidad El Bosque	*x*	*x*	*x*	✓	✓
Universidad Icesi	NA	NA	NA	✓	✓
Universidad Industrial de Santander	✓	✓	✓	✓	✓
Universidad Libre	*x*	*x*	*x*	*x*	*x*
Universidad Metropolitana	*x*	*x*	*x*	*x*	*x*
Universidad Militar Nueva Granada	*x*	*x*	✓	*x*	✓
Universidad Nacional de Colombia	✓	✓	✓	✓	✓
Universidad Pedagógica y Tecnológica de Colombia	*x*	*x*	*x*	*x*	*x*
Universidad Pontificia Bolivariana	*x*	✓	✓	✓	✓
Universidad Santiago de Cali	*x*	*x*	*x*	*x*	*x*
Universidad Simón Bolívar	*x*	NA	*x*	*x*	*x*
Universidad Surcolombiana	*x*	*x*	*x*	*x*	*x*
Universidad Tecnológica de Pereira	*x*	*x*	*x*	✓	✓
Universidad Santiago de Cali, Palmira Campus	*x*	*x*	*x*	NA	NA

✓: The university met the goal, which is determined by rejecting the null hypothesis in favor of the alternative with 95% confidence; *x*: It was not possible to determine if the university met the goal since the null hypothesis could not be rejected in favor of the alternative to include a definition; NA: The university did not register medical students for that year, either because no student classified in B+ existed or had not yet graduated the first class of students of the program.
* The universities are listed alphabetically.
Source: Own elaboration based on the data obtained in the study.

Discussion

The goal (20% of graduates in B+) of the PFDCLE for 2014 countrywide was reached by 28.6% of the medical students evaluated. However, it should be taken into account that only 18 (41.9%) of the 43 medical programs met the goal that year, a percentage that increased to 45.5% in 2015.

To the best knowledge of the authors, this is the first study that uses the Saber Pro tests to study the English proficiency level of future graduates of medical programs and that assesses whether or not the government goal established for 2014 was fulfilled

regarding the proportion of students in intermediate or higher level in English language proficiency. Previous studies that have used Saber Pro tests have done it to study different aspects of Colombian medical graduates, for example, the need to evaluate, through clinical simulation scenarios, skills that are impossible to evaluate by means of a written exam (19), the evaluation of specific skills in health professionals (20) or the importance of training competent professionals that respond to the needs of the country. (21)

The only similar study (22) uses the results of the Saber Pro 2011-2014 tests to assess the English proficiency level of the graduates of the Information Technology sector in Colombia and emphasizes on systems engineering students. The results show that the programs of the software sector did not meet the goal established by the PFDCLE for 2014 in the country (22). In other words, medical students had a better performance than systems engineering students in English.

Conclusions

Results show that the medical programs did meet the bilingualism goal established by the government for 2014. However, it should be taken into account that only 18 (41.9%) of the 43 medical programs met this goal, that is, less than half of the programs met the goal individually.

On the other hand, these results do not fully reflect the state of English language training received by medical graduates because the Saber Pro test only evaluates reading comprehension and language use skills, leaving out other linguistic skills of equal importance such as listening comprehension, and oral and written expression. These competences could be evaluated if other language proficiency tests (such as MET, IELTS, TOEFL or APTIS) were used to assess listening, reading, grammar, writing and oral communication skills. In spite of this, the English section of Saber Pro is the best and only tool available to researchers today to make a national diagnosis of this skill.

Future studies should evaluate if the English proficiency levels achieved by the students are the result of the added value that they receive during their time in the university or if they are product of primary and secondary education. Similarly, it is recommended that future works extend the analysis to other health areas such as Nursing and to other sectors such as Hotel Management and Tourism, which are also part of the Health Tourism sector. Finally, there is still a long way to go in terms of bilingualism if we take into account that this skill is essential for Colombia to achieve a global position in the health tourism sector, which is and will be key to the long-term competitiveness of the Colombian economy.

Conflicts of interest

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References

1. Colombia. Ministerio de Educacional Nacional. Colombia Very Well! Programa Nacional de inglés 2015-2025. Bogotá D.C.: MinEducación; 2014 [cited 2016 Aug 4]. Available from: https://goo.gl/qTTgXW.
2. **Man JP, Weinkauf JG, Tsang M, Sin DD.** Why do some countries publish more than others? An international comparison of research funding, English proficiency and publication output in highly ranked general medical journals. *Eur J Epidemiol.* 2004;19(8):811-7. http://doi.org/d8vqpp.
3. **Valdés-Linares MT, González-Valdés S, Díaz-Cabeza I, Verdayes-Vives A, Díaz-Lobo LM.** La enseñanza del inglés en las ciencias médicas: su repercusión social. *Rev Ciencias Médicas.* 2010;14(3):26-31.
4. Proexport Colombia. Medical Tourism Sector. Bogotá D.C.: Invest in Colombia; 2009 [cited 2016 Aug 16]. Available from: https://goo.gl/WmPrhA.
5. Colombia. Departamento Nacional de Planeación. Política de transformación productiva: un modelo de desarrollo sectorial para Colombia. Bogotá D.C.: DNP; 2010 [cited 2016 Aug 16]. Available from: https://goo.gl/MHKgST.
6. Colombia. Ministerio de Comercio, Industria y Turismo. Desarrollando sectores de clase mundial en Colombia. Bogotá D.C.: McKinsey & Company; 2009 [cited 2016 Aug 15]. Available from: https://goo.gl/Uv6FWi.
7. Colombia. Ministerio de Comercio, Industria y Turismo. Turismo de Salud Comité Sectorial Q1. Bogotá D.C.: Programa de Transformación Productiva; 2010 [cited 2016 Aug 15]. Available from: https://goo.gl/QohKiA.
8. **Divi C, Koss RG, Schmaltz SP, Loeb JM.** Language proficiency and adverse events in US hospitals. A pilot study. *Int J Qual Health Care.* 2007;19(2):60-7. http://doi.org/c599tp.
9. Migración Colombia. Turismo de salud en Colombia. Tendencias migratorias. Bogotá D.C.: Ministerio de Relaciones Exteriores; [cited 2016 Aug 17]. Available from: https://goo.gl/NRqdiV.
10. **Alonso JC, Gallo BE, Torres G.** Elementos para la construcción de una política pública de bilingüismo en el Valle del Cauca: un análisis descriptivo a partir del censo ampliado de 2005. *Estudios Gerenciales.* 2012;28(125):59-67. http://doi.org/f2kpzh.
11. Perú. Ministerio de Educación. Gobierno emprende nueva política de inglés para que más peruanos accedan a mejores oportunidades. Lima: Minedu; 2015 [cited 2017 Mar 14]. Available from: https://goo.gl/uAAx7K.
12. Chile. Ministerio de la Presidencia. Estrategia nacional de inglés 2014-2030. Satiago de Chile: Gbierno de Chile; 2014 [cited 2017 Mar 14] Available from: https://goo.gl/Kx6R8L.
13. **Holm S.** A simple sequentially rejective multiple test procedure. *Scandinavian Journal of Statistics.* 1979;6(2):65-70.
14. **Hochberg Y.** A sharper Bonferroni procedure for multiple tests of significance. *Biometrika.* 1988;75(4): 800-2. http://doi.org/c2v8s5.
15. **Hommel G.** A stagewise rejective multiple test procedure based on a modified Bonferroni test. *Biometrika.* 1998;75(2):383-6. http://doi.org/d8v4f7.
16. **Benjamini Y, Hochberg Y.** Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society. Series B (Methodological).* 1995;57(1):289-300.
17. **Yekutieli D, Benjamini Y.** Resampling-based false discovery rate controlling multiple test procedures for correlated test statistics. *Journal of Statistical Planning and Inference.* 1999;82(1-2):171-96. http://doi.org/ctfdqf.
18. R Core Team. R: A language and environment for statistical computing [software]. Vienna: R Foundation for Statistical Computing; 2016 [cited 2018 Feb 6]. Available from: https://goo.gl/HPGSnw.
19. **Delgado-Ramírez MB.** Examen de Estado de la Calidad de la Educación Superior: SABER PRO. ¿Qué indican sus resultados? Rev colomb anestesiol. 2013;41(3):177-78. http://doi.org/f2kqw6.
20. **Pinilla-Roa AE.** Evaluación de competencias profesionales en salud. *Rev Fac Med.* 2013;61(1):53-70.
21. **Pinilla-Roa AE.** Medicina y educación. *Rev Fac Med.* 2011;59(4):275-9.
22. **Alonso-Cifuentes JC, Estrada-Nates D, Martinez-Quintero DA.** ¿Se cumplió la meta de bilingüismo en los programas de educación universitaria del sector software en Colombia? *Rev. Educación En Ingeniería.* 2016;11(22):39-45.

ORIGINAL RESEARCH

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Characterization of congenital craniofacial anomalies in a specialized hospital of Risaralda, Colombia. 2010-2014

Caracterización de anomalías craneofaciales congénitas en hospital de cuarto nivel en Risaralda, Colombia, 2010-2014

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| Abstract |

Introduction: Congenital craniofacial malformations have a major impact on the lives of children and their relatives when the face is compromised since they may present along with cognitive deficits or altered facial appearance. There are no conclusive data on the presence of these malformations in the Coffee Region.

Objective: To identify the frequency of congenital craniofacial malformations during a 4-year period in a private institution of the city of Pereira, Risaralda, Colombia.

Materials and methods: Retrospective cross-sectional study. Data were collected from the medical records of 243 883 patients who were attended for the first time at a private health institution of the central-western region of Colombia. Statistical analysis was performed using the R software and Excel version 2007.

Results: Between January 2010 and December 2014, 1 807 patients with congenital craniofacial malformation were treated, which corresponds to 19.5% of the total of congenital anomalies, being cleft lip and palate the most frequent.

Conclusion: Although congenital cranial malformations occur frequently, there is little information about its etiology. Early diagnosis can prevent future complications that lead to deterioration of health or to an additional cost to the health system.

Keywords: Congenital Abnormalities; Skull; Face (MeSH).

| Resumen |

Introducción. Los defectos craneofaciales congénitos pueden causar un impacto en la vida de los niños y de sus familias cuando comprometen el rostro. Además, pueden estar acompañados de alteración de las funciones cerebrales o de la apariencia facial. No se tienen datos concluyentes sobre la presencia de estos defectos en el Eje Cafetero.

Objetivo. Identificar la frecuencia de las malformaciones craneofaciales congénitas en un periodo de cuatro años en una institución privada de la ciudad de Pereira, en Risaralda, Colombia.

Materiales y métodos. Estudio trasversal retrospectivo. La información fue recolectada a través del sistema de información de historias clínicas de pacientes que consultaron por primera vez en una institución privada de salud. El análisis estadístico fue realizado mediante el software R y Microsoft Excel versión 2007.

Resultados. Entre enero del 2010 y diciembre del 2014 se atendieron 1 807 pacientes con malformaciones craneofaciales congénitas, lo que corresponde al 19.5% del total de las anomalías congénitas. La hendidura labio-palatina fue la más frecuente.

Conclusiones. Aunque las malformaciones craneofaciales congénitas se presentan con frecuencia, se sabe muy poco de su etiología. El diagnóstico temprano puede prevenir futuras complicaciones que deterioren la salud o que generen un sobrecosto para el sistema de salud.

Palabras clave: Anomalías congénitas; Cráneo; Cara (DeCS).

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Silva-Giraldo X, Porras-Hurtado GL. [Caracterización de anomalías craneofaciales congénitas en hospital de cuarto nivel en Risaralda, Colombia, 2010-2014]. Rev. Fac. Med. 2018;66(2):223-7. English. doi: http://dx.doi.org/10.15446/revfacmed.v66n2.61551.

Introduction

The frequency of congenital malformations is 310 per 10 000 births worldwide. Among them, craniofacial malformations represent between 10-15% of cases, including ear malformations with a prevalence of 74.1 per 10 000 births, followed by cleft lip and palate with 15.9 per 10 000 births. (1) Orofacial clefts are the most common and serious, and their frequency is highly variable depending on the population.

From an embryological perspective, the development of the head and neck begins with the formation of branchial or pharyngeal arches, which appear between the fourth and fifth week of intrauterine development. These arches are involved in the formation of the neck and the first and the second arches, in particular, play an important role in the formation of the face, which develops between the fourth and the twelfth week of the embryonic period. (2) The primary palate, the alveolar ridge and the premaxilla form during the sixth week, while the secondary palate ends its formation by the twelfth week. (3) Any noxa of environmental or genetic origin during this period can alter development, resulting in craniofacial malformations. (4)

Microtia, anotia or fistulas, preauricular appendages, facial clefts and craniosynostosis usually occur in isolation in 45-50% of cases. Moreover, they can be part of syndromic pictures, considered as syndromes, sequences, field defects or associations (5,6), such as the Charge syndrome, Townes-Brocks syndrome, BOR syndrome, Treacher Collins syndrome, diabetic embryopathy and facio-auricular-vertebra syndrome. (2) Some studies suggest that between 44-64% of patients with clefts have associated anomalies.

Congenital craniofacial malformations require early interdisciplinary management since they have an impact on the lives of children and their relatives when the face is involved, leaving sequels such as cognitive deficit or alteration of facial appearance. (7) There are no conclusive data on the presence of these malformations in the Coffee Region, so it is important to define a baseline regarding the most frequent cases in the region.

This study shows the frequency of congenital craniofacial malformations during a four-year period in a private institution of the city of Pereira in Risaralda, Colombia, with the purpose of providing data that allow proposing strategies for the prevention and management of these pathologies.

Materials and methods

This is an observational, descriptive and cross-sectional retrospective research. The information was extracted from an information system called Software AMAHO and SIIS, created in 2003 and patented on July 31, 2007 before the Ministry of the Interior and Justice of Colombia, which is part of institutional development initiatives and allows the interaction between clinical history, laboratory results and consultations for retrospective research.

This system stores daily records on care provided to the consulting population. For the period between January 2010 and December 2014, 243 883 patients were attended, generating 2 258 624 consultations, of which 1 435 451 were outpatient consultations, 116 485 inpatient consultations and 706 688 dental consultations. In other words, 25.9% of the inhabitants of the department of Risaralda were treated in this institution (according to DANE 2010-2014: 938 529 inhabitants). (8)

MySQL inquiries were made in the information system with the following inclusion criteria: patients from the department of Risaralda, first diagnosis associated with codes ICD-10Q000 to Q999 and codes K0701, K0704 and K0711, which are related to craniofacial malformation. Exclusion criteria were trauma and facial tumors. The variables included in the query were: entity of origin, age (since there was no cut-off point for age, the criteria was based on life cycles), sex, diagnosis according to ICD10 and health service that made the diagnosis.

Spreadsheets were used for data analysis and then exported to Software R version 3.1.3. An analysis of relative and absolute frequencies was carried out, together with the estimation of 95% confidence intervals for the general and specific prevalence of congenital craniofacial anomaly.

This study was approved by the Ethics Committee of the Institution and, according to resolution 8430 of 1993 of the Ministry of Health and Social Protection of Colombia, this research is classified as low risk.

Results

In the period between January 2010 and August 2014, 243 883 patients were treated achieving about 25.9% coverage for the department of Risaralda and its area of influence. Regarding this population (n=243 883), records related to congenital anomalies were found in 7 529 patients (3.08%, 95% CI 3.0-3.1). Of 7 529 patients with anomalies, 19.5% (95%CI 18.6-20.4) (n=1 494) had craniofacial malformations. The distribution of cases according to the variable of age and sex is shown in Figure 1.

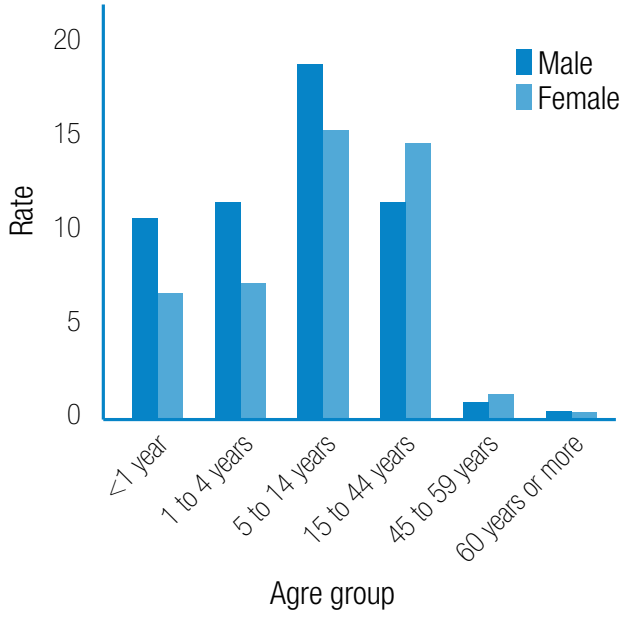


Figure 1. Frequency of patients with craniofacial anomalies by age and sex. Source: Own elaboration based on the data obtained in the study.

A higher rate of craniofacial anomalies was observed in the age group of 5-14 years, which comprises 33.4% of the cases. The male sex is predominant with 58.4%, and a higher rate of diagnoses for both sexes was observed in the age group of 5-14 years. As for location, the distribution is presented in Figure 2.

Places such as the mouth and skull represent about 60% of all craniofacial anomalies. The most frequent diagnoses include cleft lip and palate with 323 cases (18.9%) (Table 1), followed by retrognathism (11.7%), ankyloglossia (9.1%) and macrocephaly (9.0%). These diagnoses are associated with a 48.7% morbidity due to craniofacial anomaly.

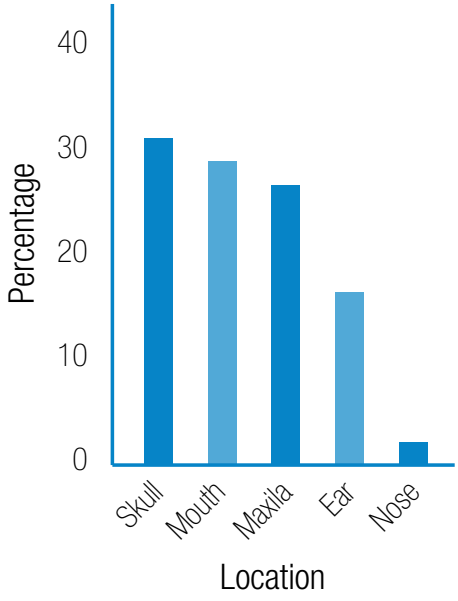


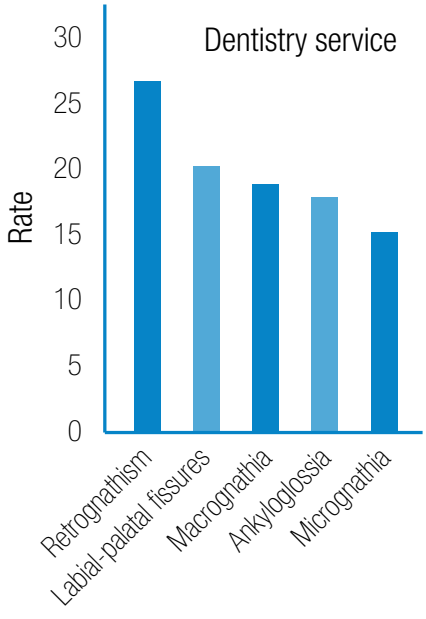
Figure 2. Frequency of craniofacial anomalies according to anatomical location.
Source: Own elaboration based on the data obtained in the study.

Table 1. Cleft lip and palate distribution.

Group	n	%
Cleft lip	36	11.1
Cleft lip and palate	133	41.2
Cleft palate	154	47.7

Source: Own elaboration based on the data obtained in the study.

However, the order of diagnostic frequency varies according to the health service that treats the patient. Figure 3 shows this variation, with a greater proportion of retrognathism and cleft lip and palate diagnoses by the dentistry service, higher diagnosis of fissures and macrocephaly by the inpatient care service, and more Down syndrome, macrocephaly and skull deformities diagnosis by the outpatient consultation service. Regarding chromosomopathies, 79% of cases are Down syndrome.



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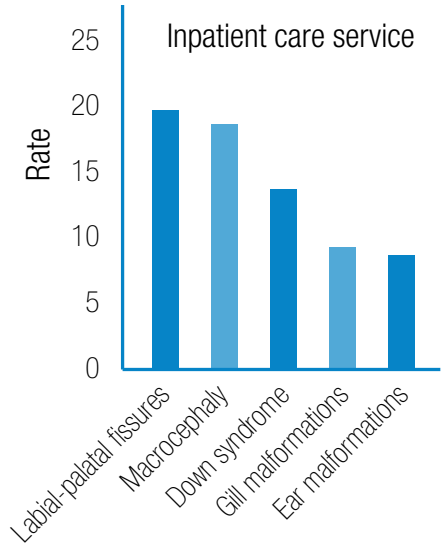

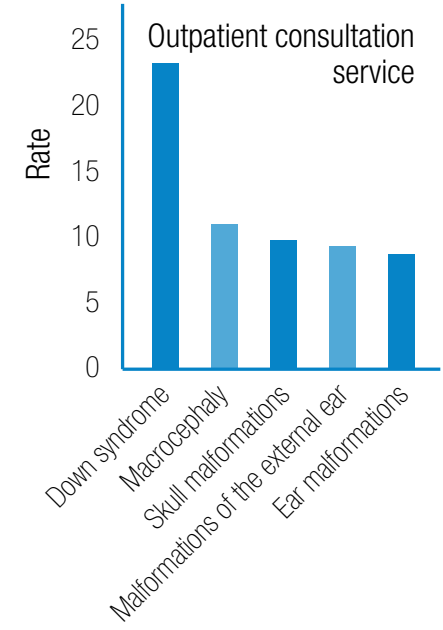

Figure 3. Frequency of patients with craniofacial anomaly by diagnosis and care service.
Source: Own elaboration based on the data obtained in the study.

Discussion

Consortiums such as FaceBase generate scientific initiatives to understand craniofacial malformations in an accelerated manner. Therefore, characterizing the population is the first step to propose diagnosis, therapy and prevention measures based on institutional reality and not on a global perspective. (9-11)

This study reports a rate of 3.1% of congenital defects, as well as a rate of 19.5% attributable to congenital craniofacial malformations among all anomalies; these figures are similar to those reported in the United States and other countries, including Colombia. (7-11) Congenital craniofacial malformations were observed more frequently in male patients, which coincides with the reports by Lisi A *et al.*, who found that these malformations affect men more than women. (12) On the other hand, 323 lip and palate fissures were found, which corresponds to 1 in every 769 attended patients, a finding similar to that found in the literature, most often unilaterally and in the male gender (Table 1).

Oral cleft is one of the most frequent craniofacial congenital malformations, with a reported total prevalence between 1 and 2 per 1 000 live births. Considering differences in embryological development, epidemiology and patterns of family segregation, two types of clefts are observed: cleft lip with or without cleft palate (CL6P) and cleft palate (CP). They are more common in men than in women with a ratio of 2:1 (10) and may have a genetic or environmental etiology. The cause is unknown in 9.2% of cases, monogenic in 3.8%, chromosomal in 4.7% and only 0.6% attributable to teratogens. (13,14)

Worldwide, microtia and anotia have a prevalence of 0.1-2.5% and 0.1-0.6%, respectively. (1,15) Microtia can occur in isolation; however, the severity of this condition is associated with other pathologies such as vertebral anomalies, macrostomy, labial fissures, renal anomalies, facial asymmetry, cardiac defects, microphthalmia, holoprosencephaly and polydactyly. (10-11,16) In the studied population, microtia was reported with a frequency of 2.1%, which differs from other studies carried out in the country, which reported it as one of the most common. This may be related to the fact that this pathology is not reported in an appropriate manner; therefore, training and awareness among health professionals is important to improve diagnosis.

The high presence of retrognathia may suggest that a second assessment of patients with this diagnosis is necessary because of its correlation with Pierre Robin sequence (classic chain of micrognathia, glossoptosis and cleft palate). (11)

The most frequent diagnosis after retrognathia is ankyloglossia, an anomaly that has been defined differently over time. In 1982, it was defined as a frenulum that prevents the protrusion of the tongue, a frenulum that extends to the papillary surface of the tongue, and fissures in the tip of the tongue during normal movements. (17) In 2005, the definition changed to frenulum extending along 25–100% of tongue's total length. (18) Ankyloglossia has a 4.2-10.7% worldwide prevalence (19). Proper diagnosis is important since this condition causes many difficulties such as limited protrusion of the tongue, difficulties for breastfeeding, impaired speech and lack of self-confidence. (20)

The high frequency of craniosynostosis in craniofacial deformities is confirmed by the literature, which reports an average of 1:2 000 live births. (21) About 60% of craniosynostoses are non-syndromic and 40% are syndromic. Although sagittal craniosynostosis is the most frequent within the non-syndromic craniosynostoses group, followed by metopic suture craniosynostosis (22), this study found a low frequency of 1:3 000 live births.

In 2010, the Colombian epidemiological surveillance system activated the mandatory reporting of congenital anomalies, which has required the development of institutional protocols for the systematic assessment of congenital anomalies in newborns. In 2012, the hospital in which the research was conducted joined the Latin American Collaborative Study of Congenital Malformations (ECLAMC by its acronym in Spanish) with a case-control methodology to intensify the search.

In 2013, the Nace una Sonrisa group, made up of professionals from the fields of Perinatology, Neonatology, Pediatrics, Genetics, Plastic Surgery, Maxillary Orthopedics, Phonoaudiology, Psychology, Social Work, Pediatric Dentistry, Maxillofacial Surgery and Orthodontics, was created to strengthen knowledge in each of these disciplines, thus achieving a comprehensive view, not only of diagnosis, but also of the treatment of craniofacial malformations.

Conclusions

The low frequency of microtia and craniosynostosis reported with respect to figures worldwide leads to intensify the active search of this cases and their proper notification. On the other hand, the characterization of the population allows greater optimization of both technological human resources and financial resources, since public health policies can be directed to address malformations with greater prevalence. Finally, an interdisciplinary team for craniofacial malformations care ensures timely management and increases the success of treatments.

Regarding the limitations of the study, the underreporting of diagnosis in hospital care and neonatology services is evident, since only some anomalies are described in the clinical history as lobed and retracted tongue, tongue hypoplasia and frenulum; only the dentistry service reports these observations as diagnosis.

Since this is a study with a cross-sectional design, including patients of any age and born in different places, it was not possible to identify the total base population to define the prevalence of craniofacial malformations in the region; only descriptions of the relative frequency were made based on medical records. Future studies should carry out an analysis of craniofacial malformations based on the identification of congenital anomalies and the epidemiological follow-up established by national standards.

Although congenital craniofacial malformations occur frequently, very little is known about their etiology. Health personnel lack clarity regarding its definition, classification and importance of diagnosing minor and major malformations, in order to look for associated pathologies.

Conflicts of interest

None stated by the authors.

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References

1. **Zarante I, López MA, Caro A, García-Reyes JC, Ospina JC.** Impact and risk factors of craniofacial malformations in a Colombian population. *Int. J. Pediatr. Otorhinolaryngol.* 2009;73(10):1434-7. http://doi.org/fdknt4.
2. **Vila-Morales D.** Clasificación de las alteraciones cefalogénicas desde una visión integradora craneomaxilofacial. *Rev. Cubana Estomatol.* 2013;50(1):2-27.
3. **Seifeldin SA.** Is alveolar cleft reconstruction still controversial? (Review of literature). *Saudi Dent J.* 2016;28(1):3-11. http://doi.org/chs6.
4. **Zarante I, Franco L, López C, Fernández N.** Frecuencia de malformaciones congénitas: evaluación y pronóstico de 52.744 nacimientos en tres ciudades colombianas. *Biomédica.* 2010;30(1):65-71. http://doi.org/b4sm.
5. **Shuper A, Merlob P, Grunebaum M, Reisner SH.** The incidence of isolated craniosynostosis in the newborn infant. *Am. J. Dis. Child.* 1985;139(1):85-6.
6. **Hunter AG, Rudd NL.** Craniosynostosis. *I.* Sagittal synostosis: its genetics and associated clinical findings in 214 patients who lacked involvement of the coronal suture(s). *Teratology.* 1976;14(2):185-93. http://doi.org/fp3tf7.
7. **Cifuentes-Cifuentes Y, Arteaga-Díaz C, Infante-Contreras C, Clavijo-López EG, Quintero-Guzmán C.** Prevalencia y Caracterización de los Recién Nacidos con Anomalías Craneofaciales en el Instituto Materno Infantil de Bogotá. *Rev. salud pública.* 2008;10(3):423-32.

8. Colombia. Departamento Nacional de Planeación. DANE. 2015. [cited 2017 Dec 27]. Available from: https://goo.gl/Np2dSi.

9. **Brinkley JF, Fisher S, Harris MP, Holmes G, Hooper JE, Jabs EW, *et al.*** The FaceBase Consortium: a comprehensive resource for craniofacial researchers. *Development.* 2016;143(14):2677-88. http://doi.org/chs9.

10. **Twigg SR, Wilkie AO.** New insights into craniofacial malformations. *Hum. Mol. Genet.* 2015;24(R1):R50-9. http://doi.org/f7vbsn.

11. **Neben CL, Roberts RR, Dipple KM, Merrill AE, Klein OD.** Modeling craniofacial and skeletal congenital birth defects to advance therapies. *Hum. Mol. Genet.* 2016;25(R2):R86-R93. http://doi.org/f9p38z.

12. **Lisi A, Botto LD, Rittler M, Castilla E, Bianca S, Bianchi F, *et al.*** Sex and congenital malformations: an international perspective. *Am. J. Med. Genet. A.* 2005;134A(1):49-57. http://doi.org/fr82bh.

13. **Rittler M, Lopez-Camelo JS, Castilla EE, Bermejo E, Cocchi G, Correa A, *et al.*** Preferential associations between oral clefts and other major congenital anomalies. *Cleft Palate Craniofac. J.* 2008;45(5):525-32. http://doi.org/brddwq.

14. **Luquetti DV, Cox TC, Lopez-Camelo J, Dutra Mda G, Cunningham ML, Castilla EE.** Preferential Associated Anomalies in 818 Cases of Microtia in South America. *Am. J. Med. Genet. A.* 2013;161A(5):1051-7. http://doi.org/f94d97.

15. **Sárközi A, Wyszynski DF, Czeizel AE.** Oral clefts with associated anomalies: findings in the Hungarian Congenital Abnormality Registry. *BMC Oral Health.* 2005;5:4. http://doi.org/bd6wzs.

16. **Luquetti DV., Heike CL, Hing AV., Cunningham ML, Cox TC.** Microtia: Epidemiology and genetics. *Am. J. Med. Genet. A.* 2012;158A(1):124-39. http://doi.org/fnbtwb.

17. **Ferrés-Amat E, Pastor-Vera T, Ferrés-Amat E, Mareque-Bueno J, Prats-Armengol J, Ferrés-Padró E.** Multidisciplinary management of ankyloglossia in childhood. Treatment of 101 cases. A protocol. *Med. Oral Patol. Oral Cir. Bucal.* 2016;21(1):e39-47.

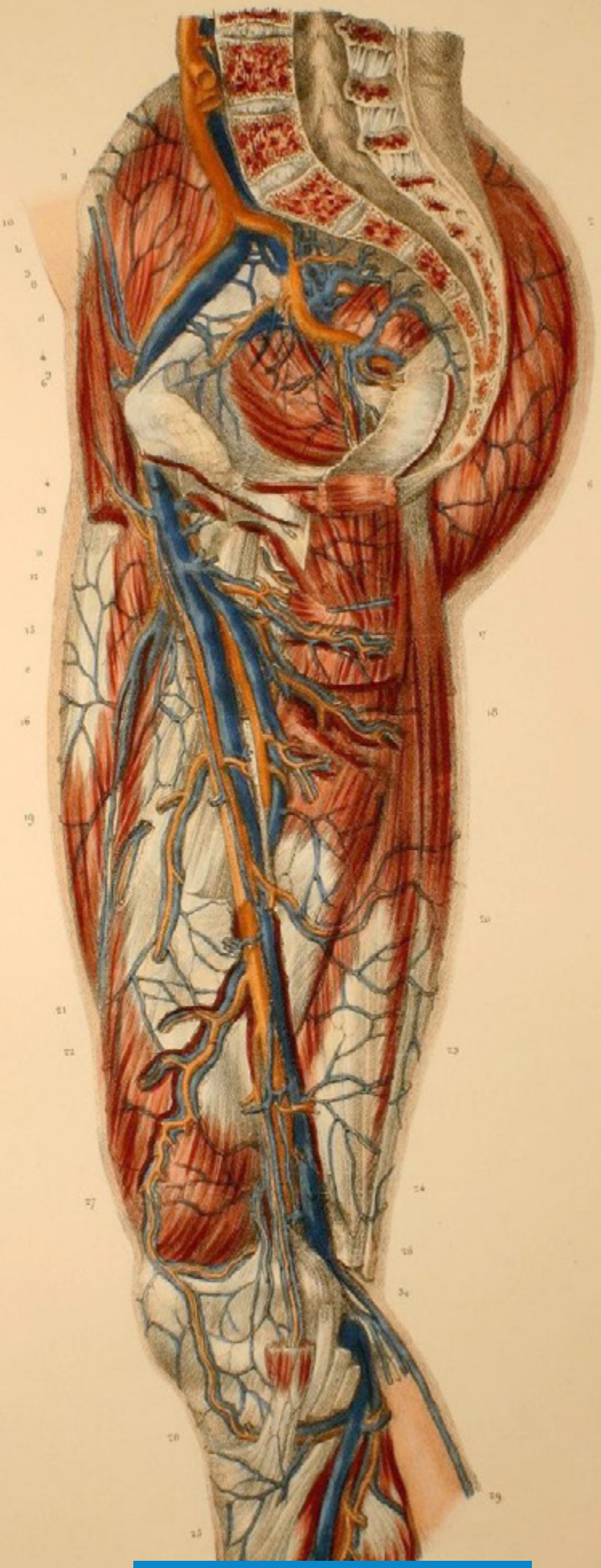
18. **Ricke LA, Baker NJ, Madlon-Kay DJ, DeFor TA.** Newborn tongue-tie: prevalence and effect on breast-feeding. *J. Am. Board Fam. Pract.* 2005;18(1):1-7.

19. **Hogan M, Westcott C, Griffiths M.** Randomized, controlled trial of division of tongue-tie in infants with feeding problems. *J. Paediatr. Child Health.* 2005;41(5-6):246-50. http://doi.org/ds7m9n.

20. **Jangid K, Alexander AJ, Jayakumar ND, Varghese S, Ramani P.** Ankyloglossia with cleft lip: A rare case report. *J. Indian Soc. Periodontol.* 2015;19(6):690-3. http://doi.org/chtf.

21. **Vila-Morales D, Leyva-Mastrapa T, Alonso-Fernández L, Sánchez-Cabrales E, Lazo-Montero JC.** Equipo cubano interdisciplinario de cirugía craneofacial en pediatría. Resultados de un quinquenio. *Rev. Cubana Estomatol.* 2010;47(1):62-80.

22. **Mathijssen IM.** Guideline for Care of Patients with the Diagnoses of Craniosynostosis: Working Group on Craniosynostosis. *J. Craniofac. Surg.* 2015;26(6):1735-807. http://doi.org/chtg.



Jean Marc Bourgery
"Traité complet de l'anatomie de l'homme"
Paris 1832-1854

REFLECTION PAPER

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Professionalism in Anesthesiology training

Profesionalismo en la formación del anestesiólogo

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| Abstract |

This reflection article seeks to define and establish the basic professionalism components required for the best practice of anesthesia. Some examples of unprofessional behavior will be identified, while exposing available tools that can be used for its correction. In consequence, professionalism is proposed as a key component for the development of anesthesiology as a medical specialty and the potential beneficial impact of its inclusion in curricular programs is assessed.

Keywords: Education; Professionalism; Students, Medical; Ethics; Professional Competence; Anesthesiology (MeSH).

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| Resumen |

En el presente artículo de reflexión se busca definir y establecer los componentes fundamentales del profesionalismo requerido para el óptimo ejercicio de la anestesiología. De este modo, se identifican algunos ejemplos de comportamiento no profesional y de las posibles herramientas positivas que se pueden aprovechar. Se propone, entonces, el profesionalismo como eje fundamental para el desarrollo de la anestesiología como especialidad médica y se evalúa el impacto benéfico derivado de su inclusión en los programas curriculares.

Palabras clave: Educación; Profesionalismo; Estudiante; Anestesiología; Ética; Competencia profesional (DeCS).

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Introduction

Life expectancy has increased thanks to medicine; however, a leading role of medical professionalism is necessary for patients to take ownership of their self-care role and achieve a better quality of life, and for physicians to provide professional care in a comprehensive way, so that patients can add more life to their years.

Professionalism is an inherent characteristic of health personnel, whose essence is to offer the best scientific, moral and human assistance. All training programs in health sciences should seek professional excellence. Specifically, anesthesiology should include didactic basis in three phases: *propaedeutic interventions* that include declarative knowledge (knowledge), procedural knowledge (know-how) and non-technical skills (knowing how to be); *demonstration interventions* that combine the different types of knowledge in high fidelity laboratories, preferably, and *practice in patients of health service delivery institutions*, where decisions are based on group autonomy (group code), protocols or treatment guidelines subject to global hospital care standards framed in professional and human care skills. (1)

In the United States, the Accreditation Council for Graduate Medical Education (ACGME) considers that professionalism is one of the six competences that should be permanent and strict considering its mandatory nature for teaching and evaluation. (2,3)

Definitions

Professionalism involves values, attitudes and technical and non-technical skills at the service of fellow human beings in a comprehensive manner, in order to achieve physical and mental well-being. This characteristic is based on humanism and altruism and should be part of the anesthesiology graduate curriculum, in such a way that it enriches its leadership in the entire work environment (intensive care unit, pain unit, surgery room, recovery room). (4)

Different tools and processes are available for the evaluation of the acquisition of basic knowledge and competence components, such as regressive supervision, compliance lists and learning curves (cumulative and in percentage). (1) However, there is no standard for teaching and qualifying competences in professionalism. Anesthesiologists in training, when exposed to patients or teamwork, lack sufficient comprehensive training (knowledge, know-how and fundamentally to be), so rapid detection and correction or appropriate reorientation by the teaching and assistance team must be guaranteed in order to achieve ethical and humanistic behavior.

Competences are appropriate actions that emerge in relation to a specific task, in a specific context. This action is achieved by acquiring and developing knowledge, skills, abilities, aptitudes and attitudes that are manifested in being, knowing, doing and knowing how to do. (5) Furthermore, competences must be addressed based on actions

for the solution of problems and decision making in the provision of health services (6), since they are a prerequisite in anesthesiology to train good professionals. (7) Although these skills are necessary, they are not sufficient. (8)

Reyes-Duque (6) states that evaluative, communicative, creative, argumentative, proactive, resolutive and psychomotor competences are highly relevant, and gives greater importance to clarifying and elucidating when considering these skills as an "installed and adequate capacity for the development, assimilation and expression of universal values, which bring humans and society together with particular values that refer to the individual and his immediate environment". (6, p62)

The medical act, beginning with the modern Hippocratic Oath, establishes a close relationship with feelings of generosity, compassion and concern: "For the most sacred of my beliefs, I promise my patients suitability, openness, commitment to anything that can best serve them, compassion, absolute discretion and confidentiality in accordance with the law." (9, p5) According to Patiño (9), professionalism is characterized by four domains: intellectual capital, intellectual autonomy in decision making, commitment to serve the society and self-regulation, aspects that have been deeply affected by the reform made to Law 100 of 1993 in Colombia.

The development of the medical profession and other health sciences requires vocation for service, although it has been relegated. (10) According to Londoño, "the teaching process does not involve mysticism or love" and "when selecting study programs (medicine, communication, diplomacy, systems, administration, design), popularity prevails and aptitude and vocation are hardly considered." (11)

Paradoxically, depersonalization of the medical act has been enhanced to the point that technology has replaced the human touch required along with semiology. It is true that the scientific impact of discoveries such as the electron microscope, biological markers obtained in the clinical laboratory, diagnostic and ultrasound imaging, telemedicine, surgery, robotics, molecular biology, anesthesia with almost computerized and increasingly precise administration and control systems, and other recent advances, have revolutionized patient care and safety. However, the one thing that has not changed despite these technological developments is the patient himself and his need for human understanding.

The patient, center of humanization

Medicine is a profession that feeds on many disciplines and focuses on the comprehensive care provided to an individual that is considered fragile since Biblical times (Ezekiel 12:20). Through medicine, the patient sometimes heals and sometimes feels relieved, but comfort should also be provided.

According to Patiño (9), the three principles of medical ethics are charity, autonomy and justice. The latter has been affected by the general health social security system, as it has led to deprofessionalize medicine and favored inequity in the provision of health services. Public hospitals that once cared for afflicted patients today are unprotected and almost extinct; thus, the medical act is subject to the profit objectives of the industry and to the power of the market. Postgraduate committees should be the first to respond to these expectations in order to achieve competences in professionalism (12), since the good example of the teachers and their experience will influence students through mirror neurons. (13)

As stated by some researchers, four essential parameters have been established to define professionalism: responsibility, ethics, altruism and humanism. (14) Responsibility implies putting the interests of the patient before those of the physician. Ethics requires moral behavior and unshakeable honest commitment. Altruism relates to empathy brought to action. Finally, humanism is the *raison d'être* of health care.

The Asociación Colombiana de Sociedades Científicas (Colombian Association of Scientific Societies) considers that "humanism has a very intimate relationship with feelings of generosity, compassion and concern" and according to Vera-Delgado, physicians "should put human being as their essential concern, in the center of reflection and as a gravitational axis of the entire universe". (15, p272)

The "first do no harm" principle, enunciated by Hippocrates more than 2 400 years ago, is violated when the professional engages in reprehensible acts such as greed, dishonesty, abuse of authority, discrimination, intimidation, sexual harassment, negligence, waste of the health resources of the institutions, fraud and undeclared conflicts of interest.

The first contact of the anesthesiologist with the patient occurs during the pre-anesthetic assessment, which should be done with enough time to establish a cordial relationship of trust that allows appropriate satisfaction and security to both. For a safe surgery, before entering the operating room *briefing* (planning) should be performed, followed by the *entry*, the *surgical pause* and, at the end of the surgery, *verification* or *exit*; finally, *debriefing* occurs. The purpose of this process is to obtain the best results in care quality. Disagreements with any member of the surgical team must be solved in other scenarios, once the surgery is completed, as the comprehensive and safe care of the patient prevails.

Another non-technical skill that influences teamwork is fluency and altruistic collaboration in labor relations. Anesthesia competence also includes not abandoning the patients at any time and controlling their homeostasis and post-operative pain in a multimodal manner. Critical patients who will undergo a surgical procedure should be managed according to their condition, anticipating complications.

Currently, the work of the surgical team and the on-call anesthesiologist goes beyond the operating room and the hospital, where the patient is provided with comprehensive pain management, close rehabilitation and follow-up of their postoperative conditions, as well as effective education to promote self-care. (16,17)

After a Delphi analysis with a group of 32 anesthesiologists dedicated to teaching (responsible for 16 anesthesia programs in Canada, 13 in England and 3 in France), a list of 36 qualities was obtained. Such qualities were grouped into the following three areas: humanistic quality (15 cases), personal development (7 cases) and metacompetences in anesthesiology (14 cases) (Table 1). (18) The first two have a generic nature and the last one relates exclusively to anesthesiology.

Most of the tasks performed in operating rooms, pain units or intensive care units are carried out by teams, and improper behavior can lead to unprofessional behavior that, in turn, can lead to adverse events. Human, communication and conflict resolution skills must be considered as a fundamental part of professional training and evaluation, since the lives of patients are at risk.

Before being exposed to the current panorama of health mercantilism, graduate anesthesiology students should receive training in professionalism through a formal subject. The teaching-learning process must be continuous and horizontal (19) and must also establish proper pedagogical development; in turn, teachers must be critical and proactive and encourage student participation in active, flexible, autonomous and comprehensive learning. (20)

Each student faces, in a unique and personal way, his/her learning process and that must be respected. In most cases, grades are more important than qualifications and it is the students themselves who self-evaluate and provide feedback. (21,22)

Table 1. Qualities of professionalism in anesthesiology.

Qualities	Median > 6	Median <6
Humanistic	Integrity Confidentiality Adherence to ethical and legal codes Respect for the patient's point of view, dignity and privacy Respect for colleagues and coworkers Responsibility for their personal actions with the patient and society Reliability Maturity Empathy	Unbiased Altruism
Personal development	Self-awareness Commitment to continuing education Acceptance of uncertainty and error Acceptance of criticism Maintenance of the personal and professional dimension	Motivation Orientation Capacity
Metacompetencies	Surveillance Response speed Teamwork Flexibility Decision-making capacity Style Confidence Communication Experience in pattern recognition	Resourcefulness Assertiveness Conflict resolution Fluency Administrative skills Leadership

Source: Own elaboration based on Kearney. (18)

The curriculum

In developed countries, where health information has surprising records, lack of ethics prevails over lack of expertise or competitiveness in medical claims. (14)

A mechanism proposed for the follow-up of postgraduate students is evaluation of the following academic-assistance aspects: professional attributes and responsibility; self-improvement and adaptability; relationship with patients, and interpersonal relationship with other members of the health team. Curricular implementation of professional training in anesthesiology should be horizontal, as is the case of some American universities. (7) For this, it is important to involve students with the precepts of responsibility, humanism and ethics.

Professionalism also involves the well-being and quality of life of human resources. Carrying out any work activity requires job stability, decent conditions, personal satisfaction, fair remuneration, confidence, etc. In Colombia, organizations and scientific and professional associations of the health sector denominated the period between April 2016 and April 2017 as the "Year of Human Resources in Health" with the purpose of drawing the government's attention to the pressing needs for dignifying work and quality of life for professionals and health workers. Statutory Law 1751 recognizes the right to health as a fundamental right and seeks to recognize the autonomy of health professionals. (23) Article 17 clearly establishes it, provided that it is exercised within a framework of self-regulation, ethics, rationality and scientific evidence. Additionally, Article 18 promotes fair and dignified working conditions, with stability and facilities to increase knowledge, in accordance with the needs of the institutions.

It can be inferred that a professional who acknowledges that the labor market offers decent salaries and working conditions can count on ideal conditions to carry out his/her work with a sense of belonging, coherence and professionalism.

Proposal for postgraduate programs

The authors propose to design a template to be applied periodically to anesthesiologists in training as a tool for learning and evaluation. It should include an evaluation of non-technical skills such as behavior of the graduate student during service, the acceptance of imposed work and respectful relationships with other members of the team, the patients, the nurses and the support staff (Table 2).

The evaluation must be supported by several teachers in different clinical rotations in order to allow the comprehensive development of students, where social and ethical aspects complement competences and prevail over any other interest. The altruistic behavior of the professional and empathy taken with responsibility and respect to practice were considered for the construction methodology of this tool, since it differs from disruptive behaviors that may manifest an underlying pathological condition that needs special attention. (24) This instrument requires validation to be applied in other clinical training environments, as in the case of proposals such as the study that compares scrupulosity with professionalism, which concluded that the first characteristic is desirable, but does not necessarily have to be part of professionalism. (25)

Table 2. Tool for the evaluation of non-technical skills of residents (physicians in training).

Name (photo included): **Year of residency:** **Rotation Hospital:**					
1. The behavior of the resident during the rotation has been appropriate					
0	1	2	3	4	5
Not observed	Poor		Good		Excellent
2. The resident accepts assigned tasks without unfounded complaints					
0	1	2	3	4	5
Not observed	Poor		Good		Excellent
3. The resident treats the support staff with respect					
0	1	2	3	4	5
Not observed	Poor		Good		Excellent
4. The interaction of the resident with other anesthesiology residents and residents of other specialties is appropriate					
0	1	2	3	4	5
Not observed	Poor		Good		Excellent
5. The resident treats patients in a respectful manner					
0	1	2	3	4	5
Not observed	Poor		Good		Excellent
6. The resident treats the nurses in a respectful manner					
0	1	2	3	4	5
Not observed	Poor		Good		Excellent
Department coordinator External observer					

Source: Own elaboration based on Dorotta *et al.* (7)

Conclusions

Anesthesiologists are health professionals who exercise the science and art of medicine; in consequence, they provide individual and collective well-being to the society. The report of the Carnegie Foundation for the Advancement of Teaching, published in 1910 and based on Flexnerism, transformed the schools of medicine with the highest humanistic values around the world. However, new modalities of health service provision have emerged that are alien to teaching methods and have enormous repercussions on patient care, such as the rupture of the doctor-patient relationship and the management of medical practice.

Furthermore, depersonalization and deprofessionalization undermine humanism, but in spite of that, they are being implemented in both undergraduate and postgraduate programs. With this in mind, it is proposed to rescue humanistic values in the postgraduate curriculum and to return to the theses raised more than 24 centuries ago by Hippocrates and taken up by Abraham Flexner, who proposed that physicians must be educated persons, in whom science, humanism and social responsibility converge in an indissoluble way.

The environment, the training method, the application and the evaluation of humanistic and ethical principles contained in professionalism have a beneficial effect for all parties involved in the care process, inside and outside the hospital: patients, health team and social security health system.

Conflicts of interest

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References

1. **Navarro-Vargas JR, Reyes-Duque G, Ramírez-Novoa E.** Aprendizaje de habilidades psicomotoras. Bogotá D.C.*:* Centro Editorial S.C.A.R.E.; 2013.
2. **Duff P.** Teaching and assessing professionalism in medicine. *Obstet Gynecol.* 2004;104(6):1362-6. http://doi.org/c7bnn6.
3. **Toledo-de Mendoza E, Mitre-Cotta RM, de Paula-Lelis V, Carvalho-Junior PM.** Assessment professionalism in students of health-related courses: a systematic review. *Interface.* 2016;20(58):679-80. http://doi.org/bjwz.
4. **Tetzlaff JE.** Professionalism in Anesthesiology. "What is it?" or "I Know It When I See It". *Anesthesiology.* 2009;110(4):700-2. http://doi.org/br83pv.
5. Colombia. Congreso de la República. Ley 1164 de 2007 (octubre 3): Por la cual se dictan disposiciones en materia del Talento Humano en Salud. Bogotá D.C.: Diario Oficial 46771: octubre 4 de 2007.
6. **Reyes-Duque G.** Formación por competencias en los programas de posgrado de anestesia. *Rev Col Anest.* 2004;32(1):55-64.
7. **Dorotta I, Staszak J, Takla A, Tetzlaff JE.** Teaching and evaluating professionalism for anesthesiology residents. *J Clin Anesth.* 2006;18(2):148-60. http://doi.org/fw6353.
8. **Glavin RJ.** Excellence in anesthesiology: the role of nontechnical skills. *Anesthesiology.* 2009;110(2):201-3. http://doi.org/czm927.
9. **Patiño JF.** El juramento hipocrático. In: Pensar la medicina. Bogotá D.C.: Universidad Nacional de Colombia; 2014. p. 206-208.
10. **Arango-Restrepo P.** ¿Ha cambiado la esencia de la medicina con los adelantos modernos? *rev.latinoam.bioét.* 2013;13 (2):60-9. http://doi.org/cjd7.
11. **Londoño JC.** La marina americana y la poesía griega. El Espectador. 2017 Jan 9 [cited 2017 Jun 6]; editorial. Available from: https://goo.gl/D5rv6L.
12. **Briggs A, Raja AS, Joyce MF, Yule SJ, Jiang W, Lipsitz SR, *et al.*** The role of nontechnical skills in simulated trauma resuscitation. *J Surg Educ.* 2015;72(4):732-9. http://doi.org/cjd8.
13. **Bautista J, Navarro JR.** Neuronas espejo y el aprendizaje en anestesia. *Rev. Fac. Med.* 2011;59(4):339-51.
14. **Papadakis MA, Osborn EH, Cooke M, Healy K.** A strategy for detection and evaluation of unprofessional behavior in medical students. University of California, San Francisco School of Medicine Clinical Clerkships Operation Committee. *Acad Med.* 1999;74(9):980-90.
15. **Vera-Delgado A.** Humanismo y medicina, y algunas reflexiones pertinentes. *Rev Col Cardiol.* 2004;11(6):270-6.
16. **Larsson J, Holmström I, Rosenqvist U.** Professional artist, good Samaritan, servant and co-ordinator: four ways of understanding the anesthetist's work. *Acta Anaesthesiol Scand.* 2003;47(7):787-93. http://doi.org/dcm8x3.
17. **Kash B, Cline K, Menser T, Zhang Y.** The perioperative surgical home (PSH). A Comprehensive Literature Review for the American Society of Anesthesiologists. College Station: Center for Health Organization Transformation; 2014 [cited 2017 Jan 23]. Available from: https://goo.gl/TE63NB.
18. **Kearney RA.** Defining professionalism in anaesthesiology. *Med Educ.* 2005;39(8):769-76. http://doi.org/d96cx9.
19. **Jaramillo J, Gaitán C.** Prácticas de enseñanza universitaria en el campo de las ciencias de la salud. *Revista Educación y Desarrollo Social.* 2010;4(1):108-29.
20. **Bain K.** Lo que hacen los mejores profesores de universidad. 2nd ed. Barcelona: Universitat de València; 2007.
21. **García-Valcárcel A.** Didáctica Universitaria. Madrid: La Muralla 2001.
22. **Larsson J.** Studying tacit knowledge in anesthesiology: a role for qualitative research. *Anesthesiology.* 2009;110(3):443-4. http://doi.org/fdk29k.
23. Colombia. Congreso de la República. Ley Estatutaria 1751 de 2015 (febrero 16): Por medio de la cual se regula el derecho fundamental a la salud y se dictan otras disposiciones. Bogotá D.C.: Diario Oficial 49427: febrero 16 de 2015.
24. American Medical Association. Physicians and disruptive behavior. AMA; 2004.
25. **Sawdon MA, Whitehouse K, Finn GM, McLachlan JC, Murray D.** Relating professionalism and conscientiousness to develop and objective, scalar, proxy measure of professionalism in anaesthetic trainees. *BMC Mel Educ.* 2017;17(1):49. http://doi.org/cjfg.

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From animal spirits to scientific revolution in Medicine (first part)

De los espíritus animales a la Revolución científica en medicina (primera parte)

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| Absctract |

Introduction: Back in the sixth century BC, as part of the evolution of Medicine, a philosophical idea was proposed to explain how the nervous system works based on elements known as animal spirits, considered for many centuries as transmitters of sensation and movement. This philosophical concept, with a speculative basis, prevailed until the seventeenth century with subtle changes, but was later outweighed by demonstrative advances in neurophysiology.

Discussion: Dogmatic tradition dictated for centuries that the animal spirits that controlled body actions were transmitted through the nerves; however, with the scientific revolution, such ideas were changed by better elaborated concepts supported by the scientific method.

Conclusion: The old concept of the functioning of the nervous system changed radically after the seventeenth century, when knowledge on morphophysiological characteristics of the nerves was expanded, opening new doors in search of more coherent explanations detached from any religious influence.

Keywords: Medicine; Science; Nervous System (MeSH).

| Resumen |

Introducción. En el desarrollo de la medicina, a partir del siglo VI a.C., se planteó una idea filosófica para explicar el funcionamiento del sistema nervioso con base en elementos conocidos como espíritus animales, considerados durante muchos siglos como agentes transmisores de las sensaciones y del movimiento. Este concepto filosófico de base especulativa prevaleció hasta el siglo XVII con sutiles modificaciones, pero después fue superado mediante demostración con los avances logrados en neurofisiología.

Discusión. Por tradición dogmática se aceptó durante muchos siglos que a través de los nervios se transmitían espíritus animales que controlaban las acciones corporales. A partir de la Revolución científica tales ideas cambiaron por conceptos mejor elaborados con apoyo del método científico.

Conclusión. El concepto que se tenía antiguamente sobre el funcionamiento del sistema nervioso cambió de forma radical a partir del siglo XVII con la ampliación del conocimiento de las características morfofisiológicas de los nervios, abriendo nuevas puertas en busca de explicaciones más coherentes y desligadas de cualquier influencia religiosa.

Palabras clave: Medicina; Ciencia; Sistema nervioso (DeCS).

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Introduction

Several bibliographical sources consulted since the sixth century BC until the seventeenth century mention ideas and philosophical concepts that were used in the past to explain the functioning of the nervous system and how the transmission of information through the nerves to control body actions was conceived.

A special type of cells, known as neurons, which are found in the nervous system, was discovered in the nineteenth century of our era, but some elements and concepts related to them were already conceived since ancient times. According to historical sources, Alcmaeon of Croton, philosopher, naturalist and doctor, of whom there are no reports regarding his date of birth and death, is considered to be the first to propose, at the end of the sixth century BC, that psychic functions had their seat in the brain. (1,2) He reached this conclusion based on clinical observations and experimental work on the intimate connection that sense organs have with the brain through communication channels or "pores" through which

sensations circulate. He also conducted detailed studies of the eyes and discovered the origin of the optic nerves. For Alcmaeon, the brain was the central organ where all sensory and psychic activities resided (3,4), therefore, it was the place where consciousness, sensations and understanding resided as well. (1)

A few years later, Hippocrates (460-371 BC), a famous physician born on the island of Cos, proposed the existence of three spirits (*pneumas*) to explain the general physiology of the human body. These three spirits (natural or vegetative, vital and animal) (5) impelled its functioning. This idea of the spirits was also supported by some Dogmatists such as Satyrus, Stratonicus, Aeficianus and Aeschrion, a follower of the Empirics. All of them thought that the diseases of the body depended on alterations of the *pneuma*. (6) At the time, physiology conceived the spirit as a special form of matter that put organs into operation.

So, Hippocrates thought that animal spirits, which are superior to the other two, came from the outside air and were taken to the brain to induce the development of intelligence (5), and that the brain was the seat of the soul. (7) Hippocrates also developed the theory of the humors, in which he reflected his belief that the body was composed of four fundamental humors: blood, phlegm, yellow bile and black bile. (8,9) Based on these postulates, Aristotle (384-322 BC) explained that the sensations of the body and those coming from the outside world were transmitted by the animal spirits in the form of vibrations, and that such spirits were light particles that moved like the wind through the blood, circulating from the heart to the brain and muscles to connect finally with the soul or vital principle, located in the pineal gland. (5)

In another part of the world, around this time, the ancient Egyptians had a similar idea. They believed that three entities were released at the time of death: the Ka, the Ba and the Akh. For the Egyptians, the Ka was the life force of the individual and was related with food intake; since humans need to eat to sustain life, food was necessary even beyond death. The Ba is what transcends, the soul; while the Akh is the luminous body. (10)

Later, Herophilus of Chalcedon (335-280 BC), renowned physician of the court of King Ptolemy II and professor in Alexandria and considered as the first anatomist to perform anatomical dissections in public, (11) made important anatomical findings, and also practiced vivisections in criminals who had been sentenced to death. (12,13) Some of these findings relate to the differences between the brain and the cerebellum, which led him to state that intelligence was located in the brain (2) and not in the heart, as Aristotle had previously proposed. He also differentiated the blood vessels and the tendons of the nerves (3,14) and classified the latter into sensory and motor nerves. Additionally, he proposed a theory about the functionality of animal spirits in which *pneuma zoticon (spiritus vitalis)*, found in the blood, was transported from the heart to the brain and transformed in the lateral ventricles into *pneuma psykhikon (spiritus animalis)* (15-17), spirit responsible for life functions, to travel through the nerves to the muscles. (18,19)

Erasistratus of Cos (304-250 BC), Herophilus's contemporary, although a little younger than him, was a Greek physician and anatomist considered to be the forefather of neurophysiology. Together with Herophilus, he founded the Alexandria School of Medicine and developed a new anti-hypocritical physiology. (20) Some of his most important contributions include the characterization and differentiation of the anterior and posterior horns of the spinal cord and their role in sensibility and motor skills, and in the distribution of the brain gyri in different species and their connection to the degree of intelligence. He also demonstrated the solid tubular structure of the nerves, which were not hollow, as was believed at that time, and that animal spirits were transported through them to allow control of muscle movement. (21,22) Erasistratus concluded that the coordinating center of psychic life was located in the cerebellum and the meninges. (20)

Although the Greek physician Galen of Pergamon (130-201 BC) made important anatomical contributions through dissections, after analyzing the nervous system and observing that it occupied the central region of the organism, he proposed that the brain controlled all other organs, and even demonstrated that the muscles were controlled by different levels of the spinal cord through a network of hollow nerves organized in two ways, one coming from the senses and another that allowed to perform all physical actions. (6)

Nevertheless, the thought of Galen was strongly influenced by old philosophical ideas, like the doctrine of the three spirits proposed by Philolaus of Croton (449-350 BC). When he explained how the brain exerted control, he affirmed that everything began with food intake and that the product of digestion was taken from the intestines to the liver where it was used to create the natural spirits. Natural spirits were then taken to the right side of the heart, where they were transformed into vital spirits. Then they were carried by the blood to the cerebral ventricles where, finally, they were converted into animal spirits. (23)

According to Galen, animal spirits propagated through the nerves to control the body. (24) This is the first known hypothesis that attempts to explain what is known today as nerve transmission; this theory was valid for more than 1 500 years without undergoing almost any modification; and then came an era of obscurantism, linked to little research and generation of new ideas. Mondino de Luzzi (1270-1326), in his book entitled *Anathomia corporis humani*, written in 1319, preserved the idea that the brain is divided into three vesicles (25) and proposed, as a new element, that the choroid plexus was the vesicle that regulated the flow of *spiritus animalis*. (26)

By the end of the Middle Ages and during the Renaissance, despite Leonardo da Vinci (1452-1519) and Andreas Vesalius (1514-1564), two brilliant anatomists, it was accepted, without further questioning, that the animal spirits that controlled the body were transmitted by the nerves. Through dissections carried out on executed criminals, Vesalius reached conclusions that contradicted established Galenic dogmas. He noticed, for example, that the structure of the brain was quite different from that proposed by Galen and that the cerebral vesicles did not contain *spiritu*, but were filled with a clear fluid: cerebrospinal fluid.

In turn, Leonardo da Vinci gave great importance to cerebral vesicles by stating that, in addition to playing a receptive and analytical role, they had a dynamic function, since they transmitted the orders for movement and human emotions. Da Vinci thought that a system of nerve pipes arose from the spinal cord through which motor impulses were transmitted to the peripheral regions of the body, and that the animal spirits that carried the sense of touch were transported through such pipes to the vesicles for processing. (27)

However, despite questioning that the nerves were not hollow, Vesalius said that they served to carry animal spirits. (28) It is believed that this thought was more related to the fear of questioning religious ideas than to his scientific conviction. At least that is deduced from the following words: "I will refrain from considering the divisions of the soul and its location, since today many censors of our very sacred and true religion can be found." (29)

During the Scientific revolution, between the sixteenth and seventeenth centuries, new ideas and knowledge emerged in the scientific world that completely transformed the ancient conceptions about nature, based largely on speculation and deduction. This transformation of scientific thought was driven mostly by René Descartes (1596-1650), a leading French philosopher, mathematician

and physicist. In his work entitled *Discourse on the method,* he defined the rules that the method should have to "rightly conducting one's reason and seeking truth in the sciences." (30) Descartes also proposed that the pineal gland was not only the material support of the divine spirit, but was responsible for the correct communication between the human machine and its environment. (31) He stated that the cerebrospinal fluid that filled the brain vesicles was under pressure and that when the mind decided to perform an action, the pineal gland turned in a particular direction. In this way, he linked the movement of the cerebrospinal fluid, which traveled from the brain to the nerves, with the genesis of movement (32), thus facilitating the distribution of animal spirits. (33)

Although Descartes influenced scientific thinking, he retained the idea of the *spiritus animalis* of his predecessors. (34) His contemporary, Niels Stensen (1638-1686), refuted this thesis and, by means of a careful dissection, revealed the correct position of the pineal gland, showing that it was a fragile structure fixed on the diencephalon and that it tended to break easily when it moved, therefore, it could not produce movements. (33)

Starting with Descartes, new knowledge had to be supported with the scientific method in order to reject ancient paradigms. For example, in the field of anatomy, Thomas Willis (1621-1675) made important contributions: he classified the cranial nerves into nine pairs (35), described the thalamus of the mammillary bodies, the arborescent arrangement of the gray and white matter of the cerebellum and the circulation of the brain with the classical figure of the polygon, which later took his name. (36) This allowed ending with Galen's paradigm of the *rete mirabile*. However, in the field of physiology, Willis made an unforgivable mistake and fell into speculations, as he continued to support the theory of animal spirits, stating that they were formed in the brain by distillation from arterial blood and then went down the nerves to the organs, where they acted as agents of sense and movements. (37)

Finally, in the seventeenth century, Galen's hypothesis began to be dismantled with the help of rudimentary microscopes that allowed establishing, by observing histological preparations of the nerves, that such structures were not hollow. At the same time, Giovanni Alfonso Borelli (1608-1679), physicist and mathematician who applied his knowledge to physiology, tried to solve his doubts about the presence of animal spirits as generators of muscular movement. For this purpose, he designed an experiment in which he submerged one of the limbs of an animal in water and then cut a muscle to see if *pneumas* came out of the wound in the form of bubbles. As he did not see any reaction, he concluded that such spirits did not exist and proposed a second hypothesis to explain the mechanism of muscular contraction, which explained that it was generated by the fermentation of some substances. (38)

Discussion

The magical and speculative thinking that prevailed in the past resulted in the formulation of explanations based on false cause-effect relationships. Such ideas were unsuccessful considering the falseness of the precepts on which they were founded. They spoke about phenomena in a superficial manner and lacked operating force in the world of reality. (39) The tradition of keeping ideas as dogmas has prevailed throughout the history of mankind, but this thought has switched from demonstration to experimentation over time, which is an intelligent theoretical-practical exercise. (40) Hence, at first, science advanced slowly due to irrational conceptions and postulates (10) such as animal spirits to explain the transmission of nerve impulses. Science gives us solid and real support taken from evidence, separating itself from religious dogmas that avoid reflection and intelligent analysis (40), as was the case of Vesalius (29), so ideas are based on reality and are not the result of mere speculative reasoning.

In the field of physiology, the concept of animal spirits as entities that emerged from the air and were transported to different parts of the body —conducting sensory information and allowing cognitive processes— was the result of the speculative reasoning that lasted until the seventeenth century, when the scientific revolution occurred. With the implementation of the scientific method applied to morphological investigations, it was possible to start proving that the nerves were not hollow structures in the way that Galen had described. (6) The physiological studies by immersion of body parts performed by Borelli (38) strongly refuted the idea that prevailed at that time in relation to the presence of animal spirits, as gaseous entities, that traveled through the nerves to generate movement.

This whole thought of revolution allowed creating a new intellectual and academic environment that was evident in almost all areas of knowledge, leading to the emergence of new theories and concepts that could be explained by experimental demonstration, more adjusted to the reason. All this made possible the development of new and better techniques of experimentation in the field of physiology easier, which allowed giving an increasingly coherent explanation to the phenomenon of nervous transmission. Finally, history led us to the concept known today as action potential or nervous impulse. Therefore, we had to separate ourselves from metaphysical and religious doctrines to modify reality (39), and thus become aware of the way how the body communicates through the nervous system.

Conclusion

The idea of animal spirits was speculative and emerged at the dawn of medicine to satisfy the need to provide an explanation from the religious "rationality" to the physiological mechanisms that allow communication between the nervous system and the different parts of the body. With the advent of the scientific method and experimental demonstration in the field of physiology, complemented by morphological studies of the nerves, it was possible to separate medical science from religious thought following the scientific revolution of the seventeenth century.

Conflicts of interest

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References

1. **Outes DL, Orlando JC.** Alcmeon de Crotona (El cerebro y las funciones psíquicas). *Rev. Arg. Clín. Neuropsiqu.* 2008;15(1):33-49.
2. **Martínez F, Decuadro-Sáenz G.** Claudio Galeno y los ventrículos cerebrales. Parte I, los antecedentes. *Neurocirugía*. 2008;19(1):58-65.
3. **De la Fuente-Freyre JA.** La biología en la Antigüedad y la Edad Media. Salamanca: Ediciones Universidad de Salamanca; 2002.
4. **Gómez-Fajardo CA.** Alcmeón de Crotona, y la gran hazaña. *Rev. Colomb. Obstet. Ginecol.* 2001;52(1):17-18.

5. **López-Muñoz F, Alamo C, García-García P.** La neurofisiología cartesiana: entre los spiritus animalis y el conarium. *Arch. Neurocien.* 2010;15(3):179-93.
6. **Peña-Quiñones G.** Galeno de Pérgamo y las Ciencias Neurológicas. *Rev. Medicina*. 2007;29(1):34-39.
7. **Laín-Entralgo P.** Historia de la medicina moderna y contemporánea. Segunda Edición. Barcelona: Editorial Científico Médica; 1963.
8. **Reale G, Antiseri D.** Historia de la Filosofía Vol 1. Bogotá: Editorial San Pablo; 2007.
9. **Jaramillo-Antillón J.** Historia y filosofía de la medicina. San José: Editorial de la Universidad de Costa Rica; 2005.
10. **Frankfort H.** Reyes y dioses. Madrid: Editorial Alianza; 1998.
11. **Dachez R.** Histoire de la médecine de l'Antiquité au XXème siècle. Paris: Tallandier; 2008.
12. **Duque-Parra JE, Barco-Ríos J, Duque-Quintero V.** Visión Histórica de la Estructura y Función del Nervio. La Visión Pre-Galénica y Galénica. *Int. J. Morphol.* 2014;32(3):987-990.
13. **Byl S.** Controverses antiques autour de la dissection et de la vivisection. *Revue belge de Philologie et d'Histoire.* 1997;75(1):113-120. http://doi.org/bm3nnz.
14. **Chapman PH.** The Alexandrian Library: crucible of a renaissance. *Neurosurgery.* 2001;49:1-13.
15. **López-Piñero JM.** Galeno de Pérgamo (C:A 130-200). El sistema nervioso en la sistematización de la medicina clásica helenística. *Mente y Cerebro.* 2007;22:8-11.
16. **Barcia-Salorio D.** Introducción histórica al modelo neuropsicológico. *Rev. Neurol.* 2004;39(7):668-681.
17. **López-Muñoz F, Rubio G, Molina JD, Alamo C.** The pineal gland as physical tool of the soul faculties: a persistent historical connection. *Neurologia.* 2012;27(3):161-8. http://doi.org/fs9t7r.
18. **Wills A.** Herophilus, Erasistratus, and the birth of neuroscience. *Lancet.* 1999;354(9191):1719-20. http://doi.org/fwjt9s.
19. **Foulon P.** Histoire des ventricules cérébraux. *Neurochirurgie*. 2000;46(3):142-6.
20. **Martín-Araguz A, Bustamante-Martínez C, Emam-Mansour MT, Moreno-Martínez JM.** Neurociencia en el Egipto faraónico y en la escuela de Alejandría. *Rev.* Neurol. 2002;34:1183-1194.
21. **Duque-Parra JE, Barco-Ríos J, Morales-Parra G.** La Disección In vivo (Vivisección): Una Visión Histórica. *Int. J. Morphol*. 2014;32(1):101-105. http://doi.org/chbj.
22. **Mora-Novaro OA, Mora-Carrrilo G.** Historia de la fisiología: breve revisión con especial referencia a la circulación, respiración, sistema nervioso y glándulas endocrinas. Tenerife: Fundación Canaria Orotava de Historia de la Ciencia; 2007.
23. **Martínez-Vidal A.** Neurociencias y revolución científica en España. La circulación neural. Madrid: CSIC; 1989.
24. **Silverthorn DU.** Fisiología humana: un enfoque integrado. Cuarta Edición. Buenos Aires: Editorial Médica Panamericana; 2009.
25. **Rengachary SS, Colen C, Dass K, Guthikonda M.** Development of anatomic science in the late middle ages: the roles played by Mondino de Luzzi and Guido da Vigevano. *Neurosurgery.* 2009;65(4):787-93. http://doi.org/b9nkg2.
26. **López-Muñoz F, Marín F, Álamo C.** El devenir histórico de la glándula pineal: De válvula espiritual a sede del alma. *Rev. Neurol.* 2010;50(1):50-7.
27. **Kemp M.** Leonardo da Vinci: Las maravillosas obras de la naturaleza y el hombre. Madrid: Ediciones AKAL*;* 2011.
28. **Barcia-Goyanes JJ.** El mito de Vesalio. Valencia: Universidad de Valencia; 1994.
29. **Giordano M.** Cerebro y mente en el siglo XXI. *Revista Digital Universitaria.* 2011;12(3):3-10.
30. **Descartes R.** Discurso del método. Vol. 39. Mario Caimi, editor. Buenos Aires: Ediciones Colihue; 2004.
31. **López-Muñoz F, Boya J.** El papel de la glándula pineal en la doctrina psicofisiológica cartesiana. *Acta Physiol. Pharmacol. Ther. Latinoam.* 1992;42:205-16.
32. **Carlson NR.** Physiology of behavior. Boston: Pearson; 2004.
33. **Strkalj G.** Niels Stensen and the discovery of the parotid duct. *Int. J. Mophol.* 2013;31(4):1491-1497. http://doi.org/chbk.
34. **Pevsner J.** Leonardo da Vinci, neurocientífico. *Mente y Cerebro*. 2005;13:78-82.
35. **Duque-Parra JE, Barco-Ríos J, Quintero-Bedoya LE.** El Concepto Histórico Posgalénico Sobre La Estructura Y Función De Los Nervios Craneales. *Int. J. Morphol.* 2015;33(4):1273-76. http://doi.org/chbm.
36. **O'Connor JP.** Thomas Willis and the background to Cerebri Anatome. *J. R. Soc. Med.* 2003;96(3):139-43.
37. **Hughes JT.** Thomas Willis 1621-1675: His Life and Work. *N. Engl. J. Med.* 1993;328:816-817. http://doi.org/dtvptt.
38. **Pope MH.** Giovanni Alfonso Borelli-the father of biomechanics. *Spine (Phila Pa 1976).* 2005;30(20):2350-5.
39. **Hinojosa A.** El pensamiento científico en Medicina. *Rev. Fac. Med.* 1970;13(4):271-8.
40. **Duque-Parra JE, Barco-Ríos J.** Enseñanza de la ciencia sin experimentación por demostración versus enseñanza por virtualización de la experimentación. *Arch. Med.* 2013;13(2):226-232.

REVIEW ARTICLE

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Systemic scleroderma: An approach from plastic surgery

Esclerodermia sistémica. Abordaje desde la cirugía plástica

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| Abstract |

Introduction: Systemic sclerosis (SSc) is an autoimmune disease of the connective tissue that is clinically characterized by dermal thickening, which occurs due to the accumulation of connective tissue, and may involve other organs and the limbs. The multifactorial etiology of this disease is related to alterations in remodeling interactions of the extracellular matrix (ECM), immune function and presence of proliferative vasculopathy under genetic and environmental influence.

Objective: To conduct a literature review on medical and surgical management from the point of view skin, hand and finger lesions surgery, as well as facial alterations in patients with systemic scleroderma.

Materials and methods: A bibliographic search was performed in the Medline, LILACS, PubMed, EMBASE and Current Contents databases, using the keywords "systemic scleroderma", "plastic surgery", "hand" and "ulcers".

Results: SSc requires a multidisciplinary management, since pharmacological therapy is indicated for some cases and complementary surgical management is better for others.

Conclusion: This pathology significantly affects the skin by causing lesions ranging from digital ulcers to facial atrophy, which are susceptible to management by plastic surgery.

Keywords: Scleroderma, Systemic; Surgery, Plastic; Hand; Leg Ulcer (MeSH).

| Resumen |

Introducción. La esclerosis sistémica (ES) es una enfermedad autoinmune del tejido conectivo que se caracteriza clínicamente por un engrosamiento cutáneo, el cual se da debido a la acumulación de tejido conectivo y puede afectar a otros órganos y a las extremidades. La etiología multifactorial de esta enfermedad corresponde a la interacción de alteraciones en el remodelamiento de la matriz extracelular, función inmunitaria y presencia de vasculopatía proliferativa bajo influencia genética y medioambiental.

Objetivo. Realizar una revisión sobre el manejo médico y quirúrgico desde el punto de vista de la cirugía plástica de las lesiones en piel y manos y las alteraciones faciales de los pacientes con ES.

Materiales y métodos. Se realizó una búsqueda bibliográfica en las bases de datos Medline, LILACS, PubMed, EMBASE y Current contents con las palabras claves esclerodermia sistémica, cirugía plástica, mano y ulceras.

Resultados. La ES requiere manejo multidisciplinario; se presentan casos en los que se indica terapia farmacológica y otros en los que el manejo es quirúrgico complementario.

Conclusión. Esta patología afecta de manera importante la piel al provocar lesiones que van desde ulceras digitales hasta atrofia facial, las cuales son susceptibles de manejo por el área de cirugía plástica.

Palabras clave: Esclerodermia sistémica; Cirugía plástica; Mano; Úlcera de la pierna (DeCS).

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Introduction

Scleroderma is a disease classified as localized and systemic; the latter has two variants: diffuse cutaneous systemic sclerosis (dcSSc), which is characterized by the rapid development of symmetric dermal thickening in the proximal and distal areas of the limbs, face and trunk, and limited cutaneous systemic sclerosis, which is characterized by symmetric dermal thickening limited to distal areas of the limbs and face. (1,2)

In general, systemic sclerosis (SSc) is an autoimmune disease of the connective tissue, clinically characterized by dermal thickening due to the accumulation of connective tissue and may involve other organs. The etiology of this disease is multifactorial and is caused by the interaction of alterations in the immune response, excessive extracellular matrix remodeling and the presence of proliferative vasculopathy, all this under genetic and environmental influence. SSc has an estimated prevalence of 10 cases per 100 000 inhabitants, which is why it is considered a rare disease, with an incidence of 4-8 cases per 10 000 inhabitants, affecting mostly women with an average age of 45 years. (1)

SSc is characterized by fibrosis that causes the thickening and hardening of the skin and other tissues. It starts with an endothelial injury and a subsequent imbalance of its repair, generating a cascade of proinflammatory events and hyperactivation of fibroblasts that constitute abnormal extracellular matrix clusters in different tissues and degrees, and almost always affecting the gastrointestinal tract, lung, kidney, heart and skin. In addition, it is associated with mortality when it manifests with interstitial lung disease and pulmonary arterial hypertension. (2)

This skin condition causes lesions ranging from digital ulcers (DU) to facial atrophy, which are susceptible to management by plastic surgery. With this in mind and considering the difficulties that could arise regarding medical and surgical management of skin lesions, hand involvement and facial alteration, this work describes the results of a detailed literature review, presenting the best therapeutic options for these patients from the point of view of plastic surgery.

Etiopathogenesis

Vascular proliferative disease

Endothelial activation has been demonstrated through the detection of increased plasma levels in intercellular adhesion molecules, endothelin 1, thrombomodulin and von Willebrand factor expression, associated with excessive apoptosis of endothelial cells. When this injury becomes chronic, platelet adhesion, leukocyte adhesion and activation of the fibrinolytic system occur, which together with the increase in vascular permeability lead to deterioration of the vascular wall. (3)

This process causes excess extracellular matrix, which leads to fibrosis and subsequent loss of tissue elasticity and reduction of vascular lumen, which ultimately result in hypoxia and tissue necrosis. Angiogenesis, when trying to supply by perfusion, produces an aberrant formation of capillaries, which is secondary to an imbalance between angiogenic and angiostatic factors. Microvasculopathy is reinforced by hyperplasia of pericytes, responsible for inhibiting cell migration and vascular proliferation. (3)

Fibrosis

The bone marrow contributes to an increase in the number of pre-fibroblastic cells through the release of pluripotent mesenchymal cells and progenitors of fibroblasts. Fibrocyte precursors migrate and accumulate in tissues according to the gradient of chemokine receptors (CRs) such as CCR3, CCR5, and CXCR4, which have been found at high levels in the skin of patients with dcSSc. The effector protein that orchestrates the whole process is TGF-βis, produced by fibroblasts, T cells, monocytes and platelets, which is released as a complex that is activated inside the ECM by the tissue injury. (4)

Oxidative stress

Superoxide anions are produced during ischemic phenomena and, together with the activation of the NF-kB pathways, generate oxidative stress. Indirect markers of reactive oxygen species have been reported in serum analysis of patients with SSc, as well as oxidative proteins and lipid peroxidation. (3)

Immune system

Alteration of humoral and cellular immunity is demonstrated by the presence of B lymphocytes with chronic CD19 and CD85 labeling, manifested by specific autoantibodies —such as anticentromere antibodies (ACA), anti-topoisomerase I antibodies (also known as Scl-70 antibodies) and anti-RNA polymerase III antibodies— and alterations in the function of fibroblasts. ACA are characteristic in localized sclerosis, which is usually more benign than the diffuse form, even though it is associated with the subsequent development of pulmonary hypertension, digital ulcers and gastrointestinal involvement. (5)

Genetic correlation

In general, the course of systemic rheumatic diseases is related to polymorphisms of the major histocompatibility complex —MHC or HLA—, associated, to a great extent, with class II antigens. (2) Genetic risk factors include protein tyrosine phosphatase (PTPN22), a non-receptor gene that produces susceptibility to SSc, diabetes *mellitus* type I, systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Other shared genes such as BANK1, IRF5 and STAT4 have also been reported. (6)

Environmental correlation

Some of the risk factors that could be etiologically related to this entity, according to some case reports, are exposure to silica and organic solvents, permanent silicone implants and contact with infectious agents such as parvovirus B19 and cytomegalovirus. The association of these viruses with endothelial damage, given the infection and the poor response of adaptive immunity, may generate profibrotic cytokine production and cause vascular injury and activation of fibroblasts. (7,8)

Classification

Scleroderma is classified as localized and systemic; the latter is divided into two categories according to the skin condition: limited scleroderma, characterized by ACA, and diffuse scleroderma, characterized by anti-topoisomerase I (Scl70). (1,2,5)

Diagnosis

In 2012, the ACR-EULAR (American College of Rheumatology/ European League against Rheumatism) committee established new classification criteria for SSc (Table 1), which increased sensitivity from 0.75 to 0.91, and specificity from 0.72 to 0.92 with respect to the 1980 criteria. Given the heterogeneity of disease presentation, differentiating isolated sclerosis from disease overlap is often difficult. The range of overlapping diseases is between 10% and 27% of cases. (6,9)

Based on the Canadian Scleroderma Research Group database, it was found that telangiectasias and ACA increase the sensitivity of SSc diagnosis from 57% to 97% in the presence of Raynaud's phenomenon (RP) and proximal skin thickening. Therefore, easily discernible clinical features (RP and telangiectasias), as well as serology, seem to be of considerable diagnostic value. (9)

Thickening of the skin of the fingers and fingertip injuries have two possible manifestations; the highest score between both manifestations will be taken into account for categorization purposes in this case. The maximum possible score is 19 and patients with a score of 9 are classified as SSc. (10)

Table 1. Criteria for systemic sclerosis.

Item	Subitem	Score
Thickening of the skin of both hands with extension proximal to the metacarpophalangeal joints		9
Thickening of the skin of the fingers	Inflammation of the fingers	2
	Sclerodactyly in fingers (distal to the metacarpophalangeal joints but proximal to interphalangeal joints)	4
Fingertip injuries	Fingertip ulcers	2
	Scarring of fingertip bites	3
Telangiectasia		2
Abnormal capillary forms in the nail beds		2
Pulmonary arterial hypertension or pulmonary interstitial disease	Pulmonary arterial hypertension and pulmonary interstitial disease	2
Raynaud's phenomenon		3
Antibodies related to scleroderma	Anticentromere Anti-topoisomerase I Anti-RNA polymerase III	3

Source: Own elaboration based on Johnson. (10)

Probable differential diagnoses that cause thickening of the skin should be considered, even if they do not appear symmetrically — as in the case of morphea (plaques, bullous and linear distribution), linear scleroderma *en coup de sabre*, progressive facial hemiatrophy and rigid skin syndrome— and diffusely —as is the case of eosinophilic fasciitis; storage diseases such as scleromyxedema, amyloidosis and nephrogenic systemic fibrosis; metabolic conditions such as phenylketonuria, cutaneous porphyria and hypothyroidism; toxic agents such as silica, polyvinyl chloride, bleomycin and toxic oil syndrome; and genetic etiologies such as progeria or Werner syndrome. (11)

Comorbidities

The type and frequency of target organ involvement in patients with scleroderma are variable. The main organs affected include the cardiovascular system with pulmonary hypertension; the pulmonary system with pulmonary hypertension and pulmonary fibrosis; the gastrointestinal tract with esophageal alteration and involvement of the small intestine; the renal system with kidney failure; the joints with arthritis, arthralgias and calcinosis; among others. (12)

Hand and systemic sclerosis

Manifestations of scleroderma in the hand include RP, digital ischemia, changes in the skin, calcinosis, and joint contractures.

In 1882, Maurice Raynaud was the first to describe a transient, acral, vasospastic phenomenon, induced by cold or stress, known as RP, which occurs in the fingers and toes and, less frequently, in the nose, ears and nipples; it may be asymmetrical and may not affect all fingers. (13,14) Typical changes in skin coloration include initial pallor, cyanosis and red fingers as an expression of the compensatory vasodilation phase. About 90% of patients with SSc suffer from RP. (15)

There are two types of presentations associated with RP: primary and secondary. The presence of RP as the only symptom, without other concomitant connective tissue disease such as SSc, Sjögren's syndrome or SLE, is defined as primary RP. On the other hand, presentations associated with the connective tissue pathologies described above are defined as secondary RP. RP is a manifestation commonly associated with SSc in up to 95% of patients, in which peripheral vascular alteration and involvement of internal organs occur. It is necessary to make a differential diagnosis between primary and secondary RP in order to guide management, taking into account that the primary form is considered a benign pathology that can show significant improvements with topical and lifestyle changes (Table 2).

Table 2. Clinical characteristics of Raynaud's phenomenon in scleroderma.

Main characteristics	Primary RP	Secondary RP
Age of onset	<30	>30
Severity of symptoms	Mild	Severe
Autoantibodies	Negative or mildly elevated	Positive
Nailfold capillaroscopy	Normal	Dilated with emergent vessels
Activation of endothelial cells	Yes	Yes
Vascular occlusion	No	Yes
Digital ulcers	No	Yes
Treatment	Usually non-pharmacological	Necessarily pharmacological

Source: Own elaboration based on Johnson. (10)

Mild to moderate symptomatology with onset at an early age may suggest primary RP, while an increase in frequency and an extension in the duration of attacks, together with other symptoms such as dyspnea and dysphagia, are more suggestive of secondary RP. Signs such as sclerodactyly, telangiectasia, ulcerations and ACA (with or without a specific pattern) on physical examination help establish an SSc diagnosis (Figure 1). (16)

In order to establish a diagnosis, it is necessary to rely on the clinical history, carry out an adequate physical examination and perform complementary paraclinical examinations —color doppler ultrasound and nailfold capillaroscopy.

Figure 1. Proximal interphalangeal joint flexion contractures with thickening of the skin.
Source: Own elaboration based on the data obtained in the study.

DUs are necrotic skin lesions on the soft part of the fingers or superimposed bony prominences. They occur in up to 50% of patients with scleroderma and are extremely painful, leading to substantial disability in the affected hand (17-19); they can develop in hands and feet.

DUs may develop due to multiple factors, including repeated microtrauma, thinning skin, dry skin and underlying calcinosis. However, chronic digital ischemia as an expression of unresolved RP is the most important risk factor for the development of ulcers in this group.

Calcinosis is the formation of calcium deposits in soft tissues —without direct joint involvement—, is more frequently associated with limited scleroderma and may be localized or extensive. The main complications associated with this pathology are skin ulcers and infection.

At the pathophysiological level, calcinosis is caused by tissue hypoxia that leads to a decrease in perfusion with subsequent inflammatory activity, which, in turn, triggers the activation of macrophages and imbalance between various mediators that produce an increase in the entry of calcium into the cells. (20)

Joint involvement occurs almost always in the interphalangeal and metacarpophalangeal joints. Proximal interphalangeal joint flexion contractures are developed by retraction in the volar surface. (21) This often leads to skin breakdown on the dorsal aspect of the joint due to tension and thinning skin. Usually, metacarpophalangeal joints are fixed in extension or hyperextension. In contrast to proximal interphalangeal joint flexion contractures, it is believed that metacarpophalangeal joint position is secondary to capsular narrowing, capsule adhesion and extensor component. (21) Early initiation of hand therapy can help limit or delay the development of disabling contractures and digital skin ulcerations.

Treatment

The management of scleroderma of the hand should be carried out by a multidisciplinary team consisting of a hand surgeon, a rheumatologist, a dermatologist and a hand therapist. (22)

Primary RP is considered a benign pathology that is not accompanied by structural alterations in most cases; therefore, complications such as DUs and gangrene should not be a frequently associated outcome. This phenomenon usually improves with non-pharmacological measures such as lifestyle modifications, which include suspending cigarette smoking, avoiding exposure to cold and wearing appropriate clothing and mechanisms to avoid psychological stress.

In cases of primary RP that does not improve with non-pharmacological measures or in secondary RP, pharmacological management should be initiated. At present, there are several pharmacological groups that, through different mechanisms of action, aim to reduce the frequency and duration of vasospastic episodes, with consequent prevention of DUs.

Calcium channel blockers

Calcium channel blockers are the first-line pharmacological treatment for patients with RP and SSc, since they have a vasodilatory effect that acts on the vascular smooth muscle. Nifedipine is used at doses of 30-120 mg/day depending on the severity of the symptoms. (23)

Prostacyclin analogs

Prostacyclines are synthesized by endothelial cells and mast cells from prostaglandins that act as potent vasodilators. Iloprostol acts by preventing platelet aggregation and formation and as a potent vasodilator; its intravenous use during a crisis is associated with a reduction in the duration of the episode, in addition to a higher cure rate. (24)

Phosphodiesterase-5 inhibitors

The drugs included in this pharmacological group act by modulating the cGMP response. Their use has been demonstrated in erectile dysfunction and pulmonary arterial hypertension; in addition, they have proven to be effective in the treatment of patients with severe RP and DUs. Sildenafil has shown benefits in reducing RP symptoms, severity and frequency of acrocyanosis in patients with SSc. (25,26)

Other phosphodiesterase-5 inhibitors that have proven to be effective in the management of severe RP are Tadalafil and Vardenafil; however, they require further studies.

Endothelin receptor antagonists

Bosentan, as an inhibitor of endothelin-1 receptors (ET-A, ET-B), is useful for the treatment of idiopathic pulmonary hypertension and associated with SSc; it is also used for DUs. (27) In special situations, combined therapy of endothelin-1 receptor antagonists and phosphodiesterase-5 inhibitors at low doses for the management of severe DUs in SSc has shown promising advances that require further studies in order to be implemented. (28)

Other vasodilator agents

Angiotensin-converting enzyme (ACE) inhibitors, such as losartan, and angiotensin II receptor blockers (ARBs) have been used in primary and secondary RP to prevent the final formation of angiotensin II, which acts as a potent vasoconstrictor. Both ACE and ARBs are a clinical option for patients with RP that do not improve or experience side effects triggered by calcium channel blockers. (29)

Prazosin, an alpha-adrenergic blocker, has been used in some studies at doses of 1-5mg 3 times a day, showing a decrease in the frequency and severity of vasospasm episodes associated with SSc and RP.

Fluoxetine, a drug belonging to the serotonin reuptake inhibitors group, has also been used for primary and secondary RP, since serotonin acts as a potent vasoconstrictor when found in large concentrations in platelets, thus inhibiting reuptake, which in theory could benefit patients suffering from RP.

Physical therapy

This treatment should be initiated since the onset of the disease and periodically, both as physical and occupational therapy, to avoid complex joint contractures or delay their development. In physical therapy, skin conditioning measures should be taken, such as massages, low frequency current, application of heat and carbon dioxide baths. (30)

Surgical treatment

For the surgical treatment of digital lesions associated with SSc, it is necessary to determine the level of immunosuppression in the patient prior to the procedure, carrying out a multidisciplinary approach with rheumatology in order to obtain immunotherapy optimization. In addition, patients should be made aware of associated risks such as delayed healing, increased risk of infection, increased anesthetic risk associated with the possibility of vasospasm in different tissues during

the procedure, possible intimal arterial injury and digital ischemia. These factors make patients with SSc a significant challenge for surgical treatment.

Surgical interventions of the hand in patients with SSc are indicated when pharmacological therapy has failed or has not been successful, almost always due to severe vasospasm crisis, recurrent ulcerated lesions and digital pain difficult to handle, leaving digital amputation as the last resort. (31)

Some general recommendations to be taken into account during the surgical procedure are wound closure without tension; using Gelpi retractor, atraumatic tissue forceps and sutures moderately; prolonging the time of permanence of the sutures when the normal cicatrization process is delayed; using local anesthesia due to local circulatory advantages; and using tourniquets, if necessary, for no more than two hours. (32)

The main surgical management options are chemical or surgical, cervical, thoracic or ultra-selective digital sympathectomy, which can be considered as emergency measures to achieve rapid vasodilation. (14,19,33-35) A predictor of success in management with sympathectomy is performing a peripheral nerve block with bupivacaine. (36)

Performing a preoperative angiography can be helpful to locate arterial obstructions, and also to define the surgical approach and the adequate planning of the procedure to be performed, considering the possibility of doing an arterial bypass, according to the obstruction to blood flow, by grafting the occluded segment to improve blood flow and the DU healing process significantly.

A study performed in 22 patients, with a mean follow-up time of 46 months after periarterial sympathectomy, showed subjective improvement in 18 patients, defined as the improvement of the healing process and decrease in pain and number of DUs. In addition, laser doppler flowmetry was performed, showing a statistically significant increase in skin perfusion after surgery with an average of 31 months during the follow-up. (37)

In general, surgical treatment is indicated in symptomatic cases of patients with calcinosis associated with difficult pain or functional limitation. (38) However, resection with curette, scalpel and, in some cases, dental drills may also be performed. The recurrence rate after resection is low in its single form, while the probability of recurrence is higher when there are multiple ulcers and often only allows a reduction in volume. (31) Other carbon dioxide laser therapies by exact ablation of superficial calcifications have been proposed to reduce symptoms and healing time by 4-10 weeks without significant tissue damage. (39,40) The severity of calcinosis is not related to the severity of the underlying disease. (32-41)

Due to excess tension in the dorsal skin of the proximal interphalangeal joints, wounds, painful ulceration with risk of infection, arthritis, joint dislocation, osteomyelitis and subsequent joint destruction with minimal traumas are likely to be observed.

Digital deformities are frequent in patients with SSc, and the most usual is the proximal interphalangeal joint flexion contractures, followed by hyperextension of the interphalangeal joint (swan neck) and skin and muscle contracture between the thumb and the second metacarpal bone.

Regarding metacarpophalangeal joints, compensatory hyperextension occurs due to a proximal interphalangeal joint flexion contracture, which can be improved with resection arthroplasty and complete removal of the metacarpal head or with prosthetic restoration. (42) Both techniques can improve 30-50º mobility, which is considerably better than the previous manual function. In theory, metacarpophalangeal joints can maintain active flexion but, over time, collateral ligaments, joint capsule and skin can severely limit the flexion of the joint.

Significant contractures in proximal interphalangeal joint flexion may lead to thinning skin and rupture of the extensor mechanism, and also to restrict severely the grip function, which requires surgical management. For this purpose, arthrodesis of the proximal interphalangeal joint flexion contracture has been proposed. Subluxations can also occur frequently, which may require bone shortening by means of osteotomies of the phalanx and arthrodesis to achieve wound closure without tension. Arthrodesis is preferably performed with Kirschner wires to reduce tissue trauma. The optimal flexion degree during arthrodesis of the proximal interphalangeal joint flexion contracture is about 30º for the index finger, increasing to 45-55º for the little finger. (42)

When removing the tourniquet, digital perfusion should be monitored; in case of absence, digital shortening osteotomies or fixation of the joint with greater flexion must be performed to decrease tension in blood vessels. (34)

To a lesser extent, cases of hyperextension in proximal interphalangeal joint flexion contracture, secondary to the metacarpophalangeal joint subluxation in flexion and similar to the swan neck in patients with rheumatoid arthritis, may be observed. As patients lose their ability to spread fingers at the metacarpophalangeal joints level, they compensate by hyperextending proximal interphalangeal joints. (43,44)

Other less frequent deformity is contracture of the first interdigital space between the thumb and the index finger, which reduces the mobility of the thumb and decreases the patient's ability to grasp large objects. The thumb is often fixed in adduction on the saddle joint and in metacarpophalangeal joint hyperextension. Therefore, trapezius resection may be necessary to restore the abduction capacity of the thumb. The fixation of the interphalangeal joint of the thumb in slight flexion can improve the grip function, also improving opposition in relation to the index or the middle finger. (35)

Surgical management of patients with SSc and hand involvement, resection of symptomatic subcutaneous calcifications and digital artery sympathectomy are available as treatment options. In case of contractures, digital arthrodesis, as well as resection arthroplasties or prosthetic replacements, can improve the grip function. (45)

Orofacial manifestations of scleroderma

Scleroderma also involves oral and facial tissues with thickening of the skin, thinning lips, deepening of wrinkles and xerostomia. In addition, clinical manifestations such as thinner pointed nose and stiffness or hypomobility of the tongue may occur, causing difficulties in speech and swallowing (Figure 2). (46)

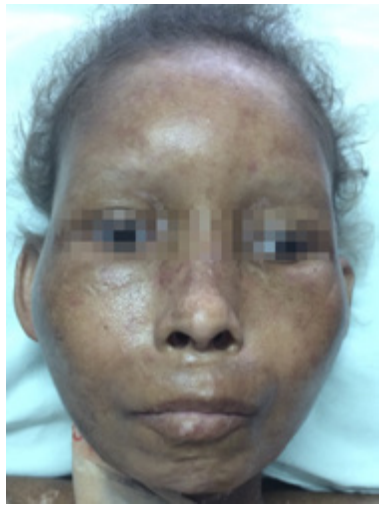

Figure 2. Thickening of the skin associated with hypotrophy in cheeks and pronounced bony prominences.
Source: Own elaboration based on the data obtained in the study.

The main oral manifestation is microstomia, which is caused by sclerosis of the perioral tissues; in addition, difficulties may arise regarding social relationships, chewing and oral hygiene. (46)

The face is the door to interpersonal relationships, so it is very important to achieve the best possible correction in patients with SSc defects. (47,48) Cutaneous manifestations include linear scleroderma, in particular the *en coup de sabre* form, and progressive facial hemiatrophy or Parry-Romberg syndrome, which is almost always observed in the face. (49)

Linear scleroderma is characterized by a clearly marked depression in the midline of the forehead that can extend to the eyebrow and involve underlying soft tissues, as well as the scalp —in the form of atrophic alopecia plates following a linear pattern—, and the face where cheeks, nose, upper lip and eyes are the most affected areas. (49) If the lesion is narrow, it can be resected and sutured by first intention; if it is broad, there are different reconstructive procedures such as autologous tissue grafting, biomaterials, pedicled flaps and free flaps.

Progressive facial hemiatrophy is characterized by unilateral facial atrophy with involvement of the skin, subcutaneous cellular tissue, fat, muscle and, in some cases, osteocartilaginous structures. In general, it resolves spontaneously and involves especially the dermatomes of one or several branches of the trigeminal nerve. This involvement favors the appearance of ocular alterations such as endophthalmos, uveitis, paralysis of the ocular musculature, ptosis or Horner's syndrome, and of deformations in the jaw with subsequent dental malocclusion, inadequate implantation of the teeth, atrophy of the roots or delay in the appearance of the teeth. This disorder is predominant in women, usually occurs during the first or second decade of life and progresses slowly for 2 to 20 years and then enters into a stationary or plateau phase. (49)

One of the most used therapeutic tools to correct these soft tissue deficits is autologous fat graft, which help improve the facial contour. (48,50) To conduct this type of treatment, adequate control of the disease is a must; the anatomical regions from where the fat is extracted include the abdomen, trochanteric areas, flanks, jowls and pubis. (47,50)

Adipocytes in these sites are rich in alpha 2 receptors and are sensitive to catecholamines; they also have antilipolytic action. The survival of these cells is better when placed in a rich medium in circulation; the most viable graft goes from a less vascularized area to a more vascularized one, for example, abdomen fat used to fill face blemishes. (47,50)

Grafted adipocytes first go through an ischemia phase with infiltration of macrophages, histiocytes and polymorphonuclear cells to clean the remains of tissues. On the fourth day, graft revascularization is initiated by host neoangiogenesis. Revascularization is centripetal and begins in the periphery: the central fat suffers ischemia and is not revascularized, unless the fragments are small. (47,50)

Lipografting is an outpatient surgery that offers good results for defects caused by scleroderma with facial hemiatrophy sequelae. It has a low rate of complications and no rejection effect because it is an autologous graft. Due to the characteristics of the adipose cells, 2 to 3 applications are required to obtain a lasting and aesthetically satisfactory result. (51)

Hyaluronic acid has been used for soft tissue augmentation with satisfactory results. Its advantages include tolerability, availability, low cost, reversibility, efficiency in volume gain, cosmetic improvement of the deformity and few side effects. Hyaluronic acid is the most common glycosaminoglycan in the skin and, when injected, it promotes growth, softening and hydration through powerful links with water. In addition, this benefit plays an important role in cell growth, membrane receptors function and adhesion. It also stimulates the production of collagen, which could explain why some patients have more long-lasting results. (52)

Xerostomia is a common finding that occurs due to fibrosis of the salivary glands and presents as a symptom of dry mouth. It can cause a high rate of periodontal disease, increase the incidence of *Candida* infections (46) and other manifestations in the jaw and the temporomandibular joint (TMJ) secondary to bone resorption, making itself clinically evident through alterations in the condyle, glenoid cavity and coronoid process. Jaw bone resorption is observed more frequently in patients with diffuse cutaneous SSc and causes marked facial sclerosis and limitation for oral opening. Systematic radiographic screening in different groups of patients with SSc shows incidence of jaw resorption between 20% and 33%. Its multifactorial etiology includes ischemia due to vasospasm, intense vasculitis, compression secondary to perivascular fibrosis and direct stress on the condyle. (46,53)

The treatment for xerostomia may be conservative with the use of devices or surgical with joint repositioning through maxillary, mandibular osteotomy and genioplasties. Macintosh *et al.* (53) reported the management of two severe cases of injury at the TMJ level associated with functional consequences such as open bites and malocclusion; in both cases, patients underwent surgery to remove the injured segment and position chondrocostal grafts with satisfactory results and restoration of occlusion with long-term maintenance.

Telangiectasia on the face and oral mucosa is caused by the dilatation of small blood vessels. They can also affect the upper limb and be a source of emotional stress because they generate a perception of disfigurement and dissatisfaction with body image. Traditionally, intense pulsed light therapy (IPL) and pulsed dye laser (PDL) have been implemented improving appearance and tonality. (46,54) PDL is associated with effects on the application site, being transient but with a significant presence of ecchymosis, edema, hypopigmentation and scarring. On the other hand, IPL can be painful and does not prevent recurrence, but it offers similar efficacy with few side effects. The findings suggest that both methods are effective; however the PDL has better results in terms of appearance than IPL. (46,54)

Skin ulcers and scleroderma

Ulcers on bony prominences are based on a surrounding avascular tissue of an atrophic nature, which is vulnerable to microtrauma and poor scarring. (55-58)

To treat and prevent ulcerations in patients with scleroderma, different alternatives are combined. Therapeutic options include pharmacological treatment, which uses vasodilators such as calcium channel blockers, alpha-adrenergic inhibitors, ACA, ARB II, nitrates, phosphodiesterase-5 inhibitors and prostacyclines —which have platelet inhibitory properties. (55-59)

Additional causes of ulceration of the skin of the limbs include peripheral arterial occlusive disease, venous insufficiency, and rheumatoid arthritis. Up to 10% of leg ulcers occur in association with rheumatoid arthritis. (60) When these conditions occur simultaneously, a combined therapeutic approach that includes pharmacological and surgical techniques is often necessary. (60,61)

Away from traditional treatments, cultured keratinocyte grafts appeared in the 1970s as an alternative to vascular, diabetic and post-traumatic ulcers. Based on these initiatives and advances in biotechnology, today, new types of grafts can be found that incorporate semi-synthetic biopolymers originated from hyaluronan benzylic ester and autologous fibroblasts, offering improvements in biointegration. The neoepithelialization capacity of the surface of the bloody area is

estimated in 2 weeks on average, while resorption of the biomaterial mediated by macrophages ends in 6 weeks. (62)

Adjuvant therapy for the treatment of ulcers

Hematopoietic progenitor cell mobilization for autologous transplantation is a useful therapeutic option in allogeneic or autologous transplantation in diseases linked to the hematopoietic system, and is applicable in cell therapy for chronic occlusive arterial disease, ulcers management and immune system reconditioning. (63)

Filgrastim, a human granulocyte-colony stimulating factor (G-CSF), is an endogenous hematopoietic growth factor that stimulates the proliferation and differentiation of neutrophil precursors and increases survival and activity of mature neutrophils, which play a critical role in innate immunity and influence the adaptive immune response. (64,65)

In turn, autologous platelet-rich plasma (PRP) —which contains components such as fibrin, interleukins, and high concentrations of angiogenic growth factors that support healing— acts as a sealing and excipient medium. In addition to its important anti-inflammatory effect, PRP has been proven to have antimicrobial activity against *Escherichia coli, Staphylococcus aureus, Candida albicans* and *Criptococcus neoformans*. (66,67)

A recent Cochrane meta-analysis showed evidence on the effect of autologous PRP on wound healing. This study included ten randomized clinical trials with 442 participants (mean age 61 years and 42% women), who had multiple causes of chronic ulceration (decubitus ulcers, arterial ulcers, venous and mixed ulcers), and exposed evidence of substantial improvement in healing time, hospital stay, length of treatment and infections. (66)

The results achieved with intralesional application of PRP in diabetic foot ulcers coincide with the healing capacity of bone marrow mononuclear cells. (68)

Conclusions

SSc almost always affects the integumentary system and is characterized by thickening of the skin and loss of elasticity. In addition, this disease may involve organs such as lungs, heart and gastrointestinal tract with catastrophic repercussions for the patient such as hypertension and pulmonary fibrosis. Etiologically, it is considered a multifactorial disease where the interaction between the environment, genetic predisposition and infections condition its onset. (69-72)

This disease occurs in the soft tissues, hands and face. In the hand, the main manifestations are DUs, RP, calcinosis and joint contractures; in the face, microstomia, *coup de sabre* and progressive facial hemiatrophy; finally, in the soft tissues, chronic ulcers in the lower limbs, which are difficult to manage and have a long evolution. (71-73)

Treatment approach to SSc should prioritize pharmacological therapy, while a surgical approach should be considered in severe cases or cases refractory to medication, always bearing in mind possible complications inherent to the pathology such as delayed healing. Patients with RP, calcinosis, facial atrophy or chronic ulcers are susceptible to management by plastic surgery.

This article addressed the consequences of this condition in the skin and soft tissues, which could be handled by plastic surgery. However, other approaches must be taken into account, since there may be other reasons that, if not treated, may lead to death; in this way, SSc should be regarded as a pathology of multidisciplinary approach.

Conflicts of interest

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References

1. **Chifflot H, Fautrel B, Sordet C, Chateelus E, Sibilia J.** Incidence and prevalence of systemic sclerosis: a systematic literature review. *Semin Arthritis Rheum.* 2008;37(4):223-35. http://doi.org/bhtnbt.
2. **Zimmermann AF, Pizzichini MM.** Atualização na etiopatogênese da esclerose sistêmica. *Rev Bras Reumatol.* 2013;53(6):516-24. http://doi.org/f2q79x.
3. **Dumoitier N, Lofek S, Mouthon L.** Pathophysiology of systemic sclerosis: state of the art in 2014. *Presse Med.* 2014;43(10 Pt 2):e267-78. http://doi.org/f6thfz.
4. **Wynn TA.** Cellular and molecular mechanisms of fibrosis. *J Pathol.* 2008;214(2):199-210. http://doi.org/cf22mt.
5. **Cox TR, Erler JT.** Remodeling and homeostasis of the extracellular matrix: implications for fibrotic diseases and cancer. *Dis Model Mech.* 2011;4(2):165-78. http://doi.org/fwqcvh.
6. **Hudson M, Fritzler MJ.** Diagnostic criteria of systemic sclerosis. *J Autoimmun.* 2014;48-49:38-41. http://doi.org/cf9s.
7. **Radic M, Martinovic-Kaliterna D, Radic J.** Infectious disease as aetiological factor in the pathogenesis of systemic sclerosis. *Neth J Med.* 2010;68(11):348-53.
8. **Zakrzewska K, Corcioli F, Carlsen KM, Giugguioli D, Fanci R, Riniei A, *et al.*** Human parvovirus B19 (B19V) infection in systemic sclerosis patients. *Intervirology.* 2009;52(5):279-82. http://doi.org/dn5gfq.
9. **Levy Y, Rotman-Pikieelny P, Ehrenfeld M, Shoenfeld Y.** Silicone breast implantation-induced scleroderma: description of four patients and a critical review of the literature. *Lupus.* 2009;18(13):1226-32. http://doi.org/bzncqg.
10. **Johnson SR.** New ACR EULAR guidelines for systemic sclerosis classification. *Curr Rheumatol Rep.* 2015;17(5):32. doi: http://doi.org/cf9w.
11. **Tyndall A, Fistarol S.** The differential diagnosis of systemic sclerosis. *Curr Opin Rheumatol.* 2013;25(6):692-9. http://doi.org/f522ng.
12. **Medina YF, Ortiz M, Barrera N, Chalem P, Motta A, Zamora F, *et al.*** Relación de los anticuerpos anti-péptido citrulinado con manifestaciones osteo-articulares en una cohorte de pacientes con esclerodermia. *Rev Colomb Reumatol.* 2011;18(3):155-62.
13. **Wigley FM.** Clinical practice. Raynaud's Phenomenon. *N Engl J Med.* 2002;347(13):1001-8. http://doi.org/dmqfqr.
14. **Herrick AL.** Contemporary management of Raynaud's phenomenon and digital ischaemic complications. *Curr Opin Rheumatol.* 2011;23(6):555-61. http://doi.org/b8472f.
15. **Block JA, Sequeira W.** Raynaud's phenomenon. *Lancet.* 2001;357(9273):2042-8. http://doi.org/c6h97g.
16. **Botzoris V, Drosos AA.** Management of Raynaud's phenomenon and digital ulcers in systemic sclerosis. *Joint Bone Spine.* 2011;78(4):341-6. http://doi.org/fft7ht.
17. **Ennis H, Vail A, Wragg E, Taylor A, Moore T, Murray A, *et al.*** A prospective study of systemic sclerosis-related digital ulcers: prevalence,

location, and functional impact. *Scand J Rheumatol.* 2013;42(6):483-6. http://doi.org/cknt.

18. **Nitsche A.** Raynaud, úlceras digitales y calcinosis en esclerodermia. *Reumatol Clin.* 2012;8(5):270-7. http://doi.org/cf9z.
19. **Steen V, Denton CP, Pope JE, Matucci-Cerinic M.** Digital ulcers: overt vascular disease in systemic sclerosis. *Rheumatology (Oxford).* 2009;48(Suppl 3):iii19-24. http://doi.org/d3gpt5.
20. **Boulman N, Slobodin G, Rozenbaum M, Rosner I.** Calcinosis in rheumatic diseases. *Semin Artritis Rheum.* 2005;34(6):805-12. http://doi.org/cwtrqf.
21. **Anandacoomarasamy A, Englert H, Manolios N, Kirkham S.** Reconstructive hand surgery for scleroderma joint contractures. *J Hand Surg Am.* 2007;32(7):1107-12. http://doi.org/cfsf84.
22. **Fox P, Chung L, Chang J.** Management of the Hand in Systemic Sclerosis. *J Hand Surg Am.* 2013;38(5):1012-6. http://doi.org/cf93.
23. **Thompson AE, Shea B, Welch V, Fenlon D, Pope JE.** Calcium-channel blockers for Raynaud's phenomenon in systemic sclerosis. *Arthritis Rheum.* 2001;44(8):1841-7. http://doi.org/dznz4z.
24. **Wigley FM, Wise RA, Seibold JR, MacCloskey DA, Kujala G, Medsger TA Jr, *et al.*** Intravenous iloprost infusion in patients with Raynaud phenomenon secondary to systemic sclerosis. A multicenter, placebo controlled, double-blind study. *Ann Intern Med.* 1994;120(3):199-206. http://doi.org/wjq.
25. **Rosenkranz S, Diet F, Karasch T, Weihrauch J, Wassermann K, Erdmann E.** Sildenafil improved pulmonary hypertension and peripheral blood flow in a patient with scleroderma-associated lung fibrosis and the Raynaud phenomenon. *Ann Intern Med.* 2003;139(10):871-3. http://doi.org/cgbr.
26. **Fries R, Shariat K, von Wilmowsky H, Böhm M.** Sildenafil in the treatment of Raynaud's phenomenon resistant to vasodilatory therapy. *Circulation.* 2005;112(19):2980-5.
27. **Korn JH, Mayes M, Matucci-Cerinic M, Rainisio M, Pope J, Hachulla E, *et al.*** Digital ulcers in systemic sclerosis: prevention by treatment with bosentan, an oral endothelin receptor antagonist. *Arthritis Rheum.* 2004;50(12):3985-93. http://doi.org/dk2wnd.
28. **Ambach A, Seo W, Bonnekoh B, Gollnick H.** Low-dose combination therapy of severe digital ulcers in diffuse progressive systemic sclerosis with the endothelin-1 receptor antagonist bosentan and the phosphodiesterase V inhibitor sildenafil. *J Dtsch Dermatol Ges.* 2009;7(10):888-91. http://doi.org/dksj3g.
29. **Dziadzio M, Denton CP, Smith R, Howell K, Blann A, Bowers E, *et al.*** Losartan therapy for Raynaud's phenomenon and scleroderma: clinical and biochemical findings in a fifteen-week, randomized, parallel-group, controlled trial. *Arthritis Rheum.* 1999;42(12):2646-55. http://doi.org/fht8zr.
30. **Schmidt J, Monnet P, Normand B, Fabry R.** Microcirulatory and clinical effects of serial percutaneous application of carbon dioxide in primary and secondary Raynaud's phenomenon. *Vasa.* 2005;34(2):93-100. http://doi.org/dspf4m.
31. **Daigeler A, Meyer M, Joneidi-Jafari H, Möcklinghoff C, Stinanu Hu, Lehnhardt M.** Handbeteiligungen im Rahmen der progressiven systemischen Sklerodermie-Möglichkeiten der Handchirurgie im interdisziplinären Konzept. *Handchir Mikrochir Plast Chir.* 2007;39(2):128-34. http://doi.org/bzjxsq.
32. **Melone CP Jr, McLoughlin JC, Beldner S.** Surgical management of the hand in scleroderma. *Curr Opin Rheumatol.* 1999;11(6):514-20.
33. **Coveliers HM, Hoexum F, Nederhoeed JH, Wisselink W, Rauwerda JA.** Thoracic sympathectomy for digital ischemia: a summary of evidence. *J Vasc Surg.* 2011;54(1):273-7. http://doi.org/dtnfx9.
34. **Cutolo M, Smith V, Furst DE, Khanna D, Herrick AL.** Points to consider-Raynaud's phenomenon in systemic sclerosis. *Rheumatology (Oxford).* 2017;56(suppl 5):v45-8. http://doi.org/gb2zh3.
35. **Fonollosa-Pla V, Simeón-Aznar CP, Vilardell-Tarrés M.** Tratamiento del fenómeno de Raynaud. *Rev Clin Esp.* 2009;209(1):21-4. http://doi.org/fn4vpd.
36. **Jones NF, Imbriglia JE, Steen VD, Medsgar TA.** Surgery for scleroderma of the hand. *J Hand Surg Am.* 1987;12(3):391-400. http://doi.org/cgbt .
37. **Ruch DS, Holden M, Smith BP, Smith TL, Koman LA.** Periarterial sympathectomy in scleroderma patients: intermediate-term follow-up. *J Hand Surg Am.* 2002;27(2):258-64. http://doi.org/c78tbp.
38. **Mendelson BC, Linscheid RL, Dobyns JH, Mullar SA.** Surgical treatment of calcinosis cutis in the upper extremity. *J Hand Surg Am.* 1977;2(4):318-24. http://doi.org/cgbv.
39. **Chamberlain AJ, Walker NP.** Successful palliation and significant remission of cutaneous calcinosis in CRSScT syndrome with carbon dioxide laser. *Dermatol Surg.* 2003;29(9):968-70.
40. **Bottomley WW, Goodfield MJ, Sheehan-Dare RA.** Digital calcification in systemic sclerosis: effective treatment with good tissue preservation using the carbon dioxide laser. *Br J Dermatol.* 1996;135(2):302-4. http://doi.org/bmnnhh.
41. **Balin SJ, Wetter DA, Andersen LK, Davis MD.** Calcinosis cutis occurring in association with autoimmune connective tissue disease. The Mayo Clinic Experience with 78 patients, 1996-2009. *Arch Dermatol.* 2012;184(4):455-62. http://doi.org/fx25v4.
42. **Nalebuff EA.** Surgery in patients with systemic sclerosis of the hand. *Clin Orthop Relat Res.* 1999;(366):91-7.
43. **Bennett RM.** Mixed connective tissue disease and other overlap syndromes. In: Kelley WN, Harris ED, Ruddy S, Sledge G, editors. Textbook of Rheumatology. Philadelphia: WB Saunders; 1985. p. 1115.
44. **Feldon P, Terrono A, Millender L, Nalebuff E.** Rheumatoid Arthritis and Other Connective Tissue Diseases. In: Wolfe SW, Pederson WC, Hotchkiss RN, Kozin SH, Cohen MS. Green's Operative Hand Surgery. 7th ed. Philadelphia: Elsevier; 2017. p. 1832-1903.
45. **Meyer MF, Daigeler A, Lehnhardt M, Steinau HU, Kelin HH.** Therapeutisches Management akraler Manifestationen der systemischen Sklerose. *Med Klin (Munich).* 2007:102(3):209-18. http://doi.org/fg6r3n.
46. **Crincoli V, Fatone L, Fanelli M, Rotolo RP, Chialà A, Favia G, *et al.*** Orofacial Manifestations and Temporomandibular Disorders of Systemic Scleroderma: An Observational Study. *Int J Mol Sci.* 2016;17(7). http://doi.org/cgbx .
47. **Méndez-Baca SI, Enríquez-Merino J, Alcalá-Pérez D.** Esclerodermia localizada: corrección mediante trasplante autólogo de grasa. Comunicación de seis casos. *Dermatol Rev Mex.* 2013;57(1):60-3.
48. **Gutiérrez GC, Hayakawa V, Franco A, Reyes L.** Lipoinyección para reconstrucción del contorno facial en S. Parry Romberg, esclerodermia y secuelas de trauma: una alternativa práctica utilizando cánula para bloqueo peridural. *Cir Plast.* 2007;17(3):168-75.
49. **Pastor-Oliver JF, Calcedo-Ascoz A, Paricio-Talayero JM, Santos-Serrano L, Fernández-Feijjóo A, Ferriol-Camacho M.** Esclerodermia lineal: Lesión en golpe de sable. Revisión de la literatura y aportación de un caso. *An Esp Pediatr.* 1998;49:499-502.
50. **Karaaltin MV, Akpinar AC, Baghaki S, Akpinar F.** Treatment of "en coup de sabre" deformity with adipose-derived regenerative cell-enriched fat graft. *J Craniofac Surg.* 2012;23(2):e103-5. http://doi.org/f3wx65.
51. **Roh MR, Jung JY, Chung KY.** Autologous Fat Transplantation for Depressed Linear Scleroderma-Induced Facial Atrophic Scars. *Dermatol Surg.* 2008;34(12):1659-65. http://doi.org/cwtshk.
52. **Thareja SK, Sadhwani D, Alan-Fenske N.** En coup de sabre morphea treated with hyaluronic acid filler. Report of a case and review of the literature. *Int J Dermatol.* 2015;54(7):823-6. http://doi.org/cgb2.
53. **MacIntosh RB, Shivapuja PK, Naqvi R.** Scleroderma and the temporomandibular joint: reconstruction in 2 variants. *J Oral Maxillofac Surg.* 2015;73(6):1199-210. http://doi.org/f7b6r2.

54. **Dinsdale G, Murray A, Moore T, Ferquson J, Wilkinson J, Richards H, *et al.*** A comparison of intense pulsed light and laser treatment of telangiectases in patients with systemic sclerosis: a within-subject randomized trial. *Rheumatology (Oxford)*. 2014;53(8):1422-30. http://doi.org/f6c5cm.

55. **Chung L, Fiorentino D.** Digital ulcers in patients with systemic sclerosis. *Autoimmun Rev.* 2006;5(2):125-8.

56. **Hummers LK, Wigley FM.** Management of Raynaud's phenomenon and digital ischemic lesions in scleroderma. *Rheum Dis Clin North Am.* 2003;29(2):293-313. http://doi.org/fh2gxh.

57. **Merkel PA, Herlyn K, Martin RW, Anderson JJ, Mayes MD, Bell P, *et al.*** Measuring disease activity and functional status in patients with scleroderma and Raynaud's phenomenon. *Arthritis Rheum.* 2002;46(9):2410-20. http://doi.org/fhd9zt.

58. **Denton CP, Korn JH.** Digital ulceration and critical digital ischemia in scleroderma. *Scleroderma Care Res.* 2003;1:12-6.

59. **Sticherling M.** Systemic sclerosis-dermatological aspects. Part 1: Pathogenesis, epidemiology, clinical findings. *J Dtsch Dermatol Ges.* 2012;10(10):705-18. http://doi.org/f4fbf6.

60. **Hafner J, Schneider, Burg G, Cassina PC.** Management of leg ulcers in patients with rheumatoid arthritis or systemic sclerosis: The importance of concomitant arterial and venous disease. *J Vasc Surg.* 2000;32(2):322-9. http://doi.org/dsg9n7.

61. **McRorie E.** Regarding "management of leg ulcers in patients with rheumatoid arthritis or systemic sclerosis: the importance of concomitant arterial and venous disease". *J Vasc Surg.* 2001;33(3):664-5. http://doi.org/dzrr5w.

62. **Giuggioli D, Sebastiani M, Cazzato M, Piaggesi A, Abatangelo G, Ferri C.** Autologous skin grafting in the treatment of severe scleroderma cutaneous ulcers: a case report. *Rheumatology (Oxford)*. 2003;42(5):694-6.

63. **Arvedson T, O'Kelly J, Yang BB.** Design Rationale and Development Approach for Pegfilgrastim as a Long-Acting Granulocyte Colony-Stimulating Factor. *BioDrugs.* 2015;29(3):185-98. http://doi.org/f7hj4v.

64. **Kästenbauer T, Hörnlein B, Skol G, Irsigler K.** Evaluation of granulocyte-colony stimulating factor (Filgrastim) in infected diabetic foot ulcers. *Diabetologia.* 2003;46(1):27-30. http://doi.org/btnrwz.

65. **Yönem A, Cakir B, Güler S, Azal OO, Corakçi A.** Effects of granulocyte-colony stimulating factor in the treatment of diabetic foot infection. *Diabetes Obes Metab.* 2001;3(5):332-7. http://doi.org/dk2sd5.

66. **Martinez-Zapata MJ, Artí-Carvajal AJ, Solà I, Expósito JA, Bolíbar I, Rodríguez L, *et al.*** Autologous platelet-rich plasma for treating chronic wounds. *Cochrane Database Syst Rev.* 2016;10:CD006899. http://doi.org/gbb4jn.

67. **Salazar-Álvarez AE, Riera-del Moral LF, García-Arranz M, Álvarez-García J, Concepción-Rodriguez NA, Riera-de Cuba L.** Uso de plasma rico en plaquetas para cicatrización de úlceras crónicas de miembros inferiores. *Actas Dermosifiliogr.* 2014;105(6):597-604. http://doi.org/f2rsrz.

68. **Kirana S, Stratmann B, Prante C, Prohaska W, Koerperich H, Lammers D, *et al.*** Autologous stem cell therapy in the treatment of limb ischaemia induced chronic tissue ulcers of diabetic foot patients. *Int J Clin Pract.* 2012;66(4):384-93. http://doi.org/fxtqrb.

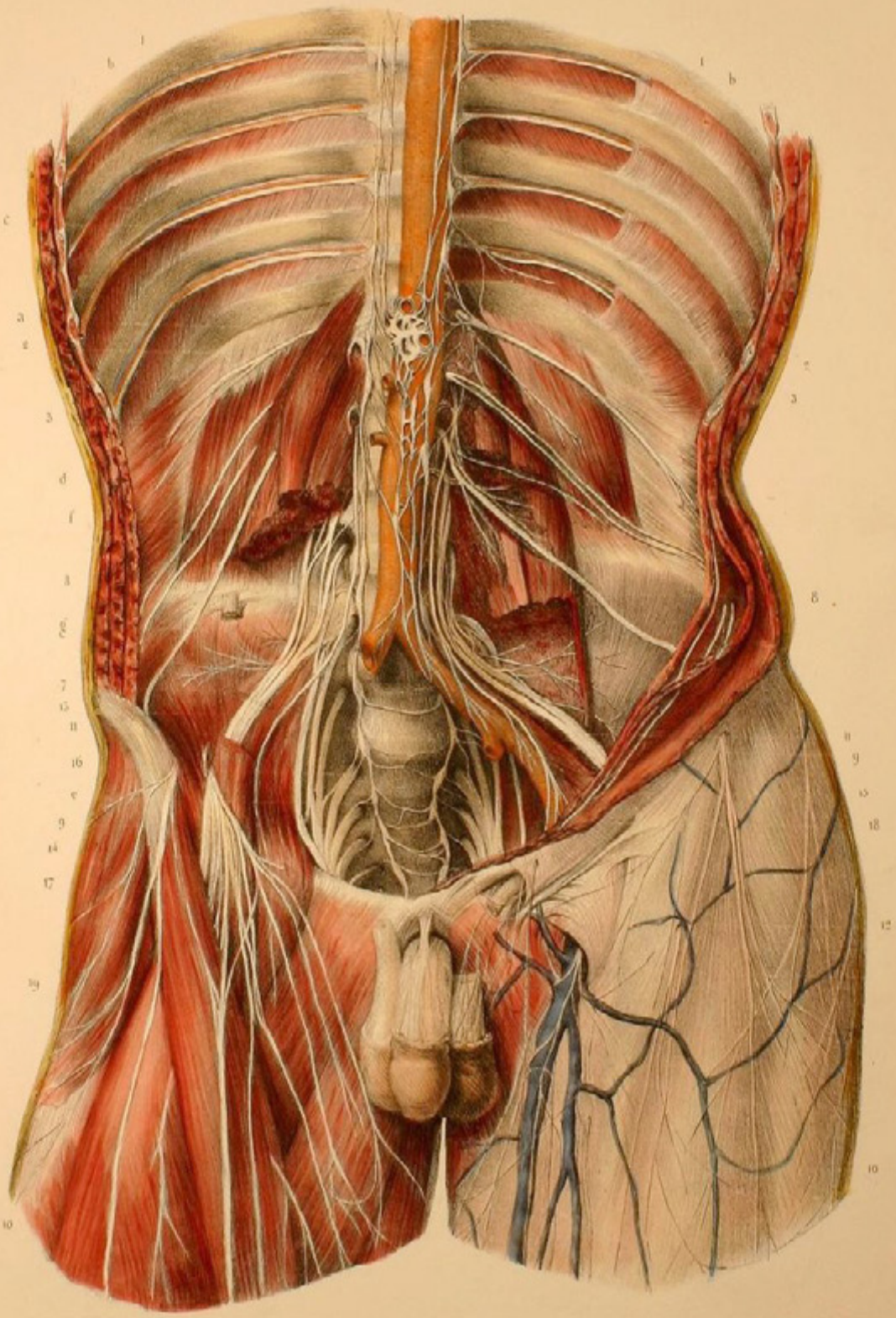
69. **Gaviria CM, Jiménez SB, Gutiérrez J.** Morfea o esclerodermia localizada. *Rev Asoc Colomb Dermatol.* 2014;22(2):126-40.

70. **Garza-Rodríguez V, Villarreal-Alarcón MA, Ocampo-Candiani J.** Etiopatogenia y tratamiento de esclerodermia. Conceptos actuales. *Rev Med Inst Mex Seguro Soc.* 2013;51(5):50-7.

71. Denton CP. Overview and classification of scleroderma disorders. Waltham: UpToDate. [Cited 2016 Jun 12]. Available from: https://goo.gl/JBaC3R.

72. **Bielsa-Marsol I.** Actualización en la clasificación y el tratamiento de la esclerodermia localizada. *Actas Dermosifiliogr.* 2013;104(8):654-66. http://doi.org/f2fnhd.

73. **Avouac J, Fransen J, Walker UA, Riccieri V, Smith V, Muller C, *et al.*** Preliminary criteria for the very early diagnosis of systemic sclerosis; results of a Delphi Consensus Study from EULAR scleroderma trial and research group. *Ann Rheum Dis.* 2011;70(3):476-81. http://doi.org/fr8jr5.



D'après nature par N.H. Jacob

JEAN MARC BOURGERY
"Traité complet de l'anatomie de l'homme"
PARIS 1832-1854

REVIEW ARTICLE

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Hypertriglyceridemia and adverse outcomes during pregnancy

Hipertrigliceridemia y consecuencias adversas en el embarazo

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| Abstract |

Introduction: During pregnancy, levels of maternal serum triglycerides increase as a physiological adaptation mechanism to meet the needs of the developing fetus. However, although an excessive increase has been associated with preeclampsia, macrosomia and preterm delivery, the levels from which measurements should be taken in each trimester to prevent complications have not been established conclusively.

Objective: To review the physiopathology, effects on mother and child, expected values in each trimester and therapeutic interventions in maternal hypertriglyceridemia.

Materials and methods: A review was made based on a search of articles in the ScienceDirect, Pubmed, Scopus, LILACS, Cochrane and SciELO databases, with the terms: Pregnancy; Hypertriglyceridemia; Maternal-Fetal Exchange; Fetal Development; Pregnancy Complications in English and its equivalents in Spanish.

Results: 59 articles met the search criteria and responded to the objectives.

Conclusions: The limited amount and the great variability of the data indicate the need to carry out further research to establish the normal triglycerides ranges during the three trimesters of pregnancy and to determine risks and effective interventions before pregnancy in order to reduce maternal and child morbidity and mortality.

Keywords: Pregnancy; Hypertriglyceridemia; Maternal-Fetal Exchange; Fetal Development; Pregnancy Complications (MeSH).

| Resumen |

Introducción. Durante el embarazo, los niveles séricos de triglicéridos maternos aumentan como un mecanismo de adaptación fisiológica para suplir las necesidades del feto en desarrollo. Pese a que el incremento excesivo se ha asociado a preeclampsia, macrosomía y parto pretérmino, no se han establecido de manera contundente los niveles a partir de los cuales se deben tomar medidas en cada trimestre para prevenir complicaciones.

Objetivo. Hacer una revisión sobre fisiopatología, efectos en madre e hijo, valores esperados en cada trimestre e intervenciones terapéuticas en hipertrigliceridemia gestacional.

Materiales y métodos. Se realizó una revisión con la búsqueda de artículos en las bases de datos ScienceDirect, PubMed, Scopus, LILACS, Cochrane y SciELO con los términos: Pregnancy; Hypertriglyceridemia; Maternal-Fetal Exchange; Fetal Development; Pregnancy Complications y sus equivalentes en español.

Resultados. Se encontraron 59 artículos que cumplieron los criterios de búsqueda y daban respuesta a los objetivos.

Conclusiones. El número limitado y la gran variabilidad de los datos indican la necesidad de realizar más investigaciones que establezcan los rangos de normalidad de los triglicéridos durante los tres trimestres del embarazo y así determinar riesgos e intervenciones eficaces antes de la gestación y reducir la morbimortalidad materno-infantil.

Palabras clave: Embarazo; Hipertrigliceridemia; Intercambio materno-fetal; Desarrollo fetal; Complicaciones del embarazo (DeCS).

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Introduction

During pregnancy, mother's physiology adapts to provide nutrients to the growing fetus. However, the imbalance in the amount of triglycerides (TG) —either before or during pregnancy— has been related to maternal-perinatal pathologies such as preeclampsia (PE) and gestational diabetes mellitus (GDM). In neonates, reported pathologies include preterm delivery (PD), dystocia, macrosomia, hypoglycemia or intrauterine growth restriction. (1-6)

In Colombia, 7 482 cases of severe maternal morbidity (SMM) were reported during the first semester of 2016, which corresponds to 27.9 mothers for every 1 000 live births (LB), and 182 cases of maternal mortality, with 49.2 cases for every 100 000 LB. (7) The main causes of SMM and maternal mortality were hypertensive disorders (62.4% and 15.5%, respectively) and hemorrhagic complications (15.5% and 18%, respectively). (7)

Exacerbated hypertriglyceridemia and insulin resistance condition an oxidative environment that leads to endothelial injury, which, in turn, has a predisposing effect on the development of PE as a hypertensive disorder of higher incidence. (8-10) Intrauterine weight gain may be associated with the elevation of TG passage through the placenta and TG production by the fetus, which would lead to a large for gestational age (LGA) fetus and, thus, possible hemorrhagic complications during delivery by overdistension and uterine rupture. (6,11,12)

Besides short-term complications associated with hypertriglyceridemia, other long-term complications involve metabolic disorders and cardiovascular diseases (CVD) that may affect the well-being of the child during adulthood and the health of the mother in her middle and late adulthood. (13-16) The objective of this work is to perform a comprehensive literature review on the pathophysiological causes, effects on mother and child, expected TG values in each trimester of pregnancy and possible therapies to manage maternal hypertriglyceridemia in a timely manner.

Increase in circulating triglycerides during pregnancy

Pregnancy is a state of metabolic stress associated with high TG levels (17), which increase during this period; the highest concentrations are observed during the third trimester. (1) This increase is related to the decrease in the synthesis of fatty acids and the activity of the lipoprotein lipase (LPL) that catalyzes the hydrolysis of TG-rich lipoproteins in the adipose tissue. (1) The activity of this enzyme decreases about 85% during a normal pregnancy. (2,17) TG levels decrease in the postpartum period and this decrease is faster in women who lactate. (18)

The abovementioned events are related to the insulin resistance that occurs during pregnancy, which may be caused by the increase of non-esterified fatty acids, changes in adipokines secretion and inflammatory factors. (1,2,17) Increased lipolysis has been associated with increased placental lactogen, progesterone, prolactin, cortisol and estrogen. (2,19) Adiponectin and apelin, which favor insulin sensitivity, decrease in the third trimester, while other adipokines and cytokines that reduce insulin sensitivity increase at the end of pregnancy, including resistin, retinol binding protein 4 (RBP4), leptin, visfatin, chemerin, adipocyte fatty acid binding protein (AFABP), tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) (2). In addition, the expression of peroxisome proliferator-activated receptor gamma (PPAR-γ) in adipose tissue decreases in the third trimester, contributing to insulin resistance. (2)

Placental passage of maternal triglycerides

1-3% of maternal fatty acids circulate in non-esterified form and enter the syncytiotrophoblast through diffusion or receptor-mediated endocytosis. (3) Low-density lipoproteins associated with TG (LDL-TG), more abundant in circulation, are hydrolyzed by intracellular lipases and cholesterol ester hydrolases. On the other hand, high density lipoproteins (HDL) and very low density lipoproteins (VLDL) bind to surface receptors and are hydrolysed extracellularly by endothelial lipase. (2,3,16) Transporters such as fatty acid transport protein 1 and 4 (FATP-1 and FATP-4), fatty acids translocase (FAT/CD36) and plasma membrane fatty acid-binding protein (FABPpm) make fatty acid uptake a more efficient process. (3,16)

At the intracellular level, the fatty acids bind to the fatty acid binding protein (FABP), which has intrinsic acetyl-CoA ligase activity. (16) Then, the syncytiotrophoblast releases fatty acids into the fetal circulation to bind to the α-fetoprotein (AFP) that takes them to the fetal liver where they are metabolized (Figure 1). (2,12,16) It should be noted that lipid droplets have been observed in the placenta and that their formation is stimulated by adipophilin. (16)

White adipose tissue is observed in the fetus since week 14 or 15, while fetal lipogenesis begins at week 12 or 20; PPAR-γ activation plays an important role in the subsequent increase of adipose tissue size. (20) Fetus weight increases fourfold from 1.6 g/kg/day to 3.4 g/kg/day since the 26th week of pregnancy, but the increase in fetal body fat depends by 20% on placental lipid transfer; the remaining tissue results from fetal lipogenesis. It is worth noting that only one third of circulating maternal glucose is used by placenta through lipolytic routes and the demand is not modified by increasing glucose levels because the utilization is saturated between 90 mg/dL and 143 mg/dL. (2)

Hypertriglyceridemia and pathologies

A study carried out in Amsterdam (n=4 008) revealed that TG increase in the first trimester of pregnancy is directly associated with pregnancy-induced hypertension, PD and LGA. (3) Likewise, a research carried out in India (n=180) found that high TG levels (≥195 mg/dL) in the second trimester are associated with a higher incidence of PD, GDM, PE and LGA. (4) Another complication is maternal pancreatitis, which must be mentioned due to its severity (Table 1). (14,18)

Table 1. Outcomes of gestational hypertriglyceridemia according to different studies.

Author	TG levels (mg/dL)	Outcome	Conclusion
El Khouly, *et al.* (5). Egypt	182.46+16.62	PE	The elevation of lipids during the first trimester of pregnancy may predict the development of PE and its severity: mild (178.31+11.42 mg/dL) or severe (190.40+11.95 mg/dL)
Jin *et al.* (21). China	278.25	LGA	In the third trimester, each time TG rises by 87.5 mg/dL, it is associated with a greater risk of GDM (OR: 1.37, IC95%: 1.18-1.58), PE (OR: 1.50, IC95%: 1.16-1.93), LGA (OR: 1.13, IC95%: 1.02-1.26) and macrosomia (OR: 1.19, CI95%: 1.02-1.39)
	308.88	PE	
	338.63	GDM	
Siddiqui (22) Saudi Arabia	271.25+70.59	PE	Hypertriglyceridemia ≥273.53 mg/dL in the third trimester may be associated with endothelial damage that leads to PE

PE: preeclampsia; TG: triglycerides; GDM: gestational diabetes mellitus; LGA: large for gestational age fetus.
Source: Own elaboration based on the data obtained in the study.

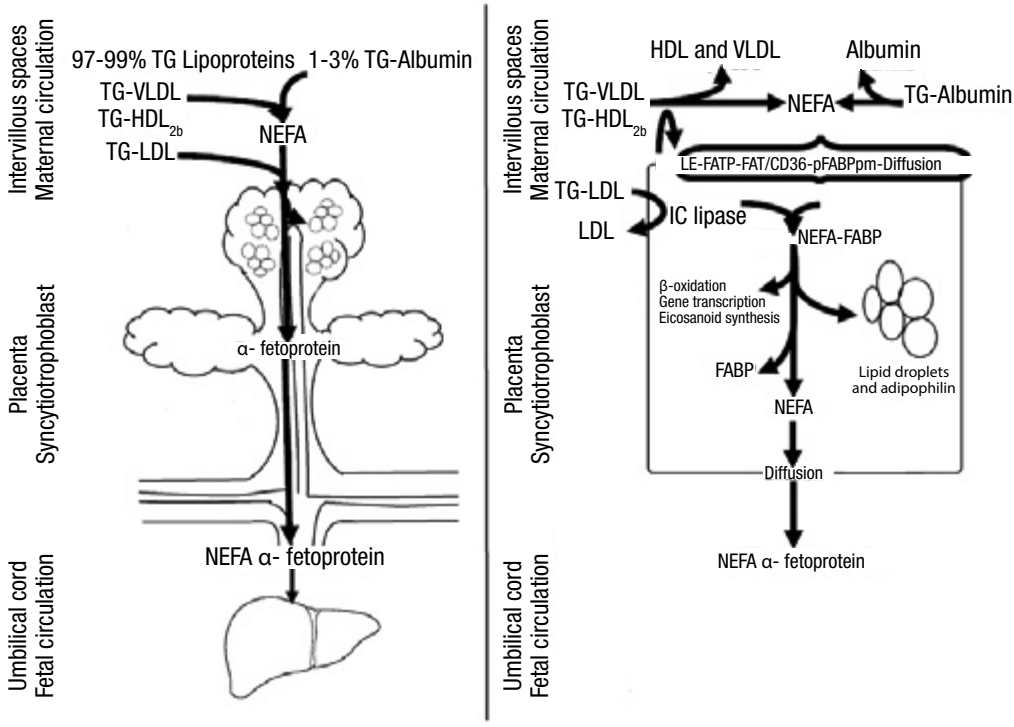

Figure 1. Passage of triglycerides through the placenta.
TG: triglycerides; VLDL: very low density lipoprotein; LDL: low density lipoprotein; HDL: high density lipoprotein; FATP: fatty acid transport protein; FAT/CD 36: fatty acid translocase; FABPpm: plasma membrane fatty acid-binding protein; IC: intracellular; FABP: fatty acid binding protein; NEFA: non-esterified fatty acids.
Source: Own elaboration based on Barrett *et al.* (16)

In the mother

Preeclampsia

Between 2% and 8% of pregnancies are complicated by PE, which is the third cause of maternal-fetal death after hemorrhage and sepsis. (14,23-25) In the mother, this condition is associated with endothelial dysfunction, hypertension, kidney disease and diabetes mellitus (DM). It also increases the risk of developing CVD and death due to kidney and liver impairment. (14) Hypertriglyceridemia, before or during pregnancy, alters the vascular development of the placenta and results from inadequate implantation or placental perfusion. (3,5,8) PE and dyslipidemia are correlated because LPL dysfunction, metabolic syndrome and increased plasma lipids occur in both. (4) These disorders stimulate peroxidation of placental lipids and trophoblast components that promote oxidative stress and form deleterious complexes in endothelial cells that cause vascular dysfunction. (4,5)

A prospective cohort study conducted in Egypt (n=251) showed that TG levels between weeks 4 and 12 of pregnancy can be predictors of PE development. (5,8) This study found that the increase in total cholesterol (TC), TG and LDL greater than 231 mg/dL, 149.5 mg/dL and 161 mg/dL, respectively, and the decrease in HDL below 42.5 mg/dL are cutoff points with positive predictive value for the development of PE, while TC and TG increase was related to severity. (5) Another study conducted in Turkey (n=52) found that TC, TG and LDL increase greater than 4%, 5% and 9.8%, respectively, and a decrease in HDL by more than 9% are associated with worse prognosis of gestational hypertensive disease. (26)

The study by Manna *et al.* (27) in Bangladesh (n=90) showed that increased TG levels are directly associated with an increase in blood pressure. In the study group, systolic and diastolic pressures were 152.4±19.8 mmHg and 103.1±12.2 mmHg, respectively, while in pregnant controls, they were 112.0±8.9 mmHg and 75.5±6.6 mmHg, respectively. (27) These numbers were associated with TG levels in the study group (242.9±36.8 mg/dL) and in the control group (184.6±12.5 mg/dL). (27) TG >181 mg/dL before week 20 increased the risk of PE by 3 to 7 times. (28)

A study conducted in Mexico with 47 normotensive women and 27 with PE or gestational hypertension in the seventh month of pregnancy showed that hypertriglyceridemia is related to hypertensive disorders in pregnancy. Researchers found that nitric oxide (NO) synthesis decreased proportionally to the increase of TG levels. (8) NO decrease may be secondary to oxidative stress increase considering the high concentration of TG or glucose that inhibits NO synthesis. (29) In this study, women with hypertensive disorders of pregnancy were treated with hydralazine, which induces NO synthesis. (8) It has been observed that the increase of fatty acids in the placenta of women with DM1 is related to reduced fetal-placental circulation and that having a family history of DM2 is closely related to an increased risk of developing hypertensive disorders during pregnancy. (2)

Gestational diabetes mellitus

The prevalence of GDM has gone from 4% to 20% in 27 years and its current incidence is 1-14%. (30,31) This pathology not only increases the risk of PE and macrosomia during pregnancy, but also predisposes the mother to the development of DM2 and CVD. (12) Mothers with GDM have hypertriglyceridemia, hypercholesterolemia, insulin resistance, low levels of adiponectin and increased intracellular concentrations of AFABP (2); therefore, they are characterized by having insulin resistance. (4,12,29)

Alterations have been found in the fetus and placenta related to imbalances in the expression and function of PPARs isotypes that increase lipid flow in women with hyperlipidemia and GDM. (2,9,10)

Concentrations of PPAR-γ and PPAR-α are low in term-placental tissue of women who developed GDM, whereas no changes are detected in PPAR-δ concentrations. (9,10) No changes were found in PPAR-γ concentrations in women with DM1; however, decreased levels of 15-deoxy-δ-12, 14-prostaglandin J2 (15dPGJ2) were observed. (9) Also, alterations in the expression of PPAR-α during the first trimester of pregnancy are associated with spontaneous abortions. (10) 15dPGJ2 increases lipid concentrations and significantly reduces NO expression in the placenta of healthy women, while it regulates the increase in the concentrations of phospholipids and cholesterol esters in the placenta of diabetic women. (9) In addition, its receptor (PPAR-γ) is decreased in these patients, which could increase NO and lipid peroxidation, markers of pro-inflammatory and pro-oxidant states. (9)

A case-control study (n=254) conducted in the USA by Han *et al.* (32) found that the measurement of the pregestational lipid profile is a predictor of GDM. This study revealed that women who developed GDM, in comparison with the controls, presented smaller LDL diameters, low concentrations of HDL and high levels of small VLDL regardless of other risk factors (body mass index —BMI—, weight gain during pregnancy, age or ethnicity) in measurements taken even up to 7 years before pregnancy. (32,33) On the other hand, the risk of developing GDM is 3.5 times higher if TG >137 mg/dL in the first trimester. In addition, every time TG increase by 20 mg/dL, the risk of developing DMG increases by 10%. (34)

Pancreatitis

Acute pancreatitis caused by gestational hypertriglyceridemia is a rare complication of pregnancy but, when it occurs, it represents high maternal and fetal morbidity and mortality (1,15,16,18) and may be complicated by pancreatic necrosis, shock, hypokalemia, PE or eclampsia. (15) The risk of developing pancreatitis increases progressively with TG >500 mg/dL. (15) Thus, during the first trimester, these increased levels are associated with a 19% risk of pancreatitis, in the second with 26%, in the third with 53% and in the postpartum with 2% (1,15), depending on the activity of pancreatic lipase and liver involvement. (15,18)

In the fetus

Macrosomia

Lipids availability and accumulation in the fetus of a mother with dyslipidemia increases the risk of developing macrosomia and PD. (6) A LB presents macrosomia if its weight is >4kg and LGA if its size is above the 90th percentile. (12,14) Giving birth to a LGA fetus increases the likelihood of prolonged labor, cesarean or postpartum hemorrhage. In addition, giving birth to fetuses with macrosomia makes women 4.2 times more susceptible to developing DM2 throughout their lives. (35) Hypoglycemia, hyperbilirubinemia, respiratory distress, cardiac hypertrophy, shoulder dystocia, clavicle fracture, and brachial plexus injuries may occur in the newborn. (36,37)

A Cuban case-control study (n=236) showed that the increase in TG levels during the third trimester was a predictor of the development of fetal macrosomia (OR:4.80, CI95%: 2.34-9.84). (6) Another study conducted in Chile in patients with well-controlled GDM and hypertriglyceridemia found that macrosomia was more frequent in women with pre-pregnancy overweight or obesity. (12,38,39) A BMI >26.1 kg/m^2 was a predictor of macrosomia regardless of hypertriglyceridemia during the first trimester of pregnancy (40), perhaps due to the fact that free fatty acids act as growth factors and, that in high concentrations, they compete for the binding site of sex hormones to albumin, which increases the levels of free hormones that could act on the placenta and the fetus, thus modifying its growth and development. (3) It is noteworthy that the levels of circulating leptin in pregnant women with GDM, PE, intrauterine growth restriction or macrosomia have not been shown to have a predictive value on the weight of the newborn. (41)

Contrary to the increase in TG, recent studies suggest that low levels of omega 3 fatty acids during prenatal life influence adiposity in children, not only in intrauterine life, but also in the postnatal period. (42,43) Low concentrations of omega 3 fatty acids are associated with lower weights. In turn, a study conducted in India identified that the placenta of term infants with low weight had lower levels of docosahexaenoic acid (DHA) compared to term neonates weighing > 2 500g. (43)

Preterm delivery

PD is the leading cause of neonatal morbidity and mortality and occurs in 12% of births. (14,44) Its risk increases to 60% if there is a history of DM1, DM2 or pregestational hyperlipidemia and to 33.3%, if there is hypertriglyceridemia in the third trimester. (44-46)

Variants in LPL

Polymorphisms in the LPL gene (S447X, N291S and D9N) are associated with exaggerated increase in TG levels during pregnancy. (17,18) In addition, two APOAV polymorphisms, -1131T>C and S19W, are related to increased VLDL secretion and increased circulating TG levels of 11% and 16.2%, respectively. (18) An interesting correlation has been found between APOAV (-1131T>C), maternal size and crown-rump length of the fetus. (18)

Measurement of triglycerides during pregnancy

In practice, measuring the concentrations of circulating TG once every trimester is advisable, since increased TG levels are normal during pregnancy (Table 2). Clinically, xanthomas on the external surface of arms, legs and buttocks, retinal lipemia, hepatosplenomegaly and lipemic serum are very suggestive of severe hypertriglyceridemia. (15)

Table 2. Normal triglycerides levels during pregnancy.

Author	Triglycerides (mg/dL)		
	Trimester 1	Trimester 2	Trimester 3
Khouly, *et al.* (Egypt) (5)	139.04±14.09		
Barrett, *et al.* (Australia) (16)	104.13±18.81	157.5±43.75	210±47.25
Siddiqui, *et al.* (Saudi Arabia) (22)			228.75±8.82
Pusukuro, *et al.* (India) (47)		188.68±20.88	216.78±20.09
Landázuri, *et al.* (Colombia) (48)	151.3±128.4	240.2±105.0	321.7±189.7
Ywaskewycz, *et al.* (Argentina) (49)	89.9±33.9	140±57.4	201.6±82.5
Becerra, *et al.* (Venezuela) (50)	97.59±6.10	172.88±10.97	215.87±12.57

Source: Own elaboration based on the data obtained in the study.

A study conducted by Landázuri *et al.* (48) in Colombia (n=422) found that TG levels were 86% higher during the second trimester of pregnancy and 137.8% in the third compared to the first. The authors

followed 56 of these pregnant women throughout their pregnancy and observed a TG increase of 58.8% from the first to the second trimester and of 112.6% from the first to the third trimester ($p<0.001$). (48) In this study, low HDL levels were observed compared to the European or North American population during pregnancy. (46,47) Low HDL serum levels could be an additional risk factor for cardiovascular or gestational diseases in Colombian mothers and their children. (51)

Studies to evaluate the lipid profile of normal pregnant women have allowed proposing physiological levels for different populations. Thus, the study conducted by Ywaskewycz *et al.* (49) (n=291) in pregnant women without complications showed a TG increase of 56% from the first to second trimester and of 124% from the first to the third trimester; in the third trimester, the increase was twofold as compared to non-pregnant controls, and no differences were observed between TG in the first trimester and TG in non-pregnant women. (49) In addition, the TG/cHDL ratio increases during pregnancy, thus indicating the presence of LDL proteins of smaller size, rich in TG, denser and with higher atherogenic risk. (49)

On the other hand, the study by Becerra *et al.* (50) (n=91) with healthy pregnant women found that TG levels increased significantly ($p<0.001$) from the first to the second and third trimesters, and that the TG/cHDL ratio was correlated to pre-pregnancy BMI, fetal abdominal circumference, estimated fetal weight and uterine height. ($p<0.01$)

Treatment of hypertriglyceridemia during pregnancy

The treatment of hypertriglyceridemia depends on how high lipids are. If moderate (200-999 mg/dL), a strict low-fat diet with nutritional support with medium-chain TG and ω-3 fatty acids is initiated while increasing physical activity. Dietary supplementation with DHA and eicosapentaenoic acid reduces the production of proinflammatory cytokines (TNF-α, IL-1, IL-6 and IL-8) and inhibits the synthesis of VLDL without altering that of HDL. (15,16,52)

If hypertriglyceridemia is severe (>1000 mg/dL), using medications such as fibrates (PPAR-α agonists), statins, niacin, heparin or insulin is considered. Other possible alternatives are carbaprostacycline and iloprost, drugs that activate PPAR-δ and glitazones, which are synthetic ligands for PPAR-γ. (15,53) However, to the extent possible, using medications should be avoided during the first trimester of pregnancy, since many are contraindicated due to the potential harm to the fetus. It should be noted that using statins and fibrates has been described in case reports.

In case dyslipidemia is refractory to drugs or nutrition, plasmapheresis is initiated. (54) This procedure is also indicated when serum lipase levels are >3 times the normal limit of this enzyme or when hypocalcemia, lactic acidosis and worsening of inflammation or organic dysfunction occur; this can also be combined with heparin infusion. (55,56) When TG levels are below 500 mg/dL, this procedure should be stopped (55,56); however, if contraindicated or not available, infusion of regular insulin with 5% dextrose is used and glucose levels must be maintained between 150 mg/dL and 200 mg/dL during therapy. (15,53) When TG levels are normalized, the next step is to perform a rigorous control of the lipid profile, long-term dietary restriction and administration of fenofibrate. (15,16) In severe hypertriglyceridemia, PD is induced considering the high risks of maternal and fetal mortality (20% and 50%, respectively) and secondary pancreatitis. (1,15,16)

A study conducted by Kern-Pessoa *et al.* (57) in Sao Paulo (n=73) found that TC and TG levels increased during pregnancy and decreased from the third to the sixth postpartum week in women with GDM. (57) In this study, LDL and TG levels increased during pregnancy in patients who received insulin, and decreased in those treated with a strict low-fat diet, rich in ω-3 fatty acids as therapy. (57)

Conclusions

During pregnancy, TG concentrations increase as a physiological adaptation mechanism, but if they reach very high levels, they become a risk factor for the mother and the child in the short and long term. The metabolic stress observed during this stage is associated with a decrease in the synthesis of fatty acids and the activity of lipoprotein lipase that elevates non-esterified fatty acids and increases insulin resistance. Greater lipolysis is associated with the increase of hormones (progesterone, prolactin and estrogens), cytokines (TNF-α and IL-6) and adipokines (leptin, visfatin and resistin), and with the decrease in adiponectin and apelin, which together reduce insulin sensitivity. For this reason, the availability of TG bound to lipoproteins such as VLDL increases for transplacental passage of fatty acids to the fetus through diffusion, hydrolysis and membrane transporters. These fatty acids reach the fetal liver attached to the α-fetoprotein.

Hypertriglyceridemia increases the risk of pregnancy complications, especially in pregnant women with a history of obesity or overweight, uncontrolled diabetes and familial dyslipidemia. In pregnant women, GDM and acute pancreatitis are the main complications of hypertriglyceridemia; on the other hand, PD, macrosomia and LGA fetuses are the main complications for the product of pregnancy.

For treatment, some case reports have described the use of statins and fibrates in pregnant women with severe hypertriglyceridemia; however, the use of these medications could generate more risks than benefits for the fetus, so its formulation is not recommended during pregnancy.

The limited number of studies and the great variability of the data indicate the need to conduct more research in Colombia to establish the normal ranges of TG during the three trimesters of pregnancy. This could facilitate diagnosis and monitoring of hypertriglyceridemia throughout pregnancy. On the other hand, it is important that health professionals understand the importance of measuring TG levels before pregnancy to determine risks and effective interventions and reduce maternal and child morbidity and mortality.

Conflicts of interest

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References

1. **Wild R, Weedin EA, Gill EA.** Women's Health Considerations for Lipid Management. *Endocrinol Metab Clin North Am.* 2016;45(1):65-85. http://doi.org/f8fxx5.
2. **Herrera E, Desoye G.** Maternal and fetal lipid metabolism under normal and gestational diabetic conditions. *Horm Mol Biol Clin Investig.* 2016;26(2):109-27. http://doi.org/cgf8.
3. **Vrijkotte TG, Krukziener N, Hutten BA, Vollebregt KC, Van Eijsden M, Twickler MB.** Maternal lipid profile during early pregnancy and pregnancy complications and outcomes: The ABCD study. *J Clin Endocrinol Metab.* 2012;97(11):3917-25. http://doi.org/f4b9ns.
4. **Niromanesh S, Shirazi M, Dastgerdy E, Sharbaf FR, Shirazi M, Khazaeipour Z.** Association of hypertriglyceridaemia with pre-eclampsia,

preterm birth, gestational diabetes and uterine artery pulsatility index. *Natl Med J India.* 2012;25(5):265-7.

5. **El Khouly NI, Sanad ZF, Saleh SA, Shabana AA, Elhalaby AF, Badr EE.** Value of first-trimester serum lipid profile in early prediction of preeclampsia and its severity: A prospective cohort study. *Hypertens Pregnancy.* 2016;35(1):73-81. http://doi.org/cgf9.
6. **Cruz J, Grandía R, Padilla L, Rodríguez S, Hernández-García P, Lang-Prieto J, *et al.*** Macrosomia Predictors in Infants Born to Cuban Mothers with Gestational Diabetes. *MEDICC Rev.* 2015;17(3):27-32.
7. Instituto Nacional de Salud. Enfermedades no trasmitibles. Bogotá, D.C.: Boletín Epidemiológico No 21; 2016.
8. **Mayret-Mesquiti M, Pérez-Méndez O, Rodríguez ME, Fortoul TI, Gorocica P, Bernal-Alcántara D, *et al.*** Hypertriglyceridemia is linked to reduced nitric oxide synthesis in women with hypertensive disorders of pregnancy. *Hypertens pregnancy.* 2007;26(4):423-31. http://doi.org/dtkhxg.
9. **Capobianco E, Martínez N, Fornes D, Higa R, Di Marco I, Basualdo MN, *et al.*** PPAR activation as a regulator of lipid metabolism, nitric oxide production and lipid peroxidation in the placenta from type 2 diabetic patients. *Mol Cell Endocrinol.* 2013;377(1-2):7-15. http://doi.org/f48stf.
10. **Jawerbaum A, Capobianco E.** Review: Effects of PPAR activation in the placenta and the fetus: Implications in maternal diabetes. *Placenta.* 2011;32(Suppl 2):S212-7. http://doi.org/bgxzfh.
11. **Olmos PR, Rigotti A, Busso D, Berkowitz L, Santos JL, Borzone GR, *et al.*** Maternal hypertriglyceridemia: A link between maternal overweight-obesity and macrosomia in gestational diabetes. *Obesity (Silver Spring).* 2014;22(10):2156-63. http://doi.org/cggb.
12. **Olmos P, Martelo G, Reimer V, Rigotti A, Busso D, Belmar C, *et al.*** La hipótesis de Pedersen no es suficiente: Otros nutrientes además de la glucosa explicarían la macrosomía fetal en pacientes diabéticas gestacionales con sobrepeso y buen control glicémico. *Rev méd Chile.* 2013;141(11):1441-8. http://doi.org/cggh.
13. **Heim C, Newport DJ, Heit S, Graham YP, Wilcox M, Bonsall R, *et al.*** Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. *JAMA.* 2000;284(5):592-7. http://doi.org/df2w76.
14. **Ferriols E, Rueda C, Gamero R, Vidal M, Payá A, Carreras R, *et al.*** Comportamiento de los lípidos durante la gestación y su relación con acontecimientos obstétricos desfavorables. *Clin Invest Arterioscl.* 2016;28(5):232-44. http://doi.org/f3gxhv.
15. **Gupta N, Ahmed S, Shaffer L, Cavens P, Blankstein J.** Severe hypertriglyceridemia induced pancreatitis in pregnancy. *Case Rep Obstet Gynecol.* 2014;2014:485-93. http://doi.org/f3gxhv.
16. **Barrett HL, Dekker-Nitert M, McIntyre HD, Callaway LK.** Normalizing metabolism in diabetic pregnancy: is it time to target lipids? *Diabetes Care.* 2014;37(5):1484-93. http://doi.org/f5zbr4.
17. **McGladdery SH, Frohlich JJ.** Lipoprotein lipase and apoE polymorphisms: relationship to hypertriglyceridemia during pregnancy. *J Lipid Res.* 2001;42(11):1905-12.
18. **Ward KJ, Shields B, Knight B, Salzmann MB, Hattersley AT, Frayling TM.** Genetic variants in Apolipoprotein AV alter triglyceride concentrations in pregnancy. *Lipids Health Dis.* 2003;2:9. http://doi.org/dccv7x.
19. **Montelongo A, Lasunción MA, Pallardo LF, Herrera E.** Longitudinal-Study of Plasma lipoproteins and Hormones During Pregnancy in Normal and Diabetic Women. *Diabetes.* 1992;41(12):1651-9. http://doi.org/cggn.
20. **Sjöström L, William-Olsson T.** Prospective studies on adipose tissue development in man. *Int J Obes.* 1981;5(6):597-604.
21. **Jin WY, Lin SL, Hou RL, Chen XY, Han T, Jin Y, *et al.*** Associations between maternal lipid profile and pregnancy complications and perinatal outcomes: a population-based study from China. *BMC Pregnancy Childbirth.* 2016;16(1):60. http://doi.org/cggp.
22. **Siddiqui I.** Maternal Serum Lipids in Women with Pre-eclampsia. *Ann Med Health Sci Res.* 2014;4(4):638-41. http://doi.org/gcb4px.
23. **Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R.** Pre-eclampsia. *Lancet.* 2010;376(9741):631-44. http://doi.org/d3cbtp.
24. **Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF.** WHO analysis of causes of maternal death: a systematic review. *Lancet.* 2006;367(9516):1066-74. http://doi.org/dst3wb.
25. **Duley L.** The Global Impact of Pre-eclampsia and Eclampsia. *Semin Perinatol.* 2009;33(3):130-7. http://doi.org/bqvddg.
26. **Kumru S, Aydin S, Gursu MF, Ozcan Z.** Changes of serum paraoxonase (an HDL-cholesterol-associated lipophilic antioxidant) and arylesterase activities in severe preeclamptic women. *Eur J Obstet Gynecol Reprod Biol.* 2004;114(2):177-81. http://doi.org/b8bnmg.
27. **Manna FN, Khanam NN, Chowdhury KA, Das SN, Kabir MA, Zubyra SJ, *et al.*** Study on Association of Maternal Serum Triglyceride with Pre-eclampsia. *Mymensingh Med J.* 2015;24(3):578-84.
28. **Qiu C, Phung TT, Vadachkoria S, Muy-Rivera M, Sanchez SE, Williams MA.** Oxidized low-density lipoprotein (Oxidized LDL) and the risk of preeclampsia. *Physiol Res.* 2006;55(5):491-500.
29. **Kadam L, Kohan-Ghadr HR, Drewlo S.** The balancing act - PPAR-γ's roles at the maternal-fetal interface. *Syst Biol Reprod Med.* 2015;61(2):65-71. http://doi.org/cghz.
30. **Bowers K, Tobias DK, Yeung E, Hu FB, Zhang C.** A prospective study of prepregnancy dietary fat intake and risk of gestational diabetes. *Am J Clin Nutr.* 2012;95(2):446-53. http://doi.org/fx2bnx.
31. **Khan R, Ali K, Khan Z, Ahmad T.** Lipid profile and glycosylated hemoglobin status of gestational diabetic patients and healthy pregnant women. *Indian J Med Sci.* 2012;66(7-8):149-54. http://doi.org/cgh2.
32. **Han ES, Krauss RM, Xu F, Sridhar SB, Ferrara A, Quesenberry CP, *et al.*** Prepregnancy adverse lipid profile and subsequent risk of gestational diabetes. *J Clin Endocrinol Metab.* 2016;101(7):2721-7. http://doi.org/f8wn58.
33. **Gunderson EP, Quesenberry CP Jr, Jacobs DR Jr, Feng J, Lewis CE, Sidney S.** Longitudinal study of prepregnancy cardiometabolic risk factors and subsequent risk of gestational diabetes mellitus: The CARDIA study. *Am J Epidemiol.* 2010;172(10):1131-43. http://doi.org/bdcc96.
34. **Enquobahrie DA, Williams MA, Butler CL, Frederick IO, Miller RS, Luthy DA.** Maternal plasma lipid concentrations in early pregnancy and risk of preeclampsia. *Am J Hypertens.* 2004;17(7):574-81. http://doi.org/bwbc23.
35. **Merzouk H, Khan NA.** Implication of lipids in macrosomia of diabetic pregnancy: can n-3 polyunsaturated fatty acids exert beneficial effects? *Clin Sci (Lond).* 2003;105(5):519-29. http://doi.org/bkxcc8.
36. **Zhang X, Decker A, Platt RW, Kramer MS.** How big is too big? The perinatal consequences of fetal macrosomia. *Am J Obstet Gynecol.* 2008;198(5):517.e1-6. http://doi.org/c9z643.
37. **Chauhan SP, Grobman WA, Gherman RA, Chauhan VB, Chang G, Magann EF, *et al.*** Suspicion and treatment of the macrosomic fetus: A review. *Am J Obstet Gynecol.* 2005;193(2):332-46. http://doi.org/bqm56b.
38. **Catalano PM.** Management of obesity in pregnancy. *Obstet Gynecol.* 2007;109(2 Pt 1):419-33. http://doi.org/fw6tnr.
39. **Ehrenberg HM, Mercer BM, Catalano PM.** The influence of obesity and diabetes on the prevalence of macrosomia. *Am J Obstet Gynecol.* 2004;191(3):964-8. http://doi.org/d38phg.
40. **Ricart W, López J, Mozas J, Pericot A, Sancho MA, González N, *et al.*** Body mass index has a greater impact on pregnancy outcomes than gestational hyperglycaemia. *Diabetologia.* 2005;48(9):1736-42. http://doi.org/bsq766.
41. **Verhaeghe J, Pintiaux A, van Herck E, Hennen G, Foidart J-M, Igout A.** Placental GH, IGF-I, IGF-Binding Protein-1, and Leptin during a Glucose Challenge Test in Pregnant Women: Relation with Maternal

Body Weight, Glucose Tolerance, and Birth Weight. *J Clin Endocrinol Metab.* 2002;87(6):2875-82. http://doi.org/cgh4.

42. **de Vries PS, Gielen M, Rizopoulos D, Rump P, Godschalk R, Hornstra G, *et al.*** Association between polyunsaturated fatty acid concentrations in maternal plasma phospholipids during pregnancy and offspring adiposity at age 7: The MEFAB cohort. *Prostaglandins Leukot Essent Fatty Acids.* 2014;91(3):81-5. http://doi.org/f6fh2b.

43. **Meher AP, Wadhwani N, Randhir K, Mehendale S, Wagh G, Joshi SR.** Placental DHA and mRNA levels of PPARγ and LXRα and their relationship to birth weight. *J Clin Lipidol.* 2016;10(4):767-74. http://doi.org/f83xmg.

44. **Steffen KM, Cooper ME, Shi M, Caprau D, Simhan HN, Dagle JM, *et al.*** Maternal and fetal variation in genes of cholesterol metabolism is associated with preterm delivery. *J Perinatol.* 2007;27(11):672-80. http://doi.org/bxgk2r.

45. **Magnussen EB, Vatten LJ, Myklestad K, Salvesen KÅ, Romundstad PR.** Cardiovascular risk factors prior to conception and the length of pregnancy: population-based cohort study. *Am J Obstet Gynecol.* 2011;204(6):526.e1-8. http://doi.org/b5qbkw.

46. **Mattison DR, Damus K, Fiore E, Petrini J, Alter C.** Preterm delivery: a public health perspective. *Paediatr Perinat Epidemiol.* 2001;15(Suppl 2):7-16. http://doi.org/dxt4g7.

47. **Pusukuru R, Shenoi AS, Kyada PK, Ghodke B, Mehta V, Bhuta K, *et al.*** Evaluation of Lipid Profile in Second and Third Trimester of Pregnancy. *J Clin Diagnostic Res.* 2016;10(3):12-6. http://doi.org/cgh6.

48. **Landázuri P, Restrepo B, Trejos J, Gallego ML, Loango-Chamorro N, Ocampo R.** Perfil lipídico por trimestres de gestación en una población de mujeres colombianas. *Rev Colomb Obstet Ginecol.* 2006;57(4):256-63.

49. **Ywaskewycz-Benítez LR, Bonneau GA, Castillo-Rascón MS, López DL, Pedrozo WR.** Perfil lipídico por trimestre de gestación en una población de mujeres adultas. *Rev Chil Obstet Ginecol.* 2010;75(4):227-33. http://doi.org/dpqh2r.

50. **Becerra-Leal AV, Salas-Paredes A, Buela L, Sosa MA, Arata-Bellabarba G, Valeri L, *et al.*** Índice trigliceridos/cHDL en el embarazo: Interrelación con índices de resistencia a la insulina y antropometría fetal. *Rev Venez Endocrinol y Metab.* 2013;11(3):141-6.

51. **Hersberger M, von Eckardstein A.** Low high-density lipoprotein cholesterol: physiological background, clinical importance and drug treatment. *Drugs.* 2003;63(18):1907-45. http://doi.org/dvm9pp.

52. **Valenzuela BR, Barrera RC, Gonzalez-Astorga M, Sanhueza CJ, Valenzuela BA.** Alpha linolenic acid (ALA) from Rosa canina, sacha inchi and chia oils may increase ALA accretion and its conversion into n-3 LCPUFA in diverse tissues of the rat. *Food Funct.* 2014;5(7):1564–72. http://doi.org/ckck.

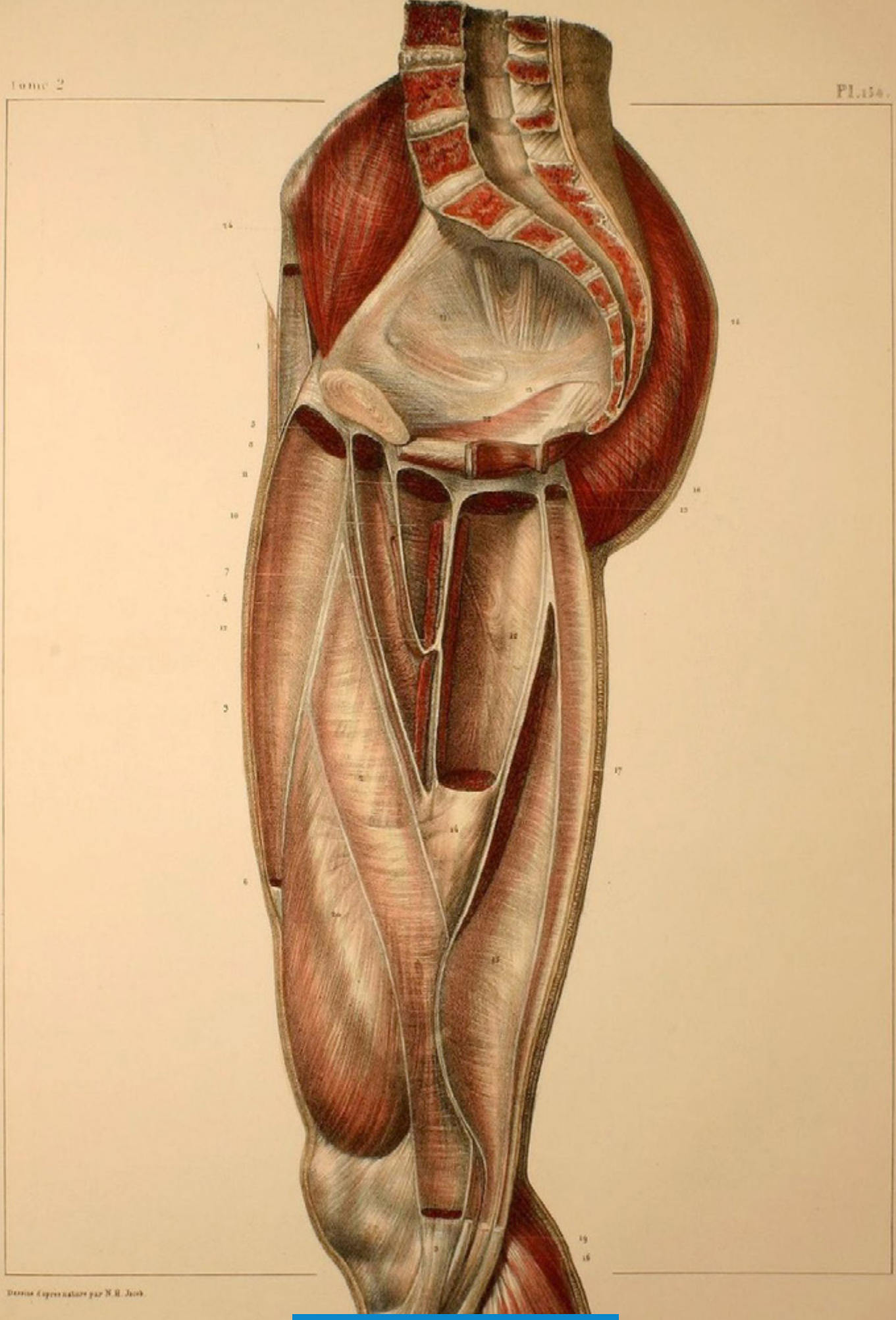
53. **Gürsoy A, Kulaksizoglu M, Sahin M, Ertugrul DT, Ozer F, Tutuncu NB, *et al.*** Severe hypertriglyceridemia-induced pancreatitis during pregnancy. *J Natl Med Assoc.* 2006;98(4):655-7.

54. **Safi F, Toumeh A, Abuissa-Qadan MA, Karaz R, AlAkdar B, Assaly R.** Management of familial hypertriglyceridemia-induced pancreatitis during pregnancy with therapeutic plasma exchange: a case report and review of literature. *Am J Ther.* 2014;21(5):e134-6. http://doi.org/cgh7.

55. **Altun D, Eren G, Cukurova Z, Hergünsel O, Yasar L.** An alternative treatment in hypertriglyceridemia-induced acute pancreatitis in pregnancy: Plasmapheresis. *J Anaesthesiol Clin Pharmacol.* 2012;28(2):252-4. http://doi.org/f3xftm.

56. **Vandenbroucke L, Seconda S, Lassel L, Le Bouar G, Poulain P.** Pancréatite aiguë secondaire à une hypertriglycéridémie majeure au cours de la grossesse. À propos d'un cas. *J Gynecol Obstet Biol Reprod (Paris).* 2009;38(5):436-9. http://doi.org/cbq964.

57. **Kern-Pessôa VN, Rodacki M, Negrato CA, Zajdenverg L.** Changes in lipid profile after treatment of women with gestational diabetes mellitus. *J Clin Lipidol.* 2016;10(2):350-5. http://doi.org/f8htrw.



Jean Marc Bourgery
"Traité complet de l'anatomie de l'homme"
Paris 1832-1854

REVIEW ARTICLE

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Risk factors associated with low birth weight in the Americas: literature review

Factores de riesgo de bajo peso al nacer en las Américas: una revisión de literatura

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| Abstract |

Introduction: Low birth weight (LBW) is one of the main risk factors that affects infant morbidity and mortality worldwide. Approximately one third of neonatal deaths are attributable to this cause.

Objective: To review the most relevant papers related to low birth weight in the Americas between 2010 and 2016.

Materials and methods: Narrative literature review. The information was obtained from the PubMed, SciELO, LILACS and Portal Regional da BVS databases, using DeCS and MeSH descriptors.

Results: Most of the studies were published between 2012 and 2015. Of 29 articles published, 11 (40.7%) dealt with sociodemographic factors, 9 (33.3%) with environmental risks, 3 (11.1%) with behavioral factors, 2 (7.4%) with prenatal or coverage controls and 2 (7.4%) were interrelated with other risk factors.

Conclusion: Most of the studies agree on the association of sociodemographic, biological and behavioral factors. Those studies that refer to the association of LBW with environmental risk factors are growing in strength.

Keywords: Infant Mortality; Risk Factors; Americas (MeSH).

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| Resumen |

Introducción. El bajo peso al nacer (BPN) es uno de los principales factores de riesgo que afecta la morbimortalidad infantil en todo el mundo; cerca de 1/3 de las muertes neonatales son atribuibles a este.

Objetivo. Revisar los artículos más relevantes sobre BPN en las Américas en el periodo de 2010-2016.

Materiales y métodos. Revisión narrativa de literatura. La información se obtuvo de las bases de datos PubMed, SciELO, LILACS, Portal Regional da BVS, con el uso de los descriptores DeCS y MeSH.

Resultados. La mayoría de los estudios fueron publicados entre el 2012 y el 2015. De los 27 artículos publicados, 11 (40.7%) fueron atribuidos a factores sociodemográficos, 9 (33.3%) a riesgos ambientales, 3 (11.1%) a factores conductuales, 2 (7.4%) a controles prenatales o por cobertura y 2 (7.4%) se interrelacionaban con otros factores de riesgo.

Conclusión. La mayoría de los estudios coinciden en la asociación de factores sociodemográficos, biológicos y conductuales. Los estudios que refieren la asociación de BPN con factores de riesgo ambientales están tomando fuerza.

Palabras clave: Mortalidad infantil; Factores de riesgo; Américas (DeCS).

González-Jiménez J, Rocha-Buelvas A. [Factores de riesgo de bajo peso al nacer en las Américas: una revisión de literatura]. Rev. Fac. Med. 2018;66(2):255-60. English. doi: http://dx.doi.org/10.15446/revfacmed.v66n2.61577.

Introduction

Research on sexual and reproductive health in Latin America is increasingly numerous in topics such as health interventions for the prevention of maternal and neonatal morbidity and mortality, specifically, those that study the increase and decrease of fertility, the use of different birth control methods, the quality of prenatal care and the prevalence of institutional delivery in rural and urban areas in certain populations and samples. All these investigations show that women are vulnerable according to their socioeconomic or educational level, employment conditions and family configuration. (1)

The World Health Organization (WHO) considers that a newborn has low birth weight (LBW) if weight is below 2 500 grams, regardless of gestational age or any other etiology. (2) Children with LBW have 40 to 200 times greater risk of dying than children with adequate weight at birth. (3,4) In the Americas, a comparison can be made

between the Latin American countries that have a LBW index of 8.6% and the United States, whose index is 0.5%. (5) Colombia is not the country with the highest LBW rate in Latin America, but it reached an index close to 8.5% in 2008. (1)

It should be noted that the State of the World's Children 2008, published by UNICEF, reported that around 20 million children worldwide are born each year with LBW, a figure that corresponds to 14.5% of all live births. (5,6) Furthermore, UNICEF found that LBW is more prevalent in developing countries because they do not measure the weight of more than half of newborns. (7)

In Colombia, the National Survey of Demography and Health (ENDS by its acronym in Spanish), conducted in 2010, reported that vulnerability to LBW is differential according to the place of occurrence of the births. For example, the risk is greater in departments like La Guajira, which do not achieve the national goal of reducing and meeting the Millennium Development Goals (MDGs). However, an improvement in the living conditions of the population and in social development opportunities was achieved (8), as deliveries took place in health facilities with a higher frequency: 88% in 2000, 92% in 2005 and 95% in 2010. (9,10) In consequence, conducting a narrative literature review on LBW in the Americas region during this decade is highly relevant.

Materials and methods

A narrative review of publications in health sciences about risk factors associated with LBW in the Americas was conducted. The research stages were: bibliographic search, data systematization, selection of articles and primary analysis, evaluation and final analysis.

During the first stage, information was collected from metasearch engines and digital databases including PubMed, SciELO, LILACS, VHL Regional Portal using DeCS (Descriptors in Health Sciences), MeSH (Medical Subject Headings) and Tripdatabase descriptors. Connectors "and" and "or", among others, were used. Likewise, a direct bibliographical search was carried out in multiple chapters of specialized texts as a complementary activity. The search was delimited as follows:

Time frame: 2010-2016.
Languages: English, Spanish and Portuguese.
Type of design: empirical studies without design limitations.
Document type: articles derived from research and review; therefore, gray literature, editorials, papers, communications and opinion articles were excluded.

Upon searching the databases, potentially selected studies were obtained and a total of 82 were retrieved. Titles, abstracts and full texts were independently examined, using the eligibility criteria specified, excluding 44 that did not have any relation to the subject of interest. Also, 11 articles were excluded because they did not deal with risk factors associated with LBW. Finally, 27 article type documents (11) were obtained as shown in Figure 1.

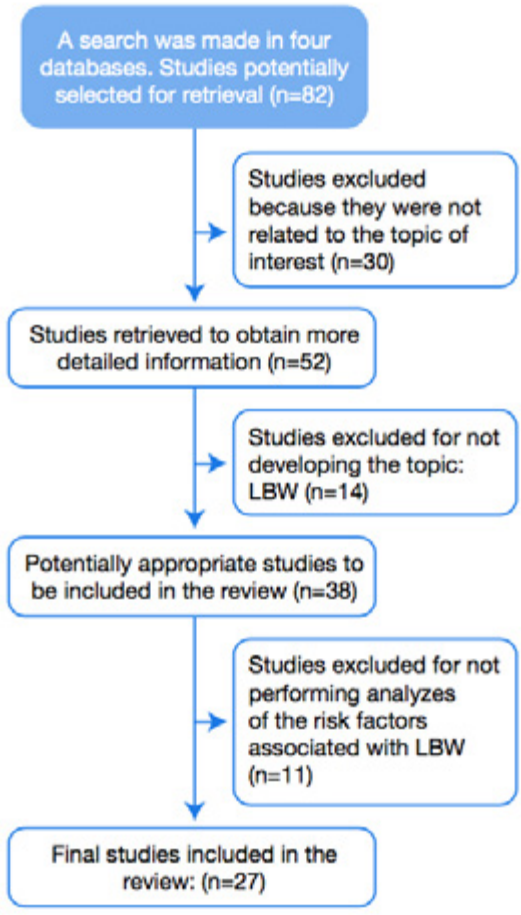

Figure 1. Flow diagram of the study. Selection process of the studies. Source: Own elaboration based on the data obtained in the study.

Once the search was completed, the second stage of information systematization was carried out, during which matrices that contained objectives, author, country, methodology and results were elaborated. These matrices would facilitate the third phase: bibliometric and methodological extraction and analysis of geographical location, year, language, designs used, service evaluated, selection of the sample and statistical analysis of the information. The fourth stage consisted of defining the articles to be included considering full-text retrieval and their consistency with the objective of the review.

Results

Of the selected studies (Tables 1 and 2), 88% were published between 2012 and 2015 (Table 3). The country with the highest number of publications is the United States with 12 (44.4%), followed by Brazil with eight (29.6%). Regarding language, most articles were published in English with 15 (51.72%), followed by Portuguese with eight (29.6%).

Table 1. Methodology used by the studies found.

Author, year	Design	Instrument	Sample	Source population and country	Statistical analysis
Da Fonseca *et al.* (12) 2014	Cases and controls	Medical records and live birth certificates	1 720 newborns	Two groups of 860 newborns each in São Paulo, Brazil	Modified Kessner Index
Pinzón *et al.* (13) 2015	Cross-sectional	Demographic survey	10 692 children	Children born to women (aged 13 to 49) included in the National Demographic and Health Survey in Bogotá, Colombia	Binomial regression

Continues.

Author, year	Design	Instrument	Sample	Source population and country	Statistical analysis
McDermott, *et al.* (14) 2014	Cohort	Medicaid and newborn's record	9 920 women	Pregnant women and their newborns, low-income families from South Carolina, USA.	Multivariate analysis
Ebisu & Bell (15) 2012	Descriptive	Birth certificates	7 098 417 births in 419 counties	Birth certificate. National Center for Health Statistics in counties with data on PM components in Atlanta, Georgia. USA	Logistic regression
Laurent *et al.* (16) 2013	Cohort	Obstetric database of the hospital network	70 000 births	Births, hospital obstetric database of Los Angeles and Orange County, Southern California, USA.	Multivariate analysis
Ghosh *et al.*(17) 2012	Cohort	Digital birth certificates	1 745 754 registered births	Digital birth certificates issued in California to identify women who gave birth between January 1, 1995 and December 31, 2006	Logistic regression
Padula *et al.* (18) 2012	Cohort	California Department of Health Services in Sacramento	All live births	Live births from the four most populated counties in the San Joaquin Valley of California, USA	Attributable risk
Cândido *et al.* (19). 2014	Cohort	Information System on Live Births (SINASC by its acronym in Portuguese)	6 147 births	Single full-term live births from the cities of the State of Mato Grosso in the Brazilian Amazon	Logistic regression
Coker *et al.* (20) 2015	Cohort	Certificates provided by the Department of Health	1 356 304 births	Births in Los Angeles County, USA	Multivariate logistic regressions
Habermann & Gouveia (8) 2014	Cases and controls		11 589 live births	Newborns with LBW and 5 814 controls matched by sex and month of birth in São Paulo. Brazil.	Multiple logistic regression adjusted for birth
Lin & Scott. (21) 2012.	Cohort	Birth certificates, databases of the National Center for Health Statistics. Vital statistics for public use	1 374 875 term births	Term births among the seven states considered, New Jersey and New York, USA	Logistic regression to estimate the association
Guimarães *et al.* (22) 2013	Cross-sectional	Interview questionnaire	4 746 pairs of mothers and their babies	Mothers and their newborns from a birth cohort in Aracaju, northeastern Brazil	Multiple logistic regression
Ferreira-Veloso *et al.* (23) 2014	Cohort	SINASC	7 466 births	Newborns: 2 426 included in 1997/98 and 5 040 in 2010. In São Luís, northeastern Brazil.	Multiple logistic regression
Neggers &Crowe. (24) 2013.	Ecological	Medical records and literature	Pregnant women and newborns	Pregnant women and newborns in the USA and Cuba	Multivariate analysis
Pinzón-Villate *et al.* (1) 2013	Retrospective descriptive	Certificates of live birth available at the DANE database	Newborns in the DANE database	Live births in Colombia in 2005-2009	Logistic regression to determine associated predictors
Britto *et al.*(25) 2013	Cross-sectional	Structured questionnaire	2 972 children	2 226 mother-child pairs from 23 neighborhoods of Chabolas, Brazil were included	Logistic regression
Bragança *et al.* (26) 2012	Ecological	SINASC	149 165 live births	Children born in Rio Grande do Sul, Brazil	Multilevel logistic regression
Silva da Oliveira *et al.* (27) 2010	Ecological	SINASC, IPEA and IBGE	Live births	Live births in the 27 Brazilian States in 2009	Bivariate analysis
Herd *et al.* (28) 2015	Descriptive	Census data files	Live births	Single live births in 2000 to women residing in 805 zip codes of California. USA	Binomial regression
Wehby *et al.* (29) 2016	Descriptive	ECLAMC (Latin American Collaborative Study of Congenital Malformations) Website, epidemiological research and surveillance program for birth defects in South America	60 480 single live births	Newborns from 71 cities in eight South American countries: Brazil, Ecuador, Uruguay, Venezuela, Argentina, Bolivia, Chile and Colombia	Logistic regression
Nascimento *et al.* (30) 2013	Ecological exploratory	Database of the Municipal Health Secretariat of Taubaté. Declaration of live births	1 817 live births with LBW.	18 915 live births in Taubaté, São Paulo, Brazil.	Data were analyzed using the TerraView program (available in https://goo.gl/aqjUMU)
Von Ehrenstein *et al.* (31) 2014	Cases and controls	U.S. Census Bureau	Newborns	(n=1 498) nested within the birth cohort in 2003 (n=58 316) in the Los Angeles County, USA	Logistic regression analysis of single and multiple variables
Fulda *et al.* (32) 2014	Cross-sectional	Birth certificates, clinical records of the Texas Department of State Health Services Vital Statistics Bureau	145 054 births	Mothers from 145 054 births recorded in Tarrant County, USA	Simple and multiple logistic regression
Loggins-Clay & Andrade. (33) 2015	Descriptive	Reference surveys, study data: Fragile Family and Child Wellbeing	3 869 births	Mother and children with LBW in black and white women in the USA	Logistic regression
Sanches-Ranzani-da Silva. (34) 2012	Systematic review	PubMed, Lilacs, SciELO, institutional repositories	64 studies	Studies on LBW in Latin America	Qualitative through systematization and analysis
Xaverius *et al.* (35) 2014	Cohort	Fetal death and birth certificates	160 913 certificates	159 547 records of live births and 1 366 death records in St. Louis, USA.	Multivariate logistic regression
Dennis &.Mollborn. (36) 2013	Cohort	Survey	10 700 live births	Live births in the USA	Bivariate analysis

SINASC: Information System on Live Births; ECLAMC: Latin-American collaborative study of congenital malformations; PM: Particulate Matter; IPEA: Institute of Applied Economic Research; IBGE: Brazilian Institute of Geography and Statistics.
Source: Own elaboration based on the data obtained in the study.

Table 2. Institutions represented and number of authors.

Institution	No. Author	Institution	No. Author
Medical School of São Paulo State University, Botucatu Campus	1	School of Medicine and Health Sciences, Universidad del Rosario, Bogotá, Colombia	1
Department of Epidemiology and Biostatistics, School of Public Health, University of South Carolina, USA.	1	Yale School of Forestry and Environmental Studies, New Haven, Connecticut, USA	1
Public Health Program, University of California, Irvine, California, USA	1	National Institute of Environmental Health Sciences, California, USA	2
National School of Public Health of Brazil.	1	California Department of Public Health, USA	4
Department of Preventive Medicine, Faculty of Medicine, University of São Paulo, São Paulo, Brazil	1	Environmental Public Health Monitoring Program of the Centers for Disease Control and Prevention, Atlanta, USA	1
Department of Public Health of the Federal University of Maranhão, Rua	1	Department of Human Nutrition, Universidad Nacional de Colombia, Bogotá, Colombia	1
Federal University of Alagoas, Maceió, Brazil	2	Federal University of Santa Maria, Santa Maria, Brazil	1
Federal University of Rio Grande do Sul, Porto Alegre, Brazil	2	School of Public Health, University of California, California, USA UU	2
National Institute of Population Medical Genetics (INAGEMP), Rio de Janeiro, Brazil	1	Latin American Collaborative Study of Congenital Malformations (ECLAMC)	2
University of Iowa College of Public Health, USA	1	University of Taubaté (UNITAU), Taubaté, São Paulo, Brazil	3
UCLA Fielding School of Public Health, University of California, Los Angeles, USA	3	Department of Family Medicine, North Texas Primary Care Practice-Based Research Network (NorTex), Texas Prevention Institute, USA	1
Department of Sociology, Institute of Behavioral Sciences, Health and Society Program, University of Colorado Boulder, Colorado, USA	1	UNT Health Sciences Center, University of North Texas, Fort Worth, Texas, USA	3
University do Vale do Rio dos Sinos (UNISINOS), Sao Leopoldo, Brazil	1	Saint Louis University, College for Public Health and Social Justice, San Luis, USA	3
Lindenwood University, St. Charles, USA	1	School of Social Sciences, University of Texas of the Permian Basin, USA	1
Department of Sociology, Institute of Behavioral Sciences, Health and Society Program, University of Colorado Boulder, Colorado, USA	1		
Total authors	54		

Source: Own elaboration based on the data obtained in the study.

Table 3. Number of studies published per year included in the review.

Year	2010	2011	2012	2013	2014	2015	2016	Total
Articles	1	0	7	6	7	4	2	27

Source: Own elaboration based on the data obtained in the study.

Regarding the results, Table 4 shows that 11 of the 27 published articles (40.7%) dealt with sociodemographic factors, 9 (33.3%) with environmental risks, 3 (11.1%) with behavioral factors, 2 (7.4 %) with prenatal or coverage controls and 2 (7.4%) correlated to other risk factors.

Table 4. Classification of articles by risk factors.

Risk factor	Number of articles	Weight %
Coverage	2	7.4%
Environmental risk	9	33.3%
Behavioral factor	3	11.1%
Sociodemographic	11	40.7%
Mixed	2	7.4%

Source: Own elaboration based on the data obtained in the study.

It is noteworthy that nine articles (33.3%) conducted between 2011 and 2015 study the environmental risk related to LBW (21), for example, the association of water soluble metals such as copper and LBW. (37) An important finding in the United States is found in four counties of Connecticut and Massachusetts that reported the association of LBW with levels higher than 2.5PM of components such as aluminum, coal, nickel, silicon, vanadium and zinc. (38) These findings on risk factors in water reported that the probability of LBW is higher in Afro-descendant infants and mothers compared to white women. (15,20)

The increase of LBW and air pollution are associated, (16,19) as is the case of benzene in contaminated air which, in addition to contributing to LBW, can cause fetal growth restriction and complications during pregnancy. (17) Prenatal exposure to air pollution is related to habitats or workplaces near high traffic congestion areas such as highways, whose traffic increases pollutants. (18,39) Finally, the presence of arsenic in the soil near housing areas is associated with LBW as well (14).

Several studies report relevant information regarding sociodemographic risk factors. An ecological study carried out in the state of Rio Grande do Sul in Brazil established that mothers who have had less than seven prenatal checkups have 3.8 times the risk of LBW. (34) This finding has been reported in the medical literature for decades, where sociodemographic, ethnic, maternal, fetal and environmental conditions were already correlated to LBW. (40)

In this way, sociodemographic aspects and the health system itself are part of the specificities of prenatal care as a prevention strategy against LBW. However, in developing countries, it is often underestimated to such an extent that guidelines and strategies established in industrialized countries are used without hesitation. (13,12) Another sociodemographic risk factor refers to maternal age as a predisposing factor, since LBW as an outcome is higher in mothers older than 35 and under 20 years of age. (34,41) Likewise, mothers with low levels of education have a higher risk of LBW. (26)

Studies that seek statistical significance between ethnic groups in the Americas and LBW (42,28) show an association with LBW prevalence in women of African descent. (29) According to a study in Caucasian and Hispanic couples with African American parents, paternal origin is an important predictor of LBW. (33) Although LBW is etiologically multifactorial, race is taken as a causal variable. (31,32,35)

Similarly, low socioeconomic status and poverty take on greater relevance in research in South American countries. (22,43) Many of them consider health as the most precarious socioeconomic condition. (44) LBW is a condition influenced by many factors: He *et al.* (45) report that its incidence depends on the pregnant woman's occupation during pregnancy; Camacho (46) states that medical risks in pregnancy such as cesarean delivery increase its probability; Rodríguez-Dominguez *et al.* (41) point that congenital anomalies increase the risk of LBW more than three times; Neggers & Crowe (24) express that anemia increases its occurrence, and Britto *et al.* (25) state that the mother's gain or loss of weight may also have an influence.

Modifiable lifestyles, such as smoking during pregnancy, have been reported as behavioral risks that trigger a series of complications that lead to LBW. (23) However, abstinence syndrome leads to sudden infant death or fetal growth restriction. (37,47)

Finally, Silva de Oliveira *et al.* (27) state that regional inequalities in living conditions, especially in access to maternal and child health, contribute to the unequal distribution of neonatal mortality.

Conclusion

The aim of this review was to summarize the most relevant findings on risk factors associated with LBW in the Americas, despite the fact that eight "best-match" publications on LBW since 2012 (48-55) were not developed in this region. Although many of these countries met the goal of reducing the LBW by more than 95%, risk factors continue to be studied. The truth is that in Latin America there are countries that continue to maintain the incidence of LBW within the regional average due to deficient maternal nutrition, low socioeconomic status and associated maternal diseases. (56)

It is worth mentioning that one of the limitations to this study was the restriction to access to all indicators and databases. Therefore, selection and systematization depended on access to the database of the Fundación Universitaria del Area Andina (Andean Region University Foundation).

Regarding the multifactorial etiology of LBW, it has been reported that most of the selected studies have agreed, for years, in the association of sociodemographic, biological and behavioral factors. In addition, the studies that refer association of LBW with environmental risk factors, particularly during maternity, carried out between 2012 and 2016, are increasingly gaining importance. The most intriguing findings in the United States include exposure to microparticles in water and soil near the oil zones of California and Texas, and exposure to air pollutants in cities like New York.

In Latin America, it is striking to see that the Amazon region has been under research, since this area is subject to enormous extractive and polluting activities. This changes the target of public policies to reduce LBW and improve the conditions of pregnant women and children in the Americas region, especially in less developed countries and territories where abandonment, social inequalities and environmental exploitation activities are becoming more frequent.

Conflicts of interest

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References

1. **Pinzón-Villate G, Márquez-Beltrán MF, Vargas-Hérnandez JE, Quiroga-Villalobos EF.** Análisis del bajo peso al nacer en Colombia, 2005-2009. *Rev. Salud Pública.* 2013;15(4):577-88.
2. Organización Mundial de la Salud. Aspectos de salud pública de bajo peso al nacer. In: Tercer Informe del Comité de Expertos en Salud Materno Infantil. Ginebra: OMS; 1961.
3. **Jafari F, Eftekhar H, Pourreza A, Mousavi J.** Socioeconomic and medical determinants of low birth weight in Iran. 20 years after establishment of a primary healthcare network. *Public Heatlh.* 2010;124:153-158. http://doi.org/bn5cz7.
4. Unicef. Progreso para la Infancia: Examen estadístico de un mundo apropiado para los niñas y niñas. Informe. New York: Unicef; 2007.
5. **Cnattingius S, Stephenson O.** The epidemiology of stillbirth. *Semin. Perinatol.* 2002;26(1):25-30.
6. Organización Mundial de la Salud. Directrices sobre la alimentación óptima de lactantes de bajo peso al nacer en los países de bajos y medianos ingresos. Serie de informes Técnicos. Ginebra: OMS; 2011.
7. Unicef. Estado Mundial de la Infancia 2016: Una Oportunidad para Cada Niño. New York: Unicef; 2016. http://doi.org/cfsz.
8. Argentina. Ministerio de salud. Plan para la reducción de la mortalidad materno infantil, de las mujeres y de las adolescentes. Presidencia de la Nación; 2010 [cited 2018 Jan 30]. Available from: https://goo.gl/4bFXju.
9. **Habermann M, Gouveia N.** Socioeconomic position and low birth weight among mothers exposed to traffic-related air pollution. *PLoS One.* 2014;9(11):e113900. http://doi.org/cfs2.
10. Colombia. Ministerio de la Protección Social. Política nacional de salud sexual y reproductiva. Bogotá; febrero de 2003 [cited 2018 Jan 30]. Available from: https://goo.gl/KixMxf.
11. **Van de Voorde C, Léonard C.** Search evidence and critical appraisal; Health services research (HSR). Bruselas: Belgian Health Care Knowledge Centre (KCE); 2007.
12. **Da Fonseca CR, Strufaldi MW, de Carvalho LR, Puccini RF.** Adequacy of antenatal care and its relationship with low birth weight in Botucatu, São Paulo, Brazil: a case-control study. *BMC Pregnancy Childbirth.* 2014;14:255. http://doi.org/f6g6qx.
13. **Pinzón-Rondón AM, Gutiérrez-Pinzón V, Madriñan-Navia H, Amin J, Aguilera-Otalvaro P, Hoyos-Martínez A.** Low birth weight and prenatal care in Colombia: a cross-sectional study. *BMC Pregnancy Childbirth.* 2015;15:118. http://doi.org/f7hmzk.
14. **McDermott S, Bao W, Aelion CM, Cai B, Lawson AB.** Does the metal content in soil around a pregnant woman's home increase the risk of low birth weight for her infant? *Environ. Geochem. Health.* 2014;36(6):1191-7. http://doi.org/f6p6p9.
15. **Ebisu K, Bell ML.** Airborne PM2.5 chemical components and low birth weight in the northeastern and mid-Atlantic regions of the United States. *Environ. Health Perspect.* 2012;120(12):1746-52. http://doi.org/cfs3.
16. **Laurent O, Wu J, Li L, Chung J, Bartell S.** Investigating the association between birth weight and complementary air pollution metrics: a cohort study. *Environ. Health.* 2013;12:18. http://doi.org/f96zm3.
17. **Ghosh JK, Wilhelm M, Su J, Goldberg D, Cockburn M, Jerrett M, *et al.*** Assessing the influence of traffic-related air pollution on risk of term low birth weight on the basis of land-use-based regression models and measures of air toxics. *Am. J. Epidemiol.* 2012;175(12):1262-74. http://doi.org/f33d83.
18. **Padula AM, Mortimer K, Hubbard A, Lurmann F, Jerrett M, Tager IB.** Exposure to traffic-related air pollution during pregnancy and term low birth weight: Estimation of causal associations in a semiparametric model. *Am. J. Epidemiol.* 2012;176(9):815-24. http://doi.org/f4cr8q.

19. **Cândido da Silva AM, Pedroso-Moi G, Echenique-Mattos I, de Souza-Hacon S.** Low birth weight at term and the presence of fine particulate matter and carbon monoxide in the Brazilian Amazon: a population-based retrospective cohort study. *BMC Pregnancy Childbirth.* 2014;14:309. http://doi.org/f6f7rj.

20. **Coker E, Ghosh J, Jerrett M, Gomez-Rubio V, Beckerman B, Cockburn M, *et al.*** Modeling spatial effects of PM2.5 on term low birth weight in Los Angeles County. *Environ. Res.* 2015;142:354-64. http://doi.org/f7wvsw.

21. **Lin GG, Scott JG.** The association of PM2.5 with full term low birth weight at different spatial scales. *Environ. Res.* 2012;100(2):130-4. http://doi.org/f6t7r6.

22. **Guimarães AM, Bettiol H, Souza Ld, Gurgel RQ, Almeida ML, Ribeiro ER, *et al.*** Is adolescent pregnancy a risk factor for low birth weight? *Rev. Saude Publica.* 2013;47(1):11-9.

23. **Ferreira-Veloso HJ, Moura da Silva AA, Bettiol H, Zubarán-Goldani M, Lamy-Filho F, Ferreira-Simões VM, *et al.*** Low birth weight in São Luís, northeastern Brazil: trends and associated factors. *BMC Pregnancy Childbirth.* 2014;14:155. http://doi.org/gbf4ks.

24. **Neggers Y, Crowe K.** Low birth weight outcomes: why better in Cuba than Alabama? *J. Am. Board Fam. Med.* 2013;26(2):187-95. http://doi.org/cftv.

25. **Britto RP, Florêncio TM, Benedito-Silva AA, Sesso R, Cavalcante JC, Sawaya AL.** Influence of maternal height and weight on low birth weight: a cross-sectional study in poor communities of northeastern Brazil. *PLoS One.* 2013;8(11):e80159. http://doi.org/cftx.

26. **Bragança-de Moraes A, Ruviaro-Zanini R, Riboldi J, Justo-Giugliani ER.** Risk factors for low birth weight in Rio Grande do Sul State, Brazil: classical and multilevel analysis. *Cad. Saude Publica.* 2012;28(12):2293–305.

27. **Silva de Oliveira G, Barros de Melo-Lima MC, de Oliveira-Lyra C, da Costa-Oliveira AG, Fernandes-Ferreira MA.** Desigualdade espacial da mortalidade neonatal no Brasil: 2006 a 2010. *Ciênc. saúde coletiva.* 2013;18(8):2431-41. http://doi.org/cj89.

28. **Herd D, Gruenewald P, Remer L, Gruendelman S.** Community Level Correlates of Low Birthweight Among African American, Hispanic and White Women in California. *Matern. Child. Health J.* 2015;19(10):2251-60. http://doi.org/f7sqzr.

29. **Wehby GL, Gili JA, Pawluk M, Castilla EE, López-Camelo JS.** Disparities in birth weight and gestational age by ethnic ancestry in South American countries. *Int. J. Public Health.* 2015;60(3):343-51. http://doi.org/f64cvm.

30. **Nascimento LF, Costa TM, Zöllner MS.** Spatial distribution of low birthweight infants in Taubaté, São Paulo, Brazil. *Rev. Paul. Pediatr.* 2013;31(4):466-72. http://doi.org/cjz3.

31. **Von Ehrenstein OS, Wilhelm M, Wang A, Ritz B.** Preterm birth and prenatal maternal occupation: the role of Hispanic ethnicity and nativity in a population-based sample in Los Angeles, California. *Am. J. Public Health.* 2014;104(Suppl 1):S65-72. http://doi.org/f6gzj7.

32. **Fulda KG, Kurian AK, Balyakina E, Moerbe MM.** Paternal race/ethnicity and very low birth weight. *BMC Pregnancy Childbirth.* 2014;14:385. http://doi.org/f6r9c6.

33. **Loggins-Clay S, Andrade FC.** The role of stress in low birthweight disparities between Black women and White women: A population-based study. *J. Paediatr. Child Health.* 2015;51(4):443-9. http://doi.org/cjz5.

34. **Sanches-Ranzani-da Silva TRS.** Fatores de risco maternos não biológicos para o baixo peso ao nascer na América Latina: revisão sistemática de literatura com meta-análise. *Einstein (São Paulo).* 2012;10(3):380-5. http://doi.org/cftr.

35. **Xaverius P, Salas J, Kiel D, Woolfolk C.** Very low birth weight and perinatal periods of risk: disparities in St. Louis. *Biomed. Res. Int.* 2014;2014:547234. http://doi.org/gb839v.

36. **Dennis JA, Mollborn S.** Young maternal age and low birth weight risk: An exploration of racial/ethnic disparities in the birth outcomes of mothers in the United States. *Soc. Sci. J.* 2013;50(4):625-34. http://doi.org/cjz7.

37. **Darrow LA, Klein M, Strickland MJ, Mulholland JA, Tolbert PE.** Ambient air pollution and birth weight in full-term infants in Atlanta, 1994–2004. *Environ. Health Perspect.* 2011;(119):731-7. http://doi.org/dhfjp6.

38. **Bell ML, Belanger K, Ebisu K, Gent JF, Lee HJ, Koutrakis P, *et al.*** Prenatal exposure to fine particulate matter and birth weight: variations by particulate constituents and sources. *Epidemiology.* 2010;21(6):884-891. http://doi.org/ckxm3h.

39. **Padula AM, Mortimer KM, Tager IB, Hammond SK, Lurmann FW, Yang W, *et al.*** Traffic-related air pollution and risk of preterm birth in the San Joaquin Valley of California. *Ann. Epidemiol.* 2014;24(12):888-95e4. http://doi.org/f6q89n.

40. **Torres-Arreola LP, Constantino-Casas P, Flores-Hernandez S, Villa-Barragan JP, Rendón- Macías E.** Socioeconomic Factors and low birth weight in Mexico. *BMC Public Health.* 2005;5:20. http://doi.org/bt7z88.

41. **Rodríguez-Domínguez PL, Hernández-Cabrera J, García-León LT.** Propuesta de acción para reducción de factores maternos en el bajo peso al nacer. *Rev. Cubana Obstet. Ginecol.* 2010;36(4):532-43.

42. **Fulda KG, Kurian AK, Balyakina E, Moerbe MM.** Paternal race/ethnicity and very low birth weight. *BMC Pregnancy Childbirth.* 2014;14:385. http://doi.org/f6r9c6.

43. **Delgado-Noguera MF.** El bajo peso al nacer: otro ejemplo de inequidad en Colombia. *Rev. Colomb. Obstet. Ginecol.* 2009;60(2):121-3.

44. **Moura-da Silva AA, Muniz-da Silva L, Barbieri MA, Bettiol H, Mendes-de Carvalho L, Sousa-Ribeiro VS, *et al.*** O paradoxo epidemiológico do baixo peso ao nascer no Brasil. *Rev. Saude Publica.* 2010;44(5):767-75. http://doi.org/fs6nz9.

45. **He Q, Johnston J, Zeitlinger J.** ChIP-nexus enables improves detection of in vivo transcription factor binding footprints. 2015;33(4):395-401.

46. **Camacho-Hubner AV.** Perfil de salud sexual y reproductiva de los y las adolescentes y jóvenes de América Latina y el Caribe Revisión bibliográfica, 1988-1998. Serie OPS/FNUAP 1. Estados Unidos: Organización Panamericana de la Salud; 2000 [cited 2018 Jan 30]. Available from: https://goo.gl/r1vZ7v.

47. **Pampel FC.** Global patterns and determinants of sex differences in smoking. *Int. J. Comp. Sociol.* 2006;47(6):466-87.

48. **Lundgren P, Kistner A, Andersson EM, Hansen Pupp I, Holmström G, Ley D, *et al.*** Low birth weight is a risk factor for severe retinopathy of prematurity depending on gestational age. *PLoS One.* 2014;9(10):e109460. http://doi.org/f22fzq.

49. **Hwang JH, Lee EH, Kim EA.** Retinopathy of Prematurity among Very-Low-Birth-Weight Infants in Korea: Incidence, Treatment, and Risk Factors. *J. Korean Med. Sci.* 2015;30(Suppl 1):S88-94. http://doi.org/cftz.

50. **Ponzio C, Palomino Z, Puccini RF, Strufaldi MW, Franco MC.** Does low birth weight affect the presence of cardiometabolic risk factors in overweight and obese children? *Eur. J. Pediatr.* 2013;172(12):1687-92. http://doi.org/f5h5gk.

51. **Negandhi PH, Negandhi HN, Zodpey SP, Ughade SN, Biranjan JR.** Risk factors for low birth weight in an Indian urban setting: a nested case control study. *Asian Pac. J. Public Health.* 2014;26(5):461-9. http://doi.org/fzxv38.

52. **Demelash H, Motbainor A, Nigatu D, Gashaw K, Melese A.** Risk factors for low birth weight in Bale zone hospitals, South-East Ethiopia : a case-control study. *BMC Pregnancy Childbirth.* 2015;15:264. http://doi.org/gb8x6s.

53. **Chakki BA, Ealla KR, Hunsingi P, Kumar A, Manidanappanavar P.** Influence of maternal periodontal disease as a risk factor for low birth weight infants in Indian population. *J. Contemp. Dent. Pract*. 2012;13(5):676-80.

54. **Lundgren M, Morgården E, Gustafsson J.** Is obesity a risk factor for impaired cognition in young adults with low birth weight? *Pediatr. Obes*. 2014;9(5):319-26. http://doi.org/f235cq.

55. **Xaverius P, Alman C, Holtz L, Yarber L.** Risk Factors Associated with Very Low Birth Weight in a Large Urban Area, Stratified by Adequacy of Prenatal Care. *Matern. Child Health J.* 2016;20(3):623-9. http://doi.org/f8fdf9.

56. **Ticona-Rendón M, Huanco-Apaza D, Ticona-Vildoso M.** Incidencia y factores de riesgo de bajo peso al nacer en población atendida en hospitales del Ministerio de Salud del Perú. *Ginecol. Obstet. Mex*. 2012;80(2):51-60.

REVIEW ARTICLE

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Oxidative stress and pesticide disease: a challenge for toxicology

Estrés oxidativo y enfermedad por pesticidas: un reto en toxicología

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| Abstract |

Introduction: In the past decades, the synthesis of chemical compounds has resulted in a high number of substances used to protect crops from pests. Most pesticides have been used in large quantities for agricultural purposes. Acute and chronic poisoning are common among agricultural workers and the general population because of their use in different fields. Toxic exposure to these compounds is a major problem for toxicology, as it has an impact on public health due to its significant morbidity and disability. These compounds, when in contact with the human body, produce neurotoxic alterations and trigger molecular mechanisms related to lipid peroxidation, where reactive oxygen species can increase intracellular oxidative processes.

Objective: To carry out a review of the scientific literature related to diseases caused by oxidative stress induced by pesticides.

Materials and methods: A review of articles in PubMed was carried out using the keywords: Oxidative stress; Pesticides; Lipid peroxidation; Toxicity. The articles related to oxidative stress induced by pesticides were selected.

Results: Some hematological, neurological, metabolic and genotoxic diseases may be related to lipid peroxidation induced by pesticides.

Conclusion: This article presents a review of the scientific literature on oxidative stress, lipid peroxidation induced by pesticides and the different related diseases that can affect the general population.

Keywords: Oxidative Stress; Pesticides; Lipid Peroxidation; Toxicity (MeSH).

| Resumen |

Introducción. En los últimos decenios, la síntesis de compuestos químicos ha producido un alto número de sustancias utilizadas para proteger los cultivos y las cosechas de las plagas. La mayoría de pesticidas han sido usados en grandes cantidades para fines agrícolas y la exposición tóxica a estos compuestos es un problema de gran envergadura para la toxicología, pues tiene impacto en la salud pública por su importante morbilidad y discapacidad. Así, las intoxicaciones agudas y crónicas pueden ser comunes entre trabajadores agrícolas y población general. Estos compuestos desencadenan mecanismos moleculares relacionados con la peroxidación lipídica, donde las especies reactivas de oxigeno pueden incrementar procesos oxidativos intracelulares.

Objetivo. Realizar una revisión de la literatura científica relacionada con enfermedades por estrés oxidativo producido por pesticidas.

Materiales y métodos. Revisión de artículos que utilizó las palabras clave Estrés oxidativo; Pesticidas; Peroxidación de lípido; Toxicidad. Se eligieron los artículos relacionados con las enfermedades por estrés oxidativo producido por pesticidas.

Resultados. Se encontró que algunas enfermedades hematológicas, neurológicas, metabólicas y genotóxicas pueden estar relacionadas con la peroxidación lipídica que producen los pesticidas.

Conclusión. Se presenta una revisión de la literatura científica sobre el estrés oxidativo, la peroxidación lipídica inducida por pesticidas y las diferentes enfermedades que pueden afectar a la población en general.

Palabras clave: Estrés oxidativo; Pesticidas; Peroxidación de lípido; Toxicidad (DeCS).

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Cortés-Iza SC, Rodríguez AI. [Estrés oxidativo y enfermedad por pesticidas: un reto en toxicología]. Rev. Fac. Med. 2018;66(2):261-7. English. doi: http://dx.doi.org/10.15446/revfacmed.v66n2.60783.

Introduction

In recent years, the development of chemical compounds has yielded a large number of substances that are used to protect crops, among them, pesticides, which are classified based on some of their main characteristics, such as acute toxicity, half-life, chemical structure and use. (1)

Pesticide poisoning by compounds such as organophosphates (OP) and carbamates is a global health issue that causes thousands of deaths each year. A report from the World Health Organization

(WHO) shows that about three million cases of OP poisoning have a deadly outcome every year around the world. (2) In 1978, the same organization classified these compounds based on their hazard level or degree of acute toxicity, defined as highly toxic chemicals that cause acute health effects as a result of a single exposure or exposures of short duration. (3)

Pesticide toxicity is measured using median lethal dose (LD50) or median lethal concentration (LC50) and is classified into four classes: IA, IB, II and III (Table 1). (3) Some of these compounds are promptly absorbed after entering the body either by inhalation or ingestion. Once absorbed, they accumulate in fat, liver, kidneys and salivary glands. (4) Pesticides are classified as non-persistent, moderately persistent, persistent and permanent in terms of half-life (Table 2) (5) and as synthetic, natural, organic, chemical and biopesticides according to their chemical nature (Table 3). (6)

Table 1. Classification of pesticides by hazard.

Class IA	Extremely hazardous	Parathion Dieldrin
Class IB	Highly hazardous	Aldrin Dichlorvos
Class II	Moderately hazardous	DDT Chlordane
Class III	Slightly hazardous	Malathion

Source: Own elaboration based on Eddleston & Phillips. (3)

Table 2. Classification of pesticides by half-life.

Non-persistent	Days-12 weeks	Malathion, diazinon
Moderately persistent	1-18 months	Parathion
Persistent	19 months -20 years	DDT, aldrin, dieldrin
Permanent	Indefinite half-life	Products manufactured from mercury, lead and arsenic

Source: Own elaboration based on Briggs & Carson. (5)

Table 3. Classification of pesticides by chemical nature.

Inorganic	Copper oxychloride, zinc oxychloride
Natural	Piretrinas
Organic and synthetic	OP, organochlorines, carbamates, biperidyls, warfarin derivatives.
Biopesticides	Trichoderma harzianum, paecilomyces lilacinus, metarhizium anisopliae, beauveria bassian

Source: Own elaboration based on (6).

These substances are used according to the activity in which pest control is required: agriculture, livestock, care of domestic animals, treatment of structures, maintenance of green areas, maintenance of water reserves, industry, home, public health, etc. (7)

In Colombia, according to the Instituto Nacional de Salud (National Institute of Health), 24 748 cases of poisoning by chemical substances were reported in the public health surveillance system (SIVIGILA by its acronym in Spanish) until the epidemiological week 39 of 2016. Although a large number of reported poisoning cases are related to the drugs group (7 918 cases), the pesticides group comes second with 6 535 cases. (8)

The main action mechanism of OP and carbamate pesticides is the inhibition of carboxyl ester hydrolases, in particular acetylcholinesterase, which leads to acetylcholine accumulation. Acetylcholinesterase is an enzyme found in the synapses of the central and peripheral nervous tissue, in neuromuscular junctions (9) and in red blood cells. There are two types of this enzyme in the body: acetylcholinesterase and pseudocholinesterase.

On the one hand, *acetylcholinesterase (AChE)* or *true cholinesterase* has an almost specific affinity with the natural substrate of acetylcholine, breaking it down into its two component parts, acetic acid and choline (ACh). On the other hand, *pseudocholinesterase (BChE)* or *non-specific enzyme* hydrolyses many different synthetic and natural esters, including acetylcholine.

Multiple BChE isoenzymes are found in the liver, blood plasma and nervous tissue, which are inhibited by OP compounds in a similar way to AChE. Organophosphates inactivate AChE by phosphorylation of the hydroxyl group of serine located in the active site of AChE. Phosphorylation occurs due to the loss of a leaving group of the organophosphate and the establishment of a covalent bond with AChE. Once AChE is activated, acetylcholine accumulates in the synaptic space, resulting in overstimulation of the muscarinic and nicotinic receptors, causing neurotoxic alterations (neuropsychological diseases, delayed neuropathy and peripheral neuropathy). Clinical effects are evident through the activation of the autonomic and central nervous system and nicotinic receptors in skeletal muscle. (10)

Patients with pesticide poisoning show a broad spectrum of toxic effects, ranging from gastrointestinal symptoms to cardiac, immunological or neurotoxic diseases. The mortality rate depends on the type of compound used, the amount ingested, the patient's health state and the opportunity for diagnosis and treatment. (11)

López-Guarnido (12) has suggested that, besides inducing the neurotoxic alterations described above, when these compounds come into contact with the organism, another molecular mechanism —lipid peroxidation— is involved with oganoclorates, carbamates and OP toxicity, since reactive oxygen species (ROS) may increase intracellular oxidative processes, producing lipid peroxidation in the membranes of certain cells.

The main objective of this review is to highlight the implication of oxidative stress as a toxic action mechanism and its association with different diseases.

Free radicals and oxidative stress

Free radicals are defined as chemical species that have one or more unpaired electrons in their outermost orbital; for a chemical compound to become a free radical, gaining or losing electrons is necessary. Unpaired electrons in the outer orbital of the molecule are highly reactive (13); by interacting with several chemical compounds free radicals give up an unpaired electron and easily take the electron from a stable molecule and join to it. (14)

It is well known that oxygen is an essential element for the survival of living organisms. This element is used by cells for organic compounds oxidation, cellular respiration, energy production, among others. Under normal conditions, molecular oxygen can accept up to four electrons in its external orbital, resulting in two water molecules. (12) However, when there is a leak of electrons, oxygen may undergo a univalent reduction by accepting an electron, divalent by accepting two electrons or trivalent by accepting three electrons, forming the so-called ROS. The products of these reactions are, respectively, superoxide anion radical, hydrogen peroxide and hydroxyl radical. ROS can react easily to cellular endogenous substrates. (12)

These endogenous substrate reactions with ROS can cause oxidative damage to different biomolecules such as lipids, proteins, nucleic acids, carbohydrates, etc. Since blood cell membranes are rich

in fatty acids, naming the action of these species on the phospholipid membranes is of particular interest, as will be seen later on. (15)

The action of reactive oxygen species on lipid chains is the most frequent oxidative process in the organism and occurs when a free radical is fixed to a carbon of the alkyl chain (a group formed by carbon and hydrogen atoms) of a fatty acid, thus beginning lipid peroxidation during a process called initiation. (12)

Fatty acids of the cell membrane are susceptible to attacks, since they contain methylene groups separated by double bonds. Once the radical lipid is generated, it reacts with oxygen forming a peroxy radical, which can give rise to endoperoxides or take a hydrogen atom of a methylene carbon from another nearby polyunsaturated fatty acid and form a new free radical lipid and a hydroperoxide. The former is combined with an oxygen molecule to produce a chain of peroxidative damage propagation. (16)

Antioxidant systems

The human body has mechanisms that counteract the harmful effects of reactive oxygen species. It is important to bear in mind that not only the human species has these mechanisms. An antioxidant is defined as a substance capable of inhibiting oxidative damage in a target molecule. (15)

Given the destructive potential of free radicals, the body has strong endogenous antioxidant mechanisms to avoid the damage they cause. This activity includes superoxide dismutase (SOD) enzymes, glutathione peroxidase (GPx), catalase (CAT) and thioredoxin reductase. There are also preventive antioxidants that are metals sequestrants such as transferrin, ceruloplasmin, albumin, among others. (17)

Other substances with antioxidant capacity can be observed, such as reduced glutathione, a tripeptide found in high concentrations in cells that have sulphydryl groups, and plays an important role in the body. Other substances such as ubiquinone (coenzyme Q), which is obtained mostly in an exogenous manner through food, vitamins E and C and carotenoids are also important antioxidants. (17) Furthermore, defense mechanisms such as superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR), among others, can exert a protective role against the effects of reactive oxygen species, induced by certain xenobiotics. (18) There are also physiological antioxidant systems such as the microvascular system, which is responsible for maintaining adequate levels of O2 in tissues by regulating blood vessel pressure. (12)

The imbalance between the production of reactive oxygen species and the compensation mechanism of antioxidant systems, both physiological and biochemical, results in reactive oxygen species, which in turn cause some processes such as lipid peroxidation in cell membranes.

Oxidative stress induced by pesticides

Often, pesticide poisoning occurs in agricultural workers such as mixers, loaders and applicators, who are in direct contact with pest control areas. Low molecular weight and high liposolubility give pesticides properties such as high absorption and high toxicity. (19)

Some studies have corroborated that acetylcholinesterase enzyme inhibition is significantly associated with the increase in reactive oxygen substances, not only in workers who are exposed to OP pesticides, but also in those exposed to bipyridyl herbicides such as paraquat, which proves oxidative stress induction through an increase in lipid peroxidation and a decrease in antioxidant capacity. (20,21)

As previously stated, ROSs increase oxidative processes within the cell and produce lipid peroxidation in cell membranes. (12) A biological effect has been suggested as a possible action mechanism of lipid peroxidation caused by pesticides on blood cells by means of an electrophilic attack on certain cellular components, process during which ROSs are generated. (22)

A study conducted by Praksam *et al.* (21) indicates that greater erythrocyte fragility and alterations in erythrocyte membrane fluidity, secondary to lipid peroxidation and generated by the oxidative stress caused by pesticides, have been observed in workers who apply them.

López *et al.* (23) indicated that different pesticides, including OPs, were reported as oxidative stress inducers due to the generation of free radicals and alteration in antioxidant defense mechanisms. This study showed that farmers exposed to pesticides had low levels of superoxide dismutase (SOD) and glutathione reductase (GR) compared to the control group. Individuals with a decrease in AChE >15% showed decreased SOD and CAT activity during the same period. Glutathione peroxidase and glucose-6-phosphate dehydrogenase remained unchanged in the exposed population.

Another study conducted by Gultekin *et al.* (24) evaluated oxidative stress in workers who used OP, synthetic pyrethroids and carbamate pesticides. The results indicated that chronic exposure to these compounds was associated with an increase in the activity of catalase, SOD and lipid peroxidation in erythrocytes ($p<0.05$). It was concluded that chronic exposure of humans to pesticides can result in stimulation of antioxidant enzymes.

Multiple studies provide evidence of the tendency of OPs to disturb oxidative balance, which leads to oxidative stress. In their study, Soltaninejad *et al.* (25) reviewed 127 articles, including 112 experimental studies, and found 15 relevant studies on humans. The appearance of lipid peroxidation in cell membrane, the alteration of antioxidant capacity levels and the protective effects of natural and synthetic antioxidants against histopathological and biochemical alterations induced by OP are the most important evidences of the implication of oxidative stress in toxicity. It was concluded that the assessment of oxidative stress parameters in blood can be useful for monitoring exposed persons.

Hematological alterations and lipid peroxidation induced by pesticides

The lipid peroxidation observed in blood cell membranes caused by chronic exposure to OP pesticides and carbamates leads to think that, in fact, it is possible to observe morphological and numerical alterations in said cells, as some studies have suggested.

Díaz *et al.* (26) studied 71 individuals exposed by accident to OP pesticides and determined the levels of cholinesterases, blood count and platelet count. The hematological assessment showed a tendency to a decrease in platelet count ($p<0.05$) with values below 109/L.

Bhatti *et al.* (27) described that the erythrocyte membrane is an excellent model for studying the interaction with prooxidants. Results of rat erythrocytes exposed to said insecticide showed damage of the erythrocyte membrane caused by oxidative stress, with an increase in lipid peroxidation and decrease in its phospholipid content.

Parrón *et al.* (28) described a decrease in the mean corpuscular hemoglobin concentration in 38% of the workers studied, without any clear anemia. This same study found that 37% of fumigators had some type of symptom or sign of toxicity, such as spontaneous abortions, depression, headache, tremor or paresthesias.

Wafa *et al.* (29) evaluated hematological alterations in workers with chronic exposure to pesticides; the results showed that leukocytes, lymphocytes, monocytes and platelet counts were significantly higher in workers exposed to pesticides than in controls. In contrast, hemoglobin and hematocrit were significantly lower in the farmer group compared

to controls. This study demonstrated that long-term exposure to pesticides leads to the alteration of some hematological parameters.

Hundekari *et al.* (30), in a study conducted in 2013 in the north of Karnataka (India) including 150 patients diagnosed with OP poisoning admitted to the hospital and 30 subjects without poisoning as controls, estimated erythrocyte cholinesterase, superoxide dismutase, erythrocyte catalase, glutathione erythrocyte peroxidase activity, as well as total plasma antioxidant capacity and hematological parameters. The study showed a significant decrease ($p < 0.001$) in total plasma antioxidant capacity at all levels of OP poisoning compared to controls.

In acute OP poisoning, there is an accentuated overproduction of reactive oxygen species leading to lipid peroxidation. Ranjbar *et al.* (31) reported that significant lipid peroxidation is accompanied by decreased total plasma antioxidant capacity and decreased erythrocyte cholinesterase activity. Due to the consumption of non-enzymatic antioxidant agents that the body cannot compensate in a short period of time, a lower total antioxidant capacity is observed.

The susceptibility of erythrocytes and lymphocytes to oxidative stress due to exposure to pesticides is a function of the general balance between the degree of oxidative stress and the antioxidant defense capacity. With all of this in mind, the compounds may directly or indirectly modify the antioxidant defense capacity of the exposed subjects and, therefore, affect their susceptibility to oxidative stress. (32)

Wesseling *et al.* (33) showed that cells continuously suffer oxidative stress, despite the increase in the activity of the antioxidant defense mechanism, as reflected in the increase of erythrocyte SOD, CAT and GPx activity. The production of free radicals is so high that it even exceeds the antioxidant defense system, thus producing lipid peroxidation. This study revealed that the white blood cell count increased significantly ($p < 0.001$) in all cases of OP poisoning and leukocytosis showed mild neutrophilia compared to controls. The results indicated a significant decrease in the mean hemoglobin value of the OP poisoning group compared to the control group, perhaps as a result of the decreased synthesis of hemoglobin. Another possible interpretation was the lack of iron incorporation in hemoglobin, which leads to a decrease in the size of red blood cells. The significant increase in the leukocyte count observed in patients intoxicated by OP meant that the immune system is activated, which could be a positive response for survival.

Alterations in neuronal cells and oxidative stress induced by pesticides

Several authors have studied the generation of ROS and their role in dopaminergic cell death. Parkinson's disease (PD), for example, is a chronic and progressive neurological disorder associated with loss of dopaminergic neurons in the substantia nigra of the brain. It is believed that oxidative stress plays an important role in dopaminergic neurotoxicity. On the other hand, respiratory chain inhibition in complex I has been described in most processes related to neuronal degeneration in PD. Environmental factors such as neurotoxins, pesticides and genetic mutations in associated proteins contribute to the mitochondrial dysfunction that precedes ROS formation. (34)

Rodríguez *et al.* (35) carried out an extensive analysis to establish the role of superoxide radical, oxidative stress and their behavior in dopaminergic cell death induced by Parkinsonian toxins. The researchers demonstrated that paraquat induces an early increase in mitochondrial oxidative stress, which precedes the increase in cytoplasmic ROS levels. This herbicide also induced the transcriptional activation of son- and NF-kB reporters and lipid peroxidation. The loss of dopaminergic neurons induced by toxins such as paraquat, rotenone and 1-methyl-4-phenylpyridinium (MPP+) is associated with oxidative stress.

Nakamura *et al.* (36) indicated that 1-methyl-4-phenylpyridinium or cyperquat [MPP (+)] is selectively toxic to dopaminergic neurons and has been widely studied as an etiological model of PD because MPP (+) is involved in both mitochondrial dysfunction and its pathogenesis. MPP (+) can inhibit mitochondrial complex I activity and its toxicity has been attributed to mitochondrial depolarization and subsequent ROS generation. MPP (+) induced death in rat fetal dopaminergic neurons selectively. Clarifying the effects of MPP (+) on energy metabolism can provide information on the dopaminergic neuronal degeneration mechanism in PD.

Zawada *et al.* (37) found that excess superoxide production in the brain predicts the loss of neuronal cells, suggesting that the death of dopaminergic neurons in the substantia nigra in PD can be an example of this condition. ROS production induced by 1-methyl-4-phenylpyridinium (MPP) (active neurotoxic metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine MPTP), a herbicide related to paraquat, activates in the dopaminergic neurons of the substantia nigra in response to superoxide-induced neurotoxicity. The results of this study led to conclude that the production of superoxide generated by NADPH oxidase present in the neurons of the substantia nigra contributes to the loss of such neurons in PD.

Čolović *et al.* (38) studied the toxic effects of the diazinon, diazoxon and 2-isopropyl-6-methyl-4-pyrimidinol degradation products and compared them with the toxic potential of the original compound. The toxicity induced by different concentrations of the investigated compounds was evaluated in vitro by analyzing acetylcholinesterase, ATPases, defense antioxidant enzymes and lactate dehydrogenase activity and the malondialdehyde level in rat brain synaptosomes. It was found that diazinon inhibits acetylcholinesterase and Na (+)/K (+) ATPase in a dose-dependent manner. Prooxidative properties were demonstrated by causing an increase (up to 10%) in the activity of antioxidant enzymes and malondialdehyde levels as a marker of lipid peroxidation. The increase in diazoxon concentrations activated CAT (up to 30%), SOD (up to 50%) and GPx (up to 30%) and significantly increased the malondialdehyde level (up to 50%).

The investigated hydrolysis product of diazinon 2-isopropyl-6-methyl-4-pyrimidinol did not alter noticeably the activity of acetylcholinesterase, Na (+)/K (+) - ATPase, CAT, GPx and the peroxidation level of lipids (up to 10%). Although this metabolite (diazinon) is known to be non-toxic, it stimulates SOD up to 30%. High concentrations of diazinon and its metabolites affect the activity of lactate dehydrogenase as a marker of synaptosomes integrity. Changes in the biochemical parameters studied in rat brain synaptosomes can serve as indicators of toxicity from exposure to OP or its byproducts. (38)

Mehta *et al.* (39) studied the effect of chlorpyrifos (O,O'-diethyl-3,5,6 phosphorothionate-trichloro-2-pyridyl, CPF), an organophosphorus insecticide, on acetylcholinesterase (AChE) activity, lipid peroxidation and different activities of ATPases on rats. The researchers found that CPF caused a significant inhibition of synaptosomal AChE activity in different regions of the brain and that the inhibition varied between 36% and 82%, depending on the dose received. Oxidative stress also occurred, which resulted in a marked increase of membrane lipid peroxidative damage in a dose-dependent manner. The levels of malondialdehyde (MDA) and 4-hydroxy-2-nonenal (4-HNE), two major end products of lipid peroxidation, increased significantly in all regions of the brain. Na+ / K+, Mg 2+ and Ca (2+) - ATPases were inhibited to different degrees in the forebrain, midbrain and hindbrain of the treated rats.

Metabolic alterations and oxidative stress induced by pesticides

According to Calderón-Salinas *et al.* (40), "using different models to study the effects of increased glucose concentration has allowed to propose that oxidative processes are involved with the pathogenesis, progression, complications and poor prognosis of diabetes *mellitus*".

In this regard, there is growing evidence that OP pesticides alter glucose homeostasis causing insulin resistance and type 2 diabetes. The formation of advanced glycosylation end products, the accumulation of lipid metabolites, the activation of inflammatory pathways and oxidative stress are involved in the pathogenesis of insulin resistance. All these molecular processes activate a series of stress pathways that involve a family of serine kinases, which in turn have a negative effect on insulin signaling. Experimental and clinical data suggest an association between these molecular mechanisms and OP compounds. Furthermore, it has recently begun to be understood that OPs promote insulin resistance and increase the risk of type 2 diabetes. (41)

Acute pancreatitis is another well-known complication of OP poisoning (42). Epidemiological findings indicate that the incidence of this pathology is high, based on several physiopathological reports. (43) The precise underlying mechanisms are not yet well defined, although it is believed that pancreatic ductal obstruction or ROS production are involved. (44-46) Oxidative stress due to acute exposure to OP has been reported (47), and it has been unequivocally demonstrated that lipid peroxidation is one of the molecular mechanisms involved in the cytotoxicity induced by them. (31,48)

In a study conducted by Joshi *et al.* (49) —in which repeated oral doses of dimethoate (DM) (20 and 40 milligrams per day for each kilogram of body weight for 30 days) were administered to rats in order to cause alterations in glucose homeostasis and biochemical alterations in the pancreas—, different signs of glucose intolerance were observed among the rats that were administered DM after an oral glucose load (3 grams per kilogram of body weight). It was also observed that DM caused a significant increase in blood glucose levels with the concomitant inhibition of acetylcholinesterase activity and the depletion of reduced glutathione contents in the pancreas. In addition, DM caused a significant pancreatic damage reflected in the increase of amylase and lipase. Likewise, a dose-related elevation was observed in ROS levels in the pancreas of the treated rats.

Genotoxicity and oxidative stress induced by pesticides

Shadnia *et al.* (11) conducted a study to evaluate genotoxicity and oxidative stress in workers who used OP. Blood leukocytes and erythrocytes were examined in a group of 21 workers who handled pesticides and an equal number of control subjects for genotoxicity and oxidative stress parameters. The tail length of the comet assay was used to measure DNA damage. Regarding lipid peroxidation, CAT, SOD and GPx activity in erythrocytes was measured and analyzed as biomarkers of oxidative stress. In addition, acetylcholinesterase activity was measured as a biomarker of toxicity. The seniority in the position of the workers in the factory was 97 months.

The results of Shadnia *et al.* (11) showed that chronic exposure (≥6 months) to OP pesticides was associated with an increase in CAT, SOD and GPx activity in erythrocytes. Acetylcholinesterase activity showed no significant differences between both groups. The results also indicated that chronic exposure to OP pesticides was associated with an increase in DNA damage. It was concluded that chronic exposure to OP pesticides can result in stimulation of antioxidant enzymes and increased DNA damage in the absence of decreased levels of acetylcholinesterase. This study proposed conducting routine monitoring of genotoxicity, concomitant with acetylcholinesterase activity, in workers occupationally exposed to OP insecticides.

In the Sultana study (50), endosulfan+ chlorpyrifos, chlorpyrifos+ profenofos and endosulfan+profenofos were used. These mixtures were evaluated in human peripheral blood lymphocyte cultures using cell viability and genotoxicity assays, and using the chromosomal aberration assay and the comet assay. The LC50 values for cytotoxicity were 3.50µM, 4.18µM and 10.5 µM for profenofos, endosulfan and chlorpyrifos, respectively. When combined in equimolar concentrations, LC50 values for cytotoxicity were 1.4µM, 1.8µM and 2.0M for chlorpyrifos+endosulfan, chlorpyrifos+profenofos and endosulfan+profenofos, respectively. High concentrations of individual pesticides (0.5-4.0µM) and low concentrations of pesticide mixtures caused significant DNA damage. These findings indicate a synergistic effect of toxicity by chlorpyrifos+endosulfan combination. The mixture of chlorpyrifos+profenofos showed additive toxicity, while an antagonistic effect was observed for the endosulfan+profenofos combination. Said synergy may be caused by complementary pesticides that act simultaneously in different ways, with an increase of their effectiveness, while an additive interaction would imply that the chemical products are acting because of the same mechanism and the same objective. According to this study, the toxicity analysis of pesticide mixtures can serve as an important biomarker of occupational exposure. (50)

Table 4 shows the main damage mechanisms found in the literature review.

Table 4. Summary of the results obtained in the review that show the main damage mechanisms.

Pesticide/ substance	Cell/ molecule	Toxicodynamics	Bibliographic reference
OP-Carbamate-organochlorines-pyrethroid-bipyridyl herbicides	Cell membranes	Increase in ROS Lipid peroxidation Decrease in antioxidant capacity (low levels of superoxide dismutase, glutathione reductase) Increased superoxide dismutase and catalase activity	(20,21,23,25)
OP-carbamate-pyrethroids	Blood	Oxidative stress Decreased platelets Damage to the erythrocyte membrane Decrease in the mean corpuscular hemoglobin concentration Increase of leukocytes, lymphocytes, monocytes and platelets Decrease in hemoglobin and hematocrit	(26-29)
Paraquat, rotenone and 1-methyl-4-phenylpyridinium (MPP+)	Neuron	Mitochondrial dysfunction ROS production Neural damage or loss	(35-37)
OP	Endocrine	Oxidative stress. Alteration in glucose homeostasis Insulin resistance Increased risk of type 2 diabetes Pancreatitis- pancreatic duct obstruction	(40-45)
OP	DNA	Oxidative stress Increase in DNA damage	(11,50)

Source: Own elaboration based on the data obtained in the study.

Conclusions

After conducting an exhaustive literature review, it is possible to conclude that oxidative stress caused by OP pesticides, carbamates and some organochlorines is a highly relevant toxicodynamic mechanism in toxic damage. This damage mechanism is related to multiple diseases that involve systems, such as the hematopoietic, endocrine and nervous systems. Those compounds are also capable of producing genotoxicity.

Although most studies were conducted in experimental animals such as rats, some of them were made in humans, showing very interesting aspects that require more documentation and research, since oxidative stress plays an important role in the development of multiple diseases.

In Colombia, research has not yet been carried out regarding the impact of these substances on hematopoietic tissue, oxidative stress induced by pesticides or alterations caused by these compounds in cell membranes of different tissues or organs, which is why it is necessary and of great importance for the health of Colombians to undertake this challenge.

Conflicts of interest

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References

1. **Ramírez JA, Lacasaña M.** Plaguicidas: clasificación, uso, toxicología y medición de la exposición. *Arch Prev Riesgos Labor.* 2001;4(2):67-75.
2. **Henao S, Finkelman J, Albert LA, de Koning HW.** Plaguicidas y salud en las Américas. Washington D.C.*:* Organización Panamericana de la Salud; 1993.
3. **Eddleston M, Phillips MR.** Self poisoning with pesticides. *BMJ.* 2004;328(7430):42-4. http://doi.org/fn9r2d.
4. **Vale JA.** Toxicokinetic and toxicodynamic aspects of organophosphorus insecticide poisoning. *Toxicol Lett.* 1998;102-103:649-52. http://doi.org/bbg6z9.
5. **Briggs SA, Carson R.** Basic guide to pesticides,their characteristics and hazards. Vol 1. Washington D.C.: Taylor y Francis; 1992.
6. Grupo de vigilancia y control de factores de riesgo ambiental. Protocolo de vigilancia y control de intoxicación aguda por plaguicidas. Bogotá D.C.: Instituto Nacional de Salud; 2010 [cited 2016 Oct 15]. Available from: https://goo.gl/WBvrjt.
7. **Ramirez JA, Lacasaña M.** Plaguicidas: clasificación, uso, toxicología y medición de la exposición. *Arch Prev Riesgos Labo.* 2001;4(2):67-75.
8. Instituto Nacional de Salud Colombia. Boletín epidemiológico semanal número 42. Bogotá D.C.: INS; 2016 [cited 2016 Oct 15]. Available from: https://goo.gl/zxRjrW.
9. **Lauwerys R, Haufroid V, Hoet P, Lison D.** Toxicologie Industrielle et intoxications professionnelles. 5th ed. París: Masson; 2007.
10. **Reiner E, Zoran Radic, Simeon-Rudolf Vera.** Mechanisms of organophosphate toxicity and detoxication with emphasis on studies in Croatia. *Arh Hig Rada Toksikol.* 2007;58:329-38. http://doi.org/fp8fkn.
11. **Shadnia S, Azizi E, Hosseini R, Khoei S, Fouladdel S, Pajoumand A, *et al.*** Evaluation of oxidative stress and genotoxicity in organophosphorus insecticide formulators. *Hum Exp Toxicol.* 2005;24(9):439-45. http://doi.org/fc55ns.
12. **López-Guarnido O.** Influencia de la exposición crónica a plaguicidas sobre diversos marcadores bioquímicos (esterasas y enzimas antioxidantes) en trabajadores de invernadero en la costa oriental de Andalucía [tesis doctoral]. Granada: Facultad de Medicina, Universidad de Granada; 2005.
13. **Webster NR, Nunn JF.** Molecular structure of free radicals and their importance in biological reactions. *Br J Anaesth.* 1998;60(1):98-108. http://doi.org/fn8gxj.
14. **Ramón-Giménez JR.** Radicales libres y antioxidantes en clínica humana. *Madrid: IDEPSA; 1993.*
15. **Abdollahi M, Ranjbar A, Shadnia S, Nikfar S, Rezaie A.** Pesticides and oxidative stress: a review. *Med Sci Monit.* 2004;10(6):RA141-7.
16. **Martínez-Cayuela M.** Toxicidad de xenobióticos mediada por radicales libres de oxígeno. *Ars Pharmaceutica.* 1998;39(1):5-18.
17. **Jaime-Novas A, González-Chamorro R, Díaz-Padrón H.** Estrés oxidativo asociado a la exposición ocupacional a sustancias químicas. *Revista Cubana de Salud y Trabajo.* 2007;8(1):52-7.
18. **Gutteridge JMC.** Oxygen radicals transition metals and ageing. Advances in age pigments research. New York: Pergamon Press. 1987.
19. **Rosenberg MDJ, O Malley M.** Plaguicidas. In: LaDou J, editor. Medicina laboral y ambiental. 2nd ed. Bogotá D.C.: Manual Moderno; 1999. p. 591.
20. **Ranjbar A, Pasalar P, Seidighi A, Abdollahi M.** Inductión of oxidative stress in paraquat formulating workers. *Toxicol Lett.* 2002;131(3):191-4. http://doi.org/c2xsr2.
21. **Prakasam A, Sethupathy S, Lalitha S.** Plasma and RBCs antioxidant status in occupational male pesticide sprayers. *Clin Chim Acta.* 2001;310(2):107-12. http://doi.org/frchzs.
22. **Dwivedi PD, Das M, Khanna SK.** Role of cytochrome P-450 in quinalphos toxicity: effect on hepatic and brain antioxidant enzymes in rats. *Food Chem Toxicol.* 1998;36(5):437-44. http://doi.org/cm2tcf.
23. **López O, Hernández AF, Rodrigo L, Gil F, Peña G, Serrano JL, *et al.*** Changes in antioxidant enzymes in humans with long-term exposure to pesticides. *Toxicol Lett.* 2007;171(3):146-53. http://doi.org/fnrf5q.
24. **Gultekin F, Kisioglu AN, Kucukoner E.** Oxidative stress in the blood of farm workers following intensive pesticide exposure. *Toxicol Ind Health.* 2011;27(9):820-5. http://doi.org/c9q5hq.
25. **Soltaninejad K, Abdollahi M.** Current opinion on the science of organophosphate pesticide and toxic stress: A systematic review. *Med Sci Monit.* 2009;15(3):75-90.
26. **Díaz V, Pistilli N, Guillén R, Melgarejo MV, Velázquez G.** Valores Hematologicos en individuos expuestos accidentalmente a insecticidas oroganfsfrados. *Mem. Inst. Investig. Cienc. Salud.* 2002;1(1):1-4.
27. **Bhatti GK, Bhatti JS, Kiran R, Sandhir R.** Biochemical and morphological perturbations in rat erythrocytes exposed to ethion: protective effect of vitamin E. *Cell Mol Biol.* 2011;57(1):70-9.
28. **Parrón T, Hernández AF, Pla A, Villanueva E.** Clinical and biochemical changes in greenhouse sprayers chronically. *Hum Exp Toxicol.* 1996;15(12):957-63. http://doi.org/csjr22.
29. **Wafa T, Nadia K, Aml N, Ikbal C, Asma K, Hedi MA, *et al.*** Oxidative stress, hematological and biochemical alterations in farmers exposed to pesticides. *J Environ Sci Health.* 2013;48(12):1058-69. http://doi.org/cf5w.
30. **Hundekari IA, Suryakar AN, Rathi DB.** Acute organo-phosphorus pesticide poisoning in North Karnataka, India: oxidative damage, haemoglobin level and total leukocyte. *Afr Health Sci.* 2013;13(1):129-36. http://doi.org/cf5x.
31. **Ranjbar A, Pasalar P, Abdollahi M.** Induction of oxidative stress and acetylcholinesterase inhibition in organophosphorous pesticide manufacturing workers. *Hum Exp Toxicol.* 2002;21(4):179-82. http://doi.org/dbkgpf.

32. **Banerjee BD, Seth V, Bhattacharya A, Pasha ST, Chakraborty AK.** Biochemical effects of some pesticides on lipid peroxidation and free radical scavengers. *Toxicol Lett.* 1999;107(1-3):33-47. http://doi.org/fm5bcz.

33. **Wesseling C, McConnell R, Partanen T, Hogstedt C.** Agricultural pesticide use in developing countries: Health effects and research needs. *Int J Health Serv.* 1997;27(2):273-308. http://doi.org/btmb9d.

34. **Blesa J, Trigo-Damas I, Quiroga-Varela A, Jackson-Lewis VR.** Oxidative stress and Parkinson's disease. *Front Neuroanat.* 2015;9:91. http://doi.org/cf5z.

35. **Rodríguez-Rocha H, García-García A, Pickett C, Li S, Jones J, Chen H, *et al.*** Compartmentalized oxidative stress in dopaminergic cell death induced by pesticides and complex I inhibitors: Distinct roles of superoxide anion and superoxide dismutases. *Free Radic Biol Med.* 2013;61:370-83. http://doi.org/f436q7.

36. **Nakamura K, Bindokas VP, Marks JD, Wright DA, Frim DM, Miller RJ, *et al.*** The selective toxicity of 1-methyl-4-phenylpyridinium to dopaminergic neurons: the role of mitochondrial complex I and reactive oxygen species revisited. *Mol Pharmacol.* 2000;58(2):271-8.

37. **Zawada WM, Banninger GP, Thornton J, Marriott B, Cantu D, Rachubinski AL, *et al.*** Generation of reactive oxygen species in 1-methyl-4-phenylpyridinium (MPP+) treated dopaminergic neurons occurs as an NADPH oxidase-dependent two-wave cascade. *J Neuroinflammation.* 2011;8:129. http://doi.org/d7mfbd.

38. **Čolović MB, Vasić VM, Avramović NS, Gajić MM, Djurić DM, Krstić DZ.** In vitro evaluation of neurotoxicity potential and oxidative stress responses of diazinon and its degradation products in rat brain synaptosomes. *Toxicol Lett.* 2015;233(1):29-37. http://doi.org/f63gkt.

39. **Mehta A, Verma RS, Srivastava N.** Chlorpyrifos-induced alterations in rat brain acetylcholinesterase, lipid peroxidation and ATPases. *Indian J Biochem Biophys.* 2005;42:54-8.

40. **Calderón-Salinas JV, Muñoz-Reyes EG, Quintanar-Escorza MA.** Estrés oxidativo y diabetes mellitus. *REB.* 2013:32(2):53-66.

41. **Lasram MM, Dhouib IB, Annabi A, El Fazaa S, Gharbi N.** A review on the molecular mechanisms involved in insulin resistance induced by organophosphorus pesticides. *Toxicology.* 2014;322:1-13. http://doi.org/f58z65.

42. **Dressel TD, Goodale RL, Ameson MA, y Borner JW.** Pancreatitis as a complication of anticholinesterase insecticide intoxication. *Ann Surg.* 1979;189(2):199-204. http://doi.org/bqmnjr.

43. **Gokalp O, Buyukvanh B, Cicek E, Ozer MK, Koyu A, Altuntas I, *et al.*** The effects of diazinon on pancreatic damage and ameliorating role of vitamin E and vitamin C. *Pestic Biochem Physiol.* 2005;81(2):123-8. http://doi.org/btspmb.

44. **Dressel TD, Goodale RL, Zweber B, Borner JW.** The effect of atropine and duct decompression on evolution of diazinon-induced canine pancreatitis. *Ann Surg.* 1982;195(4):424-34.

45. **Sevillano S, de la Mano AM, Orfao A, De Dios I.** N-acetylcysteine prevents intraacinar oxygen free radical production in pancreatic duct obstruction-induced acute pancreatitis. *Biochim Biophys Acta.* 2003;1639(3):177-84. http://doi.org/bm8x72.

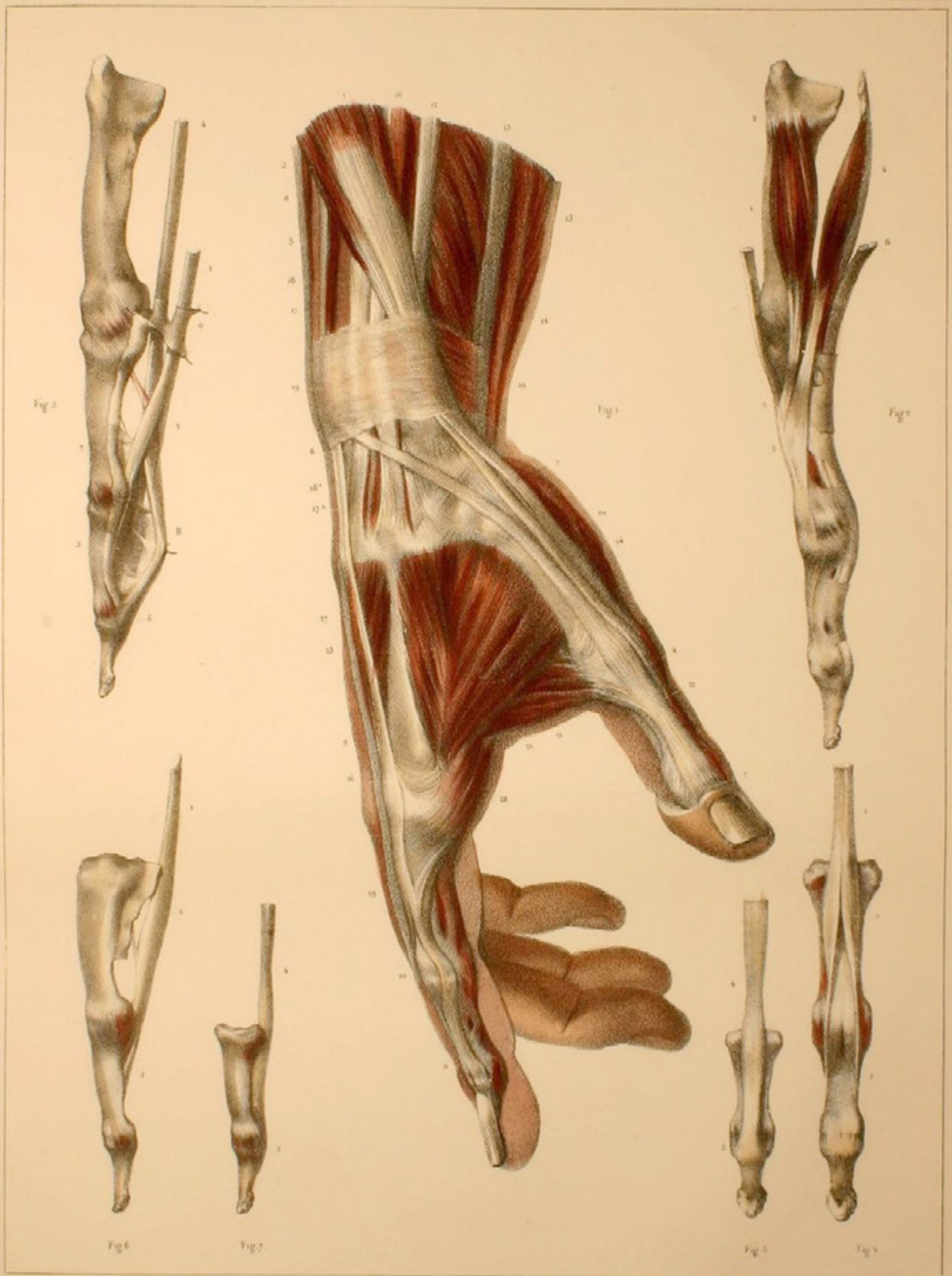
46. **Sultatos LG.** Mammalian toxicology of organophosphorous pesticides. *J Toxicol Environ Health.* 1994;43(3):271-89. http://doi.org/cjzrnc.

47. **Banerjee BD, Seth V, Ahmed RS.** Pesticide-induced oxidative stress: perspective and trends. *Rev Environ Health.* 2001;16(1):1-40. http://doi.org/fg36tn.

48. **Akhgari M, Abdollahi M, Kebryaeezadeh A, Hosseini R, Sabzevari O.** Biochemical evidence for free radical-induced lipid peroxidation as a mechanism for sub chronic toxicity of malathion in blood and liver of rats. *Hum Exp Toxicol.* 2003;22(4):205-11. http://doi.org/fqt4h3.

49. **Joshi AKR, Rajini PS.** Organophosphorus Insecticides and Glucose Homeostasis. Farzana Perveen; 2012.

50. **Sultana-Shaik A, Shaik AP, Jamil K, Alsaeed AH.** Evaluation of cytotoxicity and genotoxicity of pesticide mixtures on lymphocytes. *Toxicol Mech Methods.* 2016;26(8):588-94. http://doi.org/cf53.



Jean Marc Bourgery
"Traité complet de l'anatomie de l'homme"
Paris 1832-1854

REVIEW ARTICLE

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Biochemical events related to glial response in spinal cord injury

Eventos bioquímicos de respuesta glial en la fisiopatología de la lesión de médula espinal

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| Abstract |

Introduction: Spinal cord injury (SCI) is a devastating event with physical, psychological and socioeconomic implications. Morphophysiological changes are observed in the tissue close to the injury, which allow determining the functional recovery of the medullary segment and the effector organs that depend on the injured axonal tracts.

Objective: To describe the most relevant sequential biochemical events of glial cells response after SCI.

Materials and methods: A search of scientific publications released in the past 18 years was carried out in PubMed and Science Direct databases, with the terms spinal cord injury (SCI), SCI pathophysiology, SCI inflammation, microglia in SCI, glial scar and chondroitin sulfate proteoglycans (CSPG).

Results: The pathophysiological processes resulting from SCI are determinant for the neurological recovery of patients. Activation of glial cells plays an important role in promoting bioactive molecules and the formation of physical barriers that inhibit neural regeneration.

Conclusion: Knowledge of neurobiological changes after SCI allows a greater understanding of the pathophysiology and favors the search for new therapeutic alternatives that limit the progression of the primary injury and minimize secondary damage, responsible for neurological dysfunction.

Keywords: Spinal Cord; Microglia; Gliosis; Inflammation; Oligodendrocytes (MeSH).

| Resumen |

Introducción. La lesión de la médula espinal (LME) es un evento devastador con implicaciones físicas, psicológicas y socioeconómicas. En el tejido cercano a la lesión se instauran cambios morfofisiológicos que determinan la recuperación funcional del segmento medular y de los órganos efectores dependientes de los tractos axonales lesionados.

Objetivo. Describir los eventos bioquímicos secuenciales más relevantes de la respuesta de las células gliales posterior a la LME.

Materiales y métodos. Se realizó una búsqueda de publicaciones científicas de los últimos 18 años en las bases de datos PubMed y ScienceDirect, bajo los términos en inglés spinal cord injury (SCI), SCI pathophysiology, SCI inflammation, microglia in SCI, glial scar y chondroitin sulfate proteoglycans (CSPG).

Resultados. Los procesos fisiopatológicos que se producen después de la LME determinan la recuperación neurológica de los pacientes. La activación de las células gliales juega un papel importante, ya que promueve la producción de moléculas bioactivas y la formación de barreras físicas que inhiben la regeneración neural.

Conclusión. El conocimiento de los cambios neurobiológicos ocurridos tras la LME permite una mayor comprensión de la fisiopatología y favorece la búsqueda de nuevas alternativas terapéuticas que limiten la progresión de la lesión primaria y que minimicen el daño secundario responsable de la disfunción neurológica.

Palabras clave: Médula espinal; Microglía; Gliosis; Inflamación; Oligodendrocitos (DeCS).

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Introduction

The World Health Organization (WHO) defines spinal cord injury (SCI) as any harmful condition in said tissue, starting from the L1-L2 vertebral level, ending in the *conus medullaris* and *cauda equina*. It occurs due to multiple causes, which can be traumatic and non-traumatic, radically transforming the lifestyle of patients. (1)

Colombia does not have precise data on the incidence of spinal cord trauma or its repercussions; most studies are based on data from around the world, although they are not accurate either. In 2013, the WHO estimated an annual incidence of 40-80 new cases per million inhabitants, which means that, worldwide, between 250 000-500 000 people suffered some type of SCI, mainly due to traumatic causes, with greater occurrence in young adult men aged 18-32 years and in elderly >65 years. (1,2) In the United States, the incidence of SCI until 2016 was about 54 new cases per million people, while prevalence was estimated at a range of 245 000-330 000 people, with an average age of 42 years. (3)

Traumatic injuries correspond to about 90% of the causes of SCI, including those associated with violence, falls, car accidents, and occupational, recreational and sports injuries. Non-traumatic causes of SCI may have an infectious origin or may be related to osteoarthritis and rheumatoid arthritis. Other causes may have a congenital origin such as spina bifida and spinal stenosis or may develop due to a tumor. Certain neurodegenerative pathologies, including those caused by tuberculosis, multiple sclerosis, Alzheimer's disease and Parkinson's disease, are also involved. (1,4,5)

SCI morbidity is associated with immunosuppression due to the disruption of the sympathetic innervation of lymphoid tissues caused by neuroendocrine response related to stress and the interruption of the neural pathways that regulate the immune effector functions, which are necessary to control the diffusion of the injury. Consequently, the risk of suffering secondary metabolic, intestinal, urinary and cardiac diseases increases, leading to clinical manifestations such as chronic pain and depression which, in turn, entail a state of permanent disability that severely impacts public health given the high economic and social costs. (1,6-9)

Until now, there is no accepted treatment in the world for this condition; pharmacological options are limited and restorative therapies are unsuccessful. Therefore, despite the multiple efforts of the scientific community to elucidate the molecular mechanisms responsible for acute response in SCI and to find new treatments that allow the functional and motor recovery in patients with spinal injury, the outlook is not very encouraging. (5,10)

Some therapeutic strategies to deal with SCI aim to establish an enabling microenvironment that favors the activation of endogenous neuroprotection and regeneration mechanisms in the spinal cord to allow axonal projection, promote angiogenesis, control inhibition of the inflammatory cascade, reduce proinflammatory cytokines levels, chemokines and acute phase proteins, down-regulate adhesion molecules expression and attenuate vascular permeability. However, outcomes are usually unsatisfactory, either due to the activation of numerous signaling pathways related to the inhibition of neural growth or the limited regeneration and repair capacity of the central nervous system (CNS). (5,11,12)

On the other hand, it is important to consider the therapeutic benefit of controlling inflammation, when it occurs as a physiological response mechanism during the injury. Neuromodulation in said response should be considered, since it is usually related to beneficial conditions for neuroanatomical plasticity and protection against injury or infection, as well as to cytotoxicity states when cytokines concentrations released in the tissue exceed a certain level, altering the homeostasis of the immune system. (11,13,14)

The objective of this review is to describe glial cellular response (microglial, astrocytic and oligodendroglial) after a SCI, highlighting the harmful events that determine the progression of tissue damage and, consequently, the difficulty in recovering motor, sensory and autonomic functions in patients. Additionally, an account of inhibitory mechanisms of axonal regeneration, mainly caused by glial activation, favoring the formation of physical barriers in situ that limit timely therapeutic intervention, is also presented.

Materials and methods

A literature search was conducted in the PubMed and Science Direct databases. The following terms were used: *SCI, SCI pathophysiology, SCI inflammation, microglia in SCI, glial scar* and *chondroitin sulfate proteoglycans (CSPG)*. The 66 most relevant bibliographical references were selected, which corresponded to publications and scientific communications issued in the past 18 years related to physiopathology and glial cellular response after SCI.

Results and discussion

Neuropathological events after traumatic spinal cord injury are classified based on several characteristics. Regarding morphological aspects, SCI may be primary due to physical destruction of membranes and medullary tissue, or secondary due to the events that follow the primary injury, such as hemorrhage, edema, inflammation, reactive gliosis, ischemia, cavitations, excitotoxicity, oxidative stress and neuroglial cell death (Figure 1). Taking into account the biological response, SCI is divided into three phases (Figure 2): acute (0-48 hours after the injury), secondary (2-14 days) and chronic (months to years after the injury). (15-21)

In primary damage, it is possible to observe a vascular rupture in the focus of the injury (epicenter) with extravasation of erythrocytes, neutrophils and lymphocytes; disruption of the blood-brain barrier (BBB) and blood-spinal cord barrier (BSCB) is also observed. In secondary damage, there is infiltration of inflammatory cells and the immune system with release of cytokines, chemokines and adhesion molecules that cause the injury to spread in a centrifugal way, increasing its radius. Apoptotic and aponecrotic cell death occurs with involvement of myelin (demyelination), cellular debris, activation of the phagocytic activity of macrophages and barrier formation, known as glial scar, which creates a hostile environment that prevents or delays axonal repair.

The mechanical forces applied to the spinal cord in the primary injury cause the disruption of the endothelial and neuronal membranes, loss of tissue integrity, intraparenchymal hemorrhage, massive cell death, axonal damage and necrotic areas at the site of injury as a consequence of the reduction of blood flow. The first changes in the spinal cord are evident within the first two hours with the expansion of the hemorrhage, the development of vasogenic edema and the presence of diffuse petechiae. (20,22-24)

The loss of neuronal cells, especially due to apoptosis, is prevalent between 3-8 hours after the injury, while apoptosis extends beyond 24 hours for glial cells. Although cell loss begins in the epicenter (focus of injury), it progresses rapidly in both directions, ascending and descending with respect to the focus of the injury (Figure 1). About six hours later, the edema reaches the white matter and, at 24 hours, the hemorrhage is significantly extended, the synthesis and the release of proinflammatory mediators at the site of the lesion are increased and the surrounding tissue loses definition. (9,15,25)

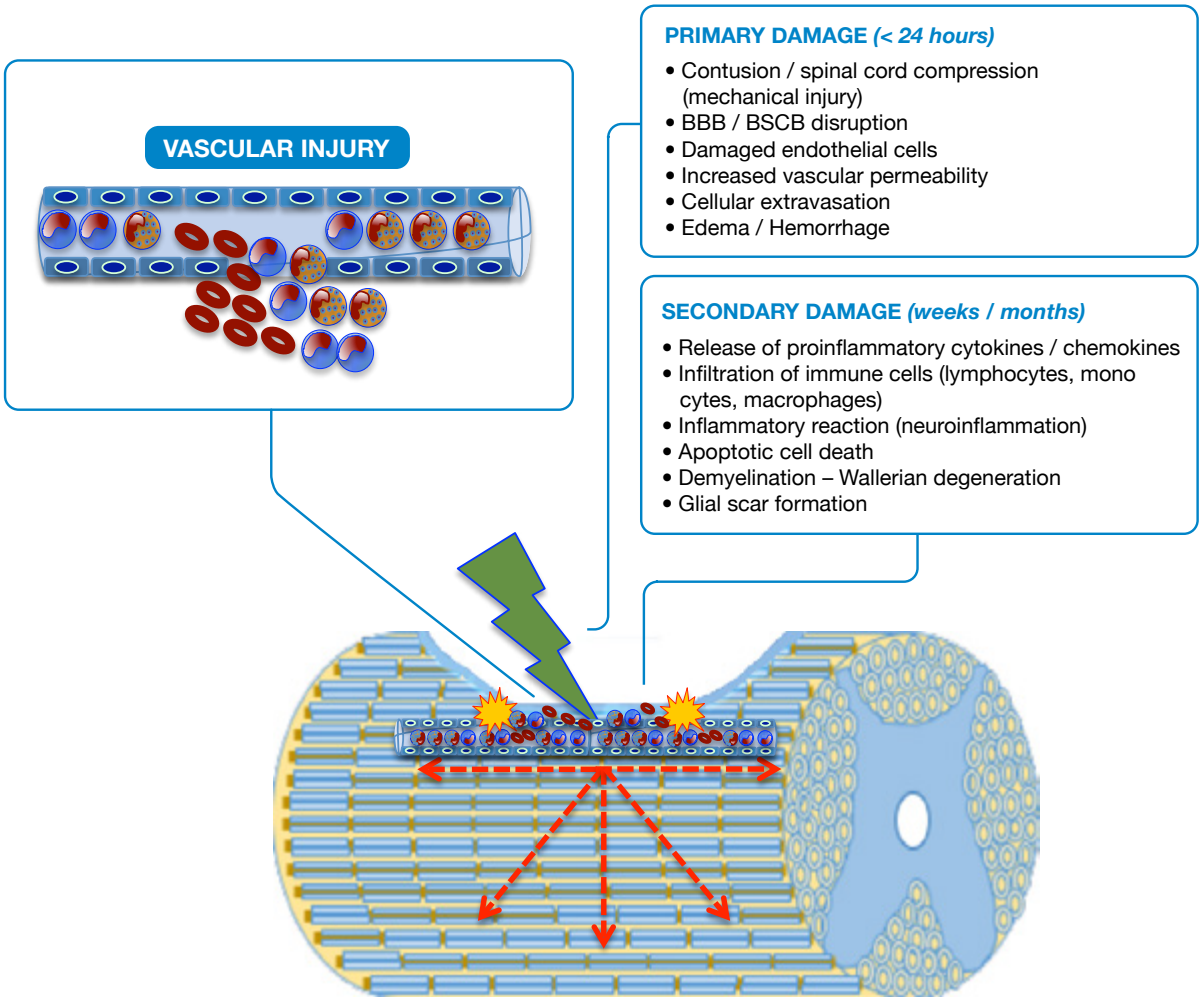


Figure 1. Schematic representation of SCI.
BBB: Blood-brain barrier; BSCB: Blood-spinal cord barrier.
Source: Own elaboration based on the data obtained in the study.

In the secondary injury, neuropathological processes are associated with accumulation of immune cells such as lymphocytes, monocytes, macrophages and granulocytes (26,27); excitotoxicity; disturbances in the ionic balance; production of free radicals by microglia activation during cellular debris phagocytosis; activation of caspases and calpains, and excessive release of excitatory neurotransmitters and inflammatory mediators. (23,28,29)

Vascular changes and blood flow —evident within the first hours after the trauma and persistent for several days and even years after spinal cord injury— lead to apoptotic cell death and axonal demyelination. Likewise, Wallerian degeneration and glial activation with accumulation of astrocyte populations in the periphery and on the surface of the injury continues to give way to the glial scar, a defense mechanism of the nervous system to isolate itself from the noxious influence of the medium (15,18,30) (Figure 2).

In addition, other pathophysiological processes are common and include: increase in blood coagulation; cellular extravasation; chemotaxis and cell adhesion; phagocytosis; angiogenesis; apoptosis; response to hypoxia and reactive oxygen species (ROS), and production and secretion of cytokines, growth factors and cytotoxic amino acids. (5,17,31,32)

Cellular response in SCI

During SCI, an active inflammatory process initiates as a defense and tissue repair mechanism, involving a series of cellular components, which respond to the immediate activation of the immune system by creating a physical barrier made up of different cells such as microglia, astrocytes, macrophages, neutrophils and natural killer (NK) cells. On the other hand, the complement system mediates to breakdown the blood-brain barrier, to remodel the extracellular matrix, in the exacerbated activation of astrocytes (reactive gliosis) and in the protection of neurons against cytotoxicity. (24,33)

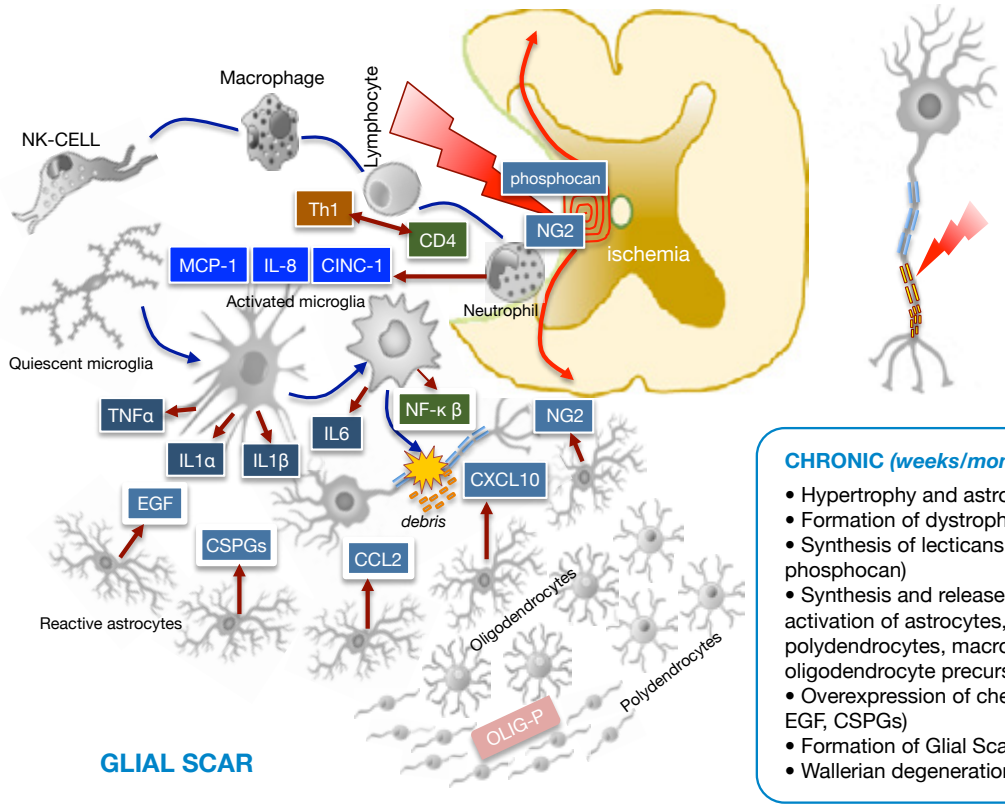
Inflammation, in response to the primary lesion, exacerbates neuronal loss and promotes secondary damage due to the rapid activation of microglia as an intrinsic self-defense line of the CNS and as a resident cell of great importance for immune response because of recruitment, migration and infiltration of neutrophils and perivascular macrophages to the site of the injury, as well as the production of adhesion molecules, metabolites of arachidonic acid and proinflammatory cytokines, both in the acute and chronic state of the injury. (31,32,34,35) This induces a cascade of biochemical events that lead to cell death caused by the mechanisms responsible for neurological deficit such as necrosis, aponecrosis, apoptosis or autophagy (Figure 2). (11,36)

ACUTE *(4-24 hours)*

- Disruption of BSCB
- Cell migration, recruitment and infiltration (lymphocytes, neutrophils, macrophages, NK cells).
- Astrocyte activation (reactive gliosis).
- Phagocytic activation of cellular debris (macrophages / microglia)
- Downregulation of CAMs (ICAM, VCAM, PE-CAM, E and P Selectins)
- Synthesis of proinflammatory cytokines (TNFα, IL1α, IL1β, IL6)
- Cell recruitment perpetuated by IL-8, MCP-1, CINC-1

SECONDARY *(2-14 days)*

- Increase in proinflammatory cytokines
- Increased activity of NF-κ β, MAPK and IFN-1
- Immune response CD4-Th1 (CD11b, CD14, CD40, CD45, CD80, CD86)
- Synthesis and release of iNOS, NO, PGs, leukotrienes
- Necrosis, aponecrosis and apoptosis



CHRONIC *(weeks/months)*

- Hypertrophy and astrocytic proliferation
- Formation of dystrophic growth cones
- Synthesis of lecticans (aggrecan, versican, phosphocan)
- Synthesis and release of NG2 by permanent activation of astrocytes, phagocytic microglia polydendrocytes, macrophages and oligodendrocyte precursors
- Overexpression of chemokines (CXCL10, CCL2, EGF, CSPGs)
- Formation of Glial Scar
- Wallerian degeneration - Neurodegeneration

Figure 2. Diagram of cell damage stages after spinal cord trauma.
BSCB: Blood-spinal cord barrier; NK cells: Natural killer cells; CAMs: Cell adhesion molecules; ICAM: Intercellular cell adhesion molecules; VCAM: Vascular cell adhesion molecules; PE-CAM: Platelet/endothelial cell adhesion molecules.
Source: Own elaboration based on the data obtained in the study.

During the acute phase, an adverse medium arises, dominated by migration and infiltration of NK cells, neutrophils and macrophages that mediate inflammatory and immune processes through molecules such as MCP-1, CINC-1, IL-8, produced by neutrophils and the Th1 isoform from activated CD4 lymphocytes. It is worth noting that astrocytosis (reactive gliosis) and microglia activate to forms with phagocytic activity and cytokine synthesis (TNFα, IL1α, IL1β and IL6).

During the secondary phase, proinflammatory cytokines increase, as well as the immune-mediated response through CD4 lymphocytes with synthesis and release of active complement molecules (CDs), and the synthesis and tissue release of iNOS, NO, PGs and leukotrienes that exacerbate the inflammatory process. In this stage, the injury radius of cell death of different types increases.

The chronic phase of SCI leads to an adverse environment for tissue repair, involving oligodendrocyte precursors (OLIG-P), polydendrocytes (NG2), activated phagocytic microglia and astroglia that overexpress chemokines. Under these conditions, Wallerian degeneration initiates in the glial scar and neurodegeneration occurs.

As seen in Figure 2, under pathological conditions and in response to molecular factors associated with damage, released after the death of neurons and astrocytes due to the primary injury in the medullary tissue, the resident microglia is activated to initiate the innate immune response, adapted and transformed to other subtypes dedicated to counteract the harmful effects of the injury. (22,35)

Although microglia is in a quiescent state in its native form and in normal conditions, thanks to the balance of inhibitory and stimulating signals, it is very sensitive to microenvironmental changes that activate its pattern recognition receptors, against which it begins to have greater motility and phagocytic activity to activate downstream signaling pathways such as the nuclear factor kappa β (NF-κβ) pathways, mitogen-activated protein kinase (MAPK) and interferon 1 (IFN-1). The activation of these pathways promotes the production and release of costimulatory molecules such as surface

antigens CD11b, CD14, CD40, CD45, CD80, CD86, proinflammatory cytokines, chemokines, nitric oxide (NO), inducible nitric oxide synthase (iNOS) and arachidonic acid derivatives such as leukotrienes and prostaglandins. (5,22,33,37)

Once activated, microglia can remain in that productive state for long periods of time, even at sites distant from the primary injury (24,25,38,39), favoring the release of anti-inflammatory (IL-4, IL-10, TGF-β) and proinflammatory cytokines (TNFα, IL-1, IL-6) that perpetuate inflammation until a chronic condition aggravates by the influx of circulating neutrophils, macrophages, lymphocytes and eosinophils, responsible, as a whole, for greater destruction and tissue loss. (11,22,25,38,40)

Clinical and experimental studies have documented the neuroinflammatory process that occurs after SCI in humans and animals. Rice *et al.* demonstrated elevated levels of IL-1α, IL-1β, IL-6, TNFα and chemokines within 15 minutes after spinal trauma in an extradural compression murine model. (13) In humans, high serum levels of IL-6, TNFα, IL-1 antagonist receptor (IL-1RA) and antibodies against myelin-associated glycoprotein (GM1) have been identified, the latter in patients with secondary and chronic SCI, between 2 and 52 weeks of evolution. (13,14)

Furthermore, the activation of microglia in patients with SCI has been proven to contribute to induction, development and maintenance of neuropathic pain states, mainly due to the production and release of proinflammatory cytokines, chemokines and extracellular proteases. (39) Similarly, microglial activation allows this cell type to adopt antigen-presenting cell functions, as well as other cells similar to macrophages, intervening in innate and adaptive immune response by expressing Toll-like receptors (TLRs), cytokines, chemokines and effector molecules such as CD86 and CD40, which allow the recruitment and activation of other immune cells (lymphocytes, macrophages and NK cells). In addition, activated microglia stimulate the expression of the major histocompatibility complex (MHC) and the response of specific CD4 and CD8 T cells. (35,36,39)

Microglial activation marks the beginning of different molecular events that determine the magnitude of the inflammatory response after the trauma, as well as the proliferation, migration and transitory recruitment of other cells at the site of the injury, which perpetuate the release of stimulating cytokines and chemokines, stimulating resident microglia (22,36,41) and causing it to evolve into phagocytic forms. Macrophages, especially neutrophils infiltrated in the injured tissue, have a major role in the inflammatory response, being neutrophils the first cells to migrate to the focus of the injury since the beginning, until reaching its maximum peak at about 24 hours. (22,31)

Neutrophils are activated by different stimuli including vascular endothelial damage, phagocytosis and production of proinflammatory substances, and promote the downregulation of intracellular CAM (I-CAM), vascular CAM (V-CAM), platelet/endothelial CAM (PE-CAM), in addition to E- and P- selectin. The release of IL-8 and chemoattractant cytokines, such as monocyte chemoattractant protein 1 (MCP-1) and cytokine-induced neutrophil chemoattractant (CINC-1), perpetuates the recruitment and activation of more neutrophils thanks to the adhesion to venous capillaries between 6-12 hours after SCI and its migration to the focus of the injury at 24 hours, in order to phagocytose cellular debris. (25,38)

At around 48 hours after spinal trauma, the number of neutrophils starts to decline while the number of monocytes increases. They will be later differentiated as macrophages, recruited and activated by TNFα and by the binding of their ligands to the complement receptor 3 (CR-3) and the mannose receptor. On the other hand, macrophages may be observed in the medullar tissue for months and even years, favoring the secretion of glutamate from proinflammatory cytokines (TNFα, IL-1, IL-6), iNOS and prostanoids. (20,25,31,37)

Along with microglia, macrophages are necessary for axonal debris phagocytosis and for promoting the production of anti-inflammatory cytokines and molecules that stimulate CNS repair, including the ciliary neurotrophic factor (CNTF), glial cell line-derived neurotrophic factor (GDNF) and insulin-like growth factor 1 (IGF-1). Some neurotrophins, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), are also involved. (20,22,25,31,37)

The orchestrated involvement of the inflammatory cells and the immune system is evident in the biological mechanisms that respond to SCI, which are related to both harmful and beneficial processes for tissue repair and regeneration through the regulation of the inflammatory response; the promotion of angiogenesis; the reduction of cytokines, chemokines and acute phase protein levels; the down-regulation in the expression of adhesion molecules; the attenuation of vascular permeability, and the maintenance of homeostasis. (28,42-44)

Glial cells, especially astrocytes, play an important role in the functioning of the CNS. They are particularly relevant for controlling the hematoencephalic and hematomedullary barrier, as well as in pH maintenance and ion and neurotransmitter homeostasis in the extracellular space, since they are anchored to the pia mater and the blood vessels from ventricular surfaces by means of GAP junctions. (45) Astrocytes surround 99% of the endothelial cells of BBB and BSCB, which favors their connection with neurons, thus allowing a rapid transfer of substances and chemical information. (28)

Inhibitory mechanisms of neuronal regeneration

CNS injuries involve complex cellular and molecular interactions initiated by the recognition of warning signals, which trigger the initial response to the trauma to repair tissue damage. The production of inflammatory molecules and immune surveillance of the CNS allow the entry of specialized cells of the immune system, such as antigen-presenting cells, dendritic cells, macrophages and activated T lymphocytes, to interact with resident cells and trigger the post-traumatic inflammatory response. (42,43) T helper cells (CD4) can change to a different phenotype according to the type of cytokines they release: Th1 produces IL-2, interferon G and TNF, while Th2 produces IL-4, IL-5, IL-6, IL-10 and IL-13. (46)

Microglia, macrophages and dendritic cells, which act as antigen-presenting cells after spinal cord injury, trigger an immune response by recruiting leukocytes in the spinal cord and by activating B and T lymphocytes, cytotoxic CD8 and CD4 helpers that increase in number simultaneously as microglia activate, and peripheral macrophages entrance within the first days after the injury. (42,47,48)

Moreover, leukocyte infiltration is known to play an important role in injury and spinal repair mechanisms, because it can exacerbate tissue damage and promote myelination and neuronal survival, depending on the microenvironment and the molecular signals that attract them to the site of injury. (48,49)

The limitation and gradual reduction in the intrinsic regeneration capacity of mature neurons is also known due to the recruitment of inflammatory cells, reactive astrogliosis and the effect of the production of axonal growth inhibitory molecules from intact polyndendrocytes and oligodendrocytes, like the fibrotic tissue or the glial scar. With this in mind, the non-permissive inhibitory environment, generated by glial cells (astrocytes, oligodendrocytes and microglia), is known to be the main obstacle for CNS regeneration after an injury, contrary to the case of the peripheral nervous system

(PNS), where a stimulating environment, product of factors that promote axonal growth, is observed. (12,50-52)

Thanks to the contributions of the scientific community, the inhibitory molecular components expressed constitutively or induced in the adult's CNS after a trauma are known today. Microglia, oligodendrocytes and astrocytes participate directly in the establishment of this hostile environment for axonal regeneration due to the production of inhibitors associated with myelin and chondroitin sulfate proteoglycans (CSPGs) present in the glial scar. (51-53)

Glial inhibitors of neuronal regeneration

The glial cells of the CNS not only provide structural and physical support, but respond promptly to injuries to provide neural protection through processes related to remyelination, phagocytosis, regulation of neurotransmitters, ionic homeostasis, maintenance of barriers (BBB and BSCB) and production of molecules of the extracellular matrix destined to the formation of the basal lamina and the perineurium. Regarding the injury, these cells respond by forming a glial scar with astrocytes that allow to isolate and protect the intact nervous tissue from future aggressions (52,54) of mature oligodendrocytes and polydendrocytes (NG2 glia) that proliferate in the CNS after neuronal damage and axonal demyelination. (55-57)

CNS myelin is formed by oligodendrocyte processes that coil several times around the axon, forming a coating called myelin sheath, interspersed by small unmyelinated or naked segments known as Ranvier nodes. After SCI, oligodendrocytes enter in an early stage of myelin deterioration, unleashing a cascade of secondary events that result in cell death, widespread and dispersed in space, by necrosis, apoptosis and autophagy. This exposes axon regeneration to highly inhibitory molecules, associated with myelin debris (Nogo, MAG, OMgp, ephrin-B3 and transmembrane semaphorin 4D) and to the glial scar formation by reactive astrocytes at the site of the injury. This condition leads to axonal demyelination and spontaneous remyelination generated by new oligodendrocytes that arise from endogenous oligodendrocyte precursor cells in the spinal cord (12,51,52,54,58-60) (Figure 3).

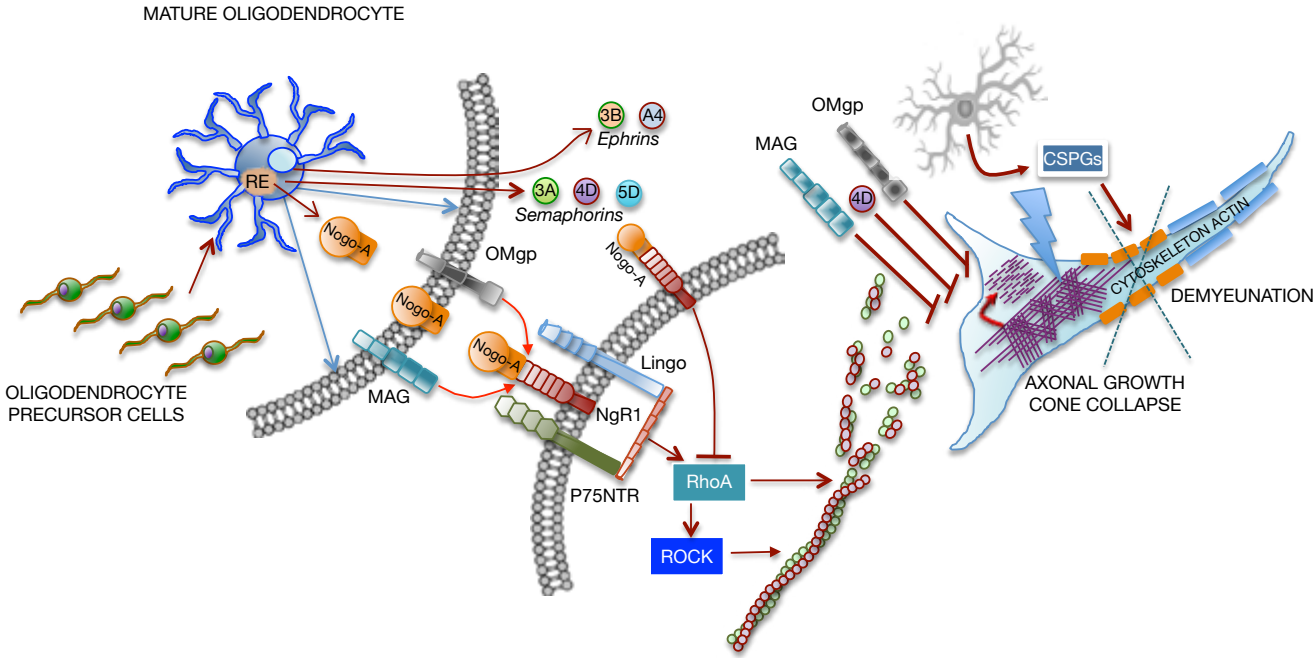


Figure 3. Representative graph of cellular and molecular interaction between mature oligodendrocytes and neurons in a SCI focus.
MAG: Myelin-associated glycoprotein; OMgp: Oligodendrocyte myelin glycoprotein.
Source: Own elaboration based on the data obtained in the study.

The axonal growth cone collapses due to the direct effect of molecules from oligodendrocytes, such as myelin-associated glycoprotein (MAG) and oligodendrocyte myelin glycoprotein (OMgp), or due to the formation of the Nogo-A complex and the NgR1- P75NTR-Lingo receptor, which activate RhoA. In turn, the rho-associated protein kinase (ROCK) is activated to prevent the polymerization of actin microtubules, which severely compromise the axonal cytoskeleton. Moreover, oligodendrocytes release transmembrane semaphorins (3A, 4D, 5D) and ephrins (3B, A4), which are involved in growth inhibition and in axonal cone collapse. On the other hand, activated astrocytes (reactants) provide chondroitin sulfate proteoglycans (CSPGs) to the neuronal environment, causing damage to the actin cytoskeleton and demyelination as shown in Figure 3.

a) Myelin-associated inhibitors

Nogo proteins are found in the endoplasmic reticulum and on the cell surface. Nogo-A is the only of its kind found naturally in myelin and is highly expressed in oligodendrocytes, motor neurons and sensory neurons, but not in astrocytes or Schwann cells. (61) Nogo-A inhibits neurites growth by binding its Nogo-66 inhibitor domain to Nogo 1 (NgR1) and PirB receptors, located on the neuronal membrane. (62) This binding forms a complex with LINGO1 and p75 transmembrane proteins in some neurons, which leads to an increase in intracellular calcium and activation of the ROCK pathway. Through RhoA signaling, the actin cytoskeleton is destabilized, resulting in growth cone collapse, which prevents the reestablishment of the injured axons. (51,59,62) On the contrary, blockade of Nogo-A or its receptors

promotes plasticity and axonal regeneration of the spinal tracts that survived the injury. (61)

Myelin-associated glycoprotein (MAG) is another axonal growth inhibitory protein and, unlike Nogo, is expressed by CNS oligodendrocytes and Schwann cells in the PNS. In the CNS, MAG is located in the periaxonal membrane by the internodal segments of the myelin sheath, whereas in the PNS, MAG is expressed in the paranodal region, in the Schmidt-Lanterman clefts and in other external mesoaxial segments, which allows establishing complexes with axonal surface receptors. (59) It is also known that MAG can be bifunctional due to its powerful inhibitory capacity in neuritic growth under in vitro conditions and for its ability to promote the growth of young neurons in vivo. (51-53,59,63)

Oligodendrocyte myelin glycoprotein (OMgp), also described as an inhibitory protein of CNS myelin, is a membrane glycoprotein located near the nodes of Ranvier and expressed in oligodendrocytes and in many types of neurons. It is related to nodal architecture, to growth-cone collapse and to the inhibition of collateral sprouting and neuritic growth. (53,59,64)

Nogo, MAG and OMgp show a high interaction affinity with the same receptor complex formed by NgR1, $p75^{NTR}$ and LINGO-1. NgR1 is a neuronal membrane receptor devoid of cytosolic domain, thus forming the complex for signal transduction. The signaling cascade initiated by Nogo, MAG and OMgp results in the activation of RhoA and its effector, Rho-kinase (ROCK). Because of the binding of p75 with the Rho-GDP dissociation inhibitor (Rho-GDI), the organization and dynamics of actin microtubules change and generate signals related to the inhibition of axonal growth by collapsing the growth cone, with the consequent limitation of functional recovery after an injury in the CNS. (51,53,61,63,64)

Other components with repulsive axonal growth activity are Semaphorin 3A, 4D and 5, and Ephrins 3B-A4. Semaphorin 4D (Sema 4D) is expressed by mature oligodendrocytes and induces growth-cone collapse; Sema 3A is expressed locally after an SCI; Ephrin 3B is expressed even in postnatal myelinated oligodendrocyte states and acts as a repellent during the projection of the corticospinal tract. (52,55,64,65)

b) Inhibitors associated with glial scar formation

The CNS responds to the injury and to the change in the local microenvironment by recruiting microglia, oligondendrocytes precursors, meningeal cells and astrocytes, to isolate the site of injury and minimize the inflammation area and cellular degeneration. However, some astrocyte populations may undergo hypertrophy, change their morphology and gene expression dramatically, and adopt a reactive phenotype (reactive astrogliosis), which may lead to the formation of a glial scar that acts as the main chemicophysical barrier for neural repair by obstructing axonal extension and reconnection, and by inhibiting collateral sprouting of injured axons in the spinal cord. The glial scar, on the other hand, favors the overexpression of proinflammatory cytokines, chemokines (CXCL10, CCL2), endothelial growth factor (EGF) and extracellular matrix molecules such as chondroitin sulfate proteoglycans (CSPGs). (22,55,56,65)

CSPGs are a family of molecules formed by a protein nucleus covalently attached to glycosaminoglycans (GAGs) expressed in the CNS, which serve as a guide during the development and modulation of synaptic connections. (4,52,55,60) Some of the CSPGs molecules expressed in the CNS are lecticans, which include aggrecan, versican, neurocan, brevican, phosphocan and the neural/glial antigen 2 (NG2) produced by astrocytes and oligodendrocytes progenitor cells, polydendrocytes, microglia and activated macrophages. In humans, after spinal trauma, NG2 and phosphacan are detectable throughout the glial scar, while neurocan and versican are only found at the epicenter of the injury. (4,52,55)

After an injury, the expression of CSPGs increases rapidly due to polydendrocytes and reactive astrocytes, especially in areas near the site of injury, forming an inhibitory regeneration gradient and stimulating the formation of dystrophic growth cones. (4,50,52,60) It is believed that CSPGs inhibit axonal growth due to non-specific laminin-binding impairment and other extracellular matrix molecules with their transmembrane receptors, and their binding to growth inhibition receptors expressed on the surface of axons. (55) However, it has been determined that the NG2 molecule expressed by polydendrocytes does not inhibit axonal growth when the plasma membrane of the polydendrocyte is intact, thanks to the close synaptic communication established between neuronal dendrites and polydendrocytes. (57) Likewise, CSPGs activate different specific signaling pathways that modulate their inhibitory activity in neural repair, such as those caused by the intracellular activation of RhoA, ROCK, AKT/PKB, mTOR, GSK-3β and protein kinase C, among others. (55)

After spinal cord injury, the activation of different cascade down signals that regulate neuronal growth is promoted. The activation of RhoA and the inactivation of Akt by phosphatase and tensin homologue deleted on chromosome 10 (PTEN) are fundamental for activating the signaling pathway produced by the mammalian target of rapamycin (mTOR), for the promotion of protein synthesis involved in axonal regeneration and, consequently, for recovering the locomotor function after the injury. (55,66) In contrast, the activation of the PI3K/Akt/mTOR pathway in reactive astrocytes is involved in the formation of the glial scar during the acute and secondary phases of the SCI. (66)

Conclusion

Knowledge and understanding of the neurobiochemical changes that occur after a SCI can contribute to develop new pharmacological therapies that minimize sensory and motor dysfunction in patients with spinal cord injuries who are prone to restoration.

The immune response triggers a cascade of biological events that exacerbate the primary injury and lead to the creation of a hostile environment for neuroregeneration, caused mainly by glial cell activation. The production of proinflammatory and inhibitory molecules of neuronal regeneration is the biggest obstacle for therapeutic intervention, which, in all cases, should seek to establish a favorable microenvironment for the activation of endogenous neuroprotection and regeneration mechanisms in the spinal cord, thus minimizing secondary damage associated with neurological deficit.

The course of SCI is relevant for the type of treatment to be followed regarding basic and applied research, since biochemical events that occur sequentially or simultaneously, as a pathophysiological response to SCI, are the product of the activity of multiple cell lineages and the great diversity of cell signaling molecules and other transient or perpetuating molecules.

Studying cellular and molecular activity of glial cells, such as astrocytes, oligodendrocytes, polydendrocytes and microglia, will allow neurology specialists, and neuroscientists in general, to understand better the process of glial scarring and neuronal death, and to make progress in the knowledge of neuropathology consequent to trauma.

Conflicts of interest

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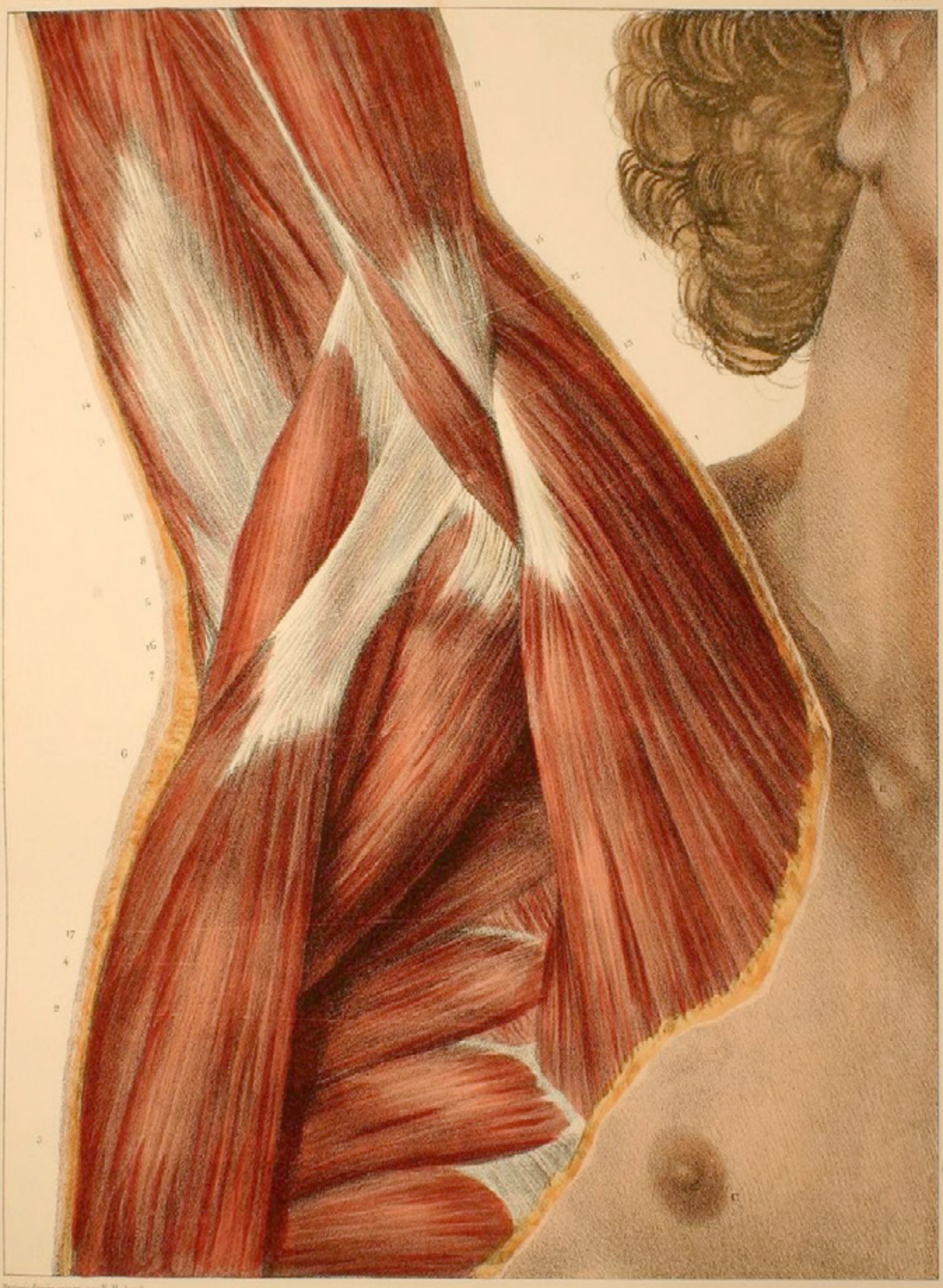
References

1. **Bickenbach J, editor.** International Perspectives on Spinal Cord Injury. Malta: Word Healt Organization; 2013.
2. **Lee BB, Cripps RA, Fitzharris M, Wing PC.** The global map for traumatic spinal cord injury epidemiology: update 2011, global incidence rate. *Spinal Cord.* 2014;52(2):10-6. http://doi.org/f5rrb5.
3. National Spinal Cord Injury Statistical Center. Facts and Figures at a Glance. Birmingham: University of Alabama at Birmingham; 2017.
4. **Siebert JR, Conta Steencken A, Osterhout DJ.** Chondroitin Sulfate Proteoglycans in the Nervous System: Inhibitors to Repair. *Biomed Res. Int.* 2014;2014:845323. http://doi.org/gb85cv.
5. **Wen T, Hou J, Wang F, Zhang Y, Zhang T, Sun T.** Comparative analysis of molecular mechanism of spinal cord injury with time based on bioinformatics data. *Spinal Cord.* 2015;(5):1-8. http://doi.org/f8qw48.
6. **Held KS, Steward O, Blanc C, Lane TE.** Impaired immune responses following spinal cord injury lead to reduced ability to control viral infection. *Exp. Neurol.* 2010;226(1):242–53. http://doi.org/ftgc94.
7. **Kjell J, Olson L.** Rat models of spinal cord injury: from pathology to potential therapies. *Dis. Model. Mech.* 2016 Oct;9(10):1125-37. http://doi.org/f3vfrp.
8. **Ning GZ, Wu Q, Li YL, Feng SQ.** Epidemiology of traumatic spinal cord injury in Asia: a systematic review. *J. Spinal Cord Med.* 2012;35(4):229-39. http://doi.org/f37p3m.
9. **Thakore NP, Samantaray S, Park S, Nozaki K, Smith JA, Cox A, *et al.*** Molecular Changes in Sub-lesional Muscle Following Acute Phase of Spinal Cord Injury. *Neurochem. Res.* 2016;41(1-2):44-52. http://doi.org/f8cd4m.
10. **Stein A, Panjwani A, Sison C, Rosen L, Chugh R, Metz C, *et al.*** Pilot study: elevated circulating levels of the proinflammatory cytokine macrophage migration inhibitory factor in patients with chronic spinal cord injury. *Arch. Phys. Med. Rehabil.* 2013;94(8):1498-507. http://doi.org/f46pmq.
11. **Esposito E, Cuzzocrea S.** Anti-TNF therapy in the injured spinal cord. *Trends Pharmacol. Sci.* 2011 Feb;32(2):107-15. http://doi.org/d3hjmq.
12. **Okano H, Sakaguchi M, Ohki K, Suzuki N, Sawamoto K.** Regeneration of the central nervous system using endogenous repair mechanisms. *J. Neurochem.* 2007;102(5):1459-65. http://doi.org/bcsfwd.
13. **Rice T, Larsen J, Rivest S, Yong VW.** Characterization of the early neuroinflammation after spinal cord injury in mice. *J. Neuropathol. Exp. Neurol.* 2007;66(3):184-95. http://doi.org/c3ftgh.
14. **Davies AL, Hayes KC, Dekaban GA.** Clinical correlates of elevated serum concentrations of cytokines and autoantibodies in patients with spinal cord injury. *Arch. Phys. Med. Rehabil.* 2007;88(11):1384-93. http://doi.org/btv8pw.
15. **Ahn YH, Lee G, Kang SK.** Molecular insights of the injured lesions of rat spinal cords: Inflammation, apoptosis, and cell survival. *Biochem. Biophys. Res. Commun.* 2006;348(2):560-70. http://doi.org/d2nx53.
16. **Ballesteros-Plaza V, Marré-Pacheco B, Martínez-Aguilar C, Fleiderman-Valenzuela JF, Zamorano-Pérez JJ.** Lesion de la médula espinal. Actualización bibliográfica: fisiopatología y tratamiento inicial. *Columna.* 2012;11(1):73-6. http://doi.org/cjnp.
17. **Chamankhah M, Eftekharpour E, Karimi-Abdolrezaee S, Boutros PC, San-Marina S, Fehlings MG.** Genome-wide gene expression profiling of stress response in a spinal cord clip compression injury model. *BMC Genomics.* 2013;14:583. http://doi.org/f5kncp.
18. **Mann CM, Kwon BK.** An Update on the Pathophysiology of Acute Spinal Cord Injury. *Semin. Spine Surg.* 2007;19(4):272-9. http://doi.org/cj33sh.
19. **Olby N.** The pathogenesis and treatment of acute spinal cord injuries in dogs. *Vet. Clin. North Am. Small Anim. Pract.* 2010;40(5):791-807. http://doi.org/dgt8g7.
20. **Oudega M.** Inflammatory response after spinal cord injury. *Exp. Neurol.* 2013;250:151-5. http://doi.org/cjnq.
21. **Zhou X, He X, Ren Y.** Function of microglia and macrophages in secondary damage after spinal cord injury. *Neural. Regen. Res.* 2014;9(20):1787-95. http://doi.org/cjnr.
22. **Jin X, Yamashita T.** Microglia in central nervous system repair after injury. *J. Biochem.* 2016;159(5):491-6. http://doi.org/f8mkk5.
23. **Leal-Filho MB.** Spinal cord injury: From inflammation to glial scar. *Surg. Neurol. Int.* 2011;2:112. http://doi.org/bfwh78.
24. **Sinescu C, Popa F, Grigorean VT, Onose G, Sandu AM, Popescu M, *et al.*** Molecular basis of vascular events following spinal cord injury. *J. Med. Life.* 2010;3(3):254-61.
25. **Profyris C, Cheema SS, Zang D, Azari MF, Boyle K, Petratos S.** Degenerative and regenerative mechanisms governing spinal cord injury. *Neurobiol. Dis.* 2004;15(3):415-36. http://doi.org/fnkj5g.
26. **Kindt TJ, Goldsby RA, Osborne BA.** Inmunología de Kuby. 6th ed. Mexico D.F.: McGraw-Hill Interamericana Editores S.A; 2007.
27. **Toche P.** Visión panorámica del sistema inmune. *Rev. Méd. Clín. Condes.* 2012;23(4):446-57. http://doi.org/f2x5k4.
28. **Lewis KM, Turner RJ, Vink R.** Blocking Neurogenic Inflammation for the Treatment of Acute Disorders of the Central Nervous System. *Int. J. Inflam.* 2013;2013:578480. http://doi.org/gb64tk.
29. **McDonough A, Hoang AN, Monterrubio AM, Greenhalgh S, Martínez-Cerdeño V.** Compression injury in the mouse spinal cord elicits a specific proliferative response and distinct cell fate acquisition along rostro-caudal and dorso-ventral axes. *Neuroscience.* 2013;254:1-17. http://doi.org/f5hpb9.
30. **Caballero-Chacón S, Nieto-Sampedro M.** Fisiopatología de la lesión medular. Revisión de literatura. *Vet. Mex.* 2005;36(1):75-86.
31. **Carlson SL, Parrish ME, Springer JE, Doty K, Dossett L.** Acute inflammatory response in spinal cord following impact injury. *Exp. Neurol.* 1998;151(1):77-88. http://doi.org/fv89hb.
32. **Zhang H, Wang Y.** Identification of molecular pathway changes after spinal cord injury by microarray analysis. *J. Orthop. Surg. Res.* 2016;11(1):101. http://doi.org/f84zpv.
33. **Peruzzotti-Jametti L, Donegá M, Giusto E, Mallucci G, Marchetti B, Pluchino S.** The role of the immune system in central nervous system plasticity after acute injury. *Neuroscience.* 2014;283:210-21. http://doi.org/f7rdj8.
34. **Enrique-Santos D.** Fisiopatología de la respuesta inflamatoria durante el perioperatorio. *Rev. Mex. Anestesiol.* 2007;30(Suppl 1):157-9.
35. **Yang I, Han SJ, Kaur G, Crane C, Parsa AT.** The Role of Microglia in Central Nervous System Immunity and Glioma Immunology. *J. Clin. Neurosci.* 2010;17(1):6-10. http://doi.org/dq3b84.
36. **Streit WJ, Mrak RE, Griffin WS.** Microglia and neuroinflammation: a pathological perspective. *J. Neuroinflammation.* 2004;1(1):14. http://doi.org/cppzp4.
37. **Mukaino M, Nakamura M, Yamada O, Okada S, Morikawa S, Renault-Mihara F, *et al.*** Anti-IL-6-receptor antibody promotes repair of spinal cord injury by inducing microglia-dominant inflammation. *Exp. Neurol.* 2010;224(2):403-14. http://doi.org/cz5prt.
38. **Pineau I, Sun L, Bastien D, Lacroix S.** Astrocytes initiate inflammation in the injured mouse spinal cord by promoting the entry of neutrophils

and inflammatory monocytes in an IL-1 receptor/MyD88-dependent fashion. *Brain Behav. Immun.* 2010;24(4):540-53. http://doi.org/fw5vsq.

39. **Schomberg D, Olson JK.** Immune responses of microglia in the spinal cord: contribution to pain states. *Exp. Neurol.* 2012;234(2):262-70. http://doi.org/fx4x62.
40. **Morino T, Ogata T, Horiuchi H, Takeba J, Okumura H, Miyazaki T, *et al.*** Delayed neuronal damage related to microglia proliferation after mild spinal cord compression injury. *Neurosci. Res.* 2003;46(3):309-18.
41. **Tian DS, Xie MJ, Yu ZY, Zhang Q, Wang YH, Chen B, *et al.*** Cell cycle inhibition attenuates microglia induced inflammatory response and alleviates neuronal cell death after spinal cord injury in rats. *Brain Res.* 2007;1135(1):177-85. http://doi.org/d4d3m9.
42. **Vergara U.** Sistema nervioso central y regulación de la respuesta inmune. *Avances en Ciencias Veterinarias.* 2011;26(1):41-52.
43. **Olazabal-Olarreaga IM, Gil-Alberdi L, Arias-Navalón JA.** El sistema inmune y su función en el sistema nervioso central. *Biociencias.* 2014;11:1-21.
44. **Silva NA, Sousa N, Reis RL, Salgado AJ.** From basics to clinical: a comprehensive review on spinal cord injury. *Prog. Neurobiol.* 2014;114:25-57. http://doi.org/f53bfx.
45. **Ramírez-Expósito MJ, Martínez-Martos JM.** Estructura y funciones de la macroglía en el sistema nervioso central. Respuesta a procesos degenerativos. *Rev. Neurol*. 1998;26(152):600-11.
46. **Ramos-Linares V, Rivero-Burón R, Piqueras-Rodríguez JA, García-López LJ, Oblitas-Guadalupe LA.** Psiconeuroinmunología: Conexiones entre sistema nervioso y sistema inmune. *Suma Psicológica.* 2008;15(1):115-42.
47. **Plemel JR, Wee Yong V, Stirling DP.** Immune modulatory therapies for spinal cord injury- Past, present and future. *Exp. Neurol.* 2014;258:91-104. http://doi.org/f6grwn.
48. **Popovich PG, Jones TB.** Manipulating neuroinflammatory reactions in the injured spinal cord: Back to basics. *Trends Pharmacol. Sci.* 2003;24(1):13-7.
49. **Trivedi A, Olivas AD, Noble-Haeusslein LJ.** Inflammation and Spinal Cord Injury: Infiltrating Leukocytes as Determinants of Injury and Repair Processes. *Clin. Neurosci. Res.* 2007;6(5):283-92. http://doi.org/fs3qvn.
50. **Anderson MA, Burda JE, Ren Y, Ao Y, O'Shea TM, Kawaguchi R, *et al.*** Astrocyte scar formation aids central nervous system axon regeneration. *Nature.* 2016;532(7598):195-200. http://doi.org/f8h48z.
51. **Huebner EA, Strittmatter SM.** Axon Regeneration in the Peripheral and Central Nervous Systems. *Results Probl. Cell. Differ.* 2009;48:339-51. http://doi.org/bfx48x.
52. **Yiu G, He Z.** Glial inhibition of CNS axon regeneration. *Nat. Rev. Neurosci.* 2006;7(8):617-27. http://doi.org/dtxbjh.
53. **Chaudhry N, Filbin MT.** Myelin-associated inhibitory signaling and strategies to overcome inhibition. *J. Cereb. Blood Flow Metab.* 2007;27(6):1096-107. http://doi.org/chf573.
54. **Fitch MT, Silver J.** CNS injury, glial scars, and inflammation: Inhibitory extracellular matrices and regeneration failure. *Exp. Neurol.* 2008;209(2):294-301. http://doi.org/bwbpzd.
55. **Sharma K, Selzer ME, Li S.** Scar-mediated inhibition and CSPG receptors in the CNS. *Exp. Neurol.* 2012;237(2):370-8. http://doi.org/f39c36.
56. **Yuan YM, He C.** The glial scar in spinal cord injury and repair. *Neurosci. Bull.* 2013;29(4):421-35. http://doi.org/f5brvg.
57. **Nishiyama A, Komitova M, Suzuki R, Zhu X.** Polydendrocytes (NG2 cells): multifunctional cells with lineage plasticity. *Nat. Rev. Neurosci.* 2009;10(1):9-22. http://doi.org/dcbrzn.
58. **Sun F, He Z.** Neuronal intrinsic barriers for axon regeneration in the adult CNS. *Curr. Opin. Neurobiol.* 2010;20(4):510-8. http://doi.org/ccznx5.
59. **Filbin MT.** Myelin-associated inhibitors of axonal regeneration in the adult mammalian CNS. *Nat. Rev. Neurosci.* 2003;4(9):703-13. http://doi.org/fbnq4m.
60. **Plemel JR, Keough MB, Duncan GJ, Sparling JS, Yong VW, Stys PK, *et al.*** Remyelination after spinal cord injury: is it a target for repair? *Prog. Neurobiol.* 2014;117:54-72. http://doi.org/f57jcb.
61. **Young W.** Spinal Cord Regeneration. *Cell Transplant.* 2014;23(4-5):573-611. http://doi.org/f6s94w.
62. **Schwab ME.** Functions of Nogo proteins and their receptors in the nervous system. *Nat. Rev. Neurosci.* 2010;11(12):799-811. http://doi.org/dx8th7.
63. **Baldwin KT, Giger RJ.** Insights into the physiological role of CNS regeneration inhibitors. *Front. Mol. Neurosci.* 2015;8:23. http://doi.org/cjqm.
64. **Muramatsu R, Yamashita T.** Concept and molecular basis of axonal regeneration after central nervous system injury. *Neurosci. Res.* 2014;78:45-9. http://doi.org/f5s4cj.
65. **Kawano H, Kimura-Kuroda J, Komuta Y, Yoshioka N, Li HP, Kawamura K, *et al.*** Role of the lesion scar in the response to damage and repair of the central nervous system. *Cell Tissue Res.* 2012;349(1):169-80. http://doi.org/f33fjc.
66. **Chen CH, Sung CS, Huang SY, Feng CW, Hung HC, Yang SN, *et al.*** The role of the PI3K/Akt/mTOR pathway in glial scar formation following spinal cord injury. *Exp. Neurol.* 2016;278:27-41. http://doi.org/f8fnhz.



Jean Marc Bourgery
"Traité complet de l'anatomie de l'homme"
Paris 1832-1854

CASE REPORT

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Acute abdomen and perforated duodenal ulcer in an adolescent: case report

Abdomen agudo quirúrgico, úlcera duodenal perforada en un adolescente: reporte de caso

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| Abstract |

Acute abdominal pain is one of the most frequent reasons for consultation in emergency departments. Its causes are diverse and are divided into surgical and medical. Surgical causes may be traumatic, obstructive or inflammatory. The last category includes perforated hollow viscus as a complication of duodenal ulcer, a rare condition in pediatrics.

This paper presents the case of a previously healthy 14-year-old adolescent who attended the emergency department due to the sudden onset and rapid progression of abdominal pain in the right hypochondrium, which radiated to the lower back on the same side. This condition was associated with vasovagal symptoms and was initially managed as urolithiasis, considering clinical deterioration and obvious signs of generalized peritonitis, which required a diagnostic laparoscopy followed by laparotomy by pediatric surgery.

Perforated duodenal ulcer was diagnosed during the procedure as the cause of the symptoms. This paper intends to show the experience of clinical cases with an initial diagnostic error and include complicated duodenal ulcer as a differential diagnosis.

Keywords: Acute Abdomen; Duodenal Ulcer; Pediatrics (MeSH).

Zarate-Suarez LA, Urquiza-Suárez YL, García CF, Padilla-Mantilla DA, Mendoza MC. Acute abdomen and perforated duodenal ulcer in an adolescent: case report. Rev. Fac. Med. 2018;66(2):279-281. English. doi: http://dx.doi.org/10.15446/revfacmed.v66n2.59798.

| Resumen |

El dolor abdominal agudo es uno de los principales motivos de consulta en los servicios de urgencias, sus causas son diversas y se dividen en quirúrgicas y médicas. En este artículo se hace mención a las causas quirúrgicas que pueden ser de tipo traumático, obstructivo o inflamatorio. En esta última categoría se encuentra la perforación de víscera hueca como complicación de ulcera duodenal, entidad poco frecuente en la edad pediátrica.

Se presenta el caso de un adolescente de 14 años, previamente sano, quien consultó a urgencias de medicina general por dolor abdominal de inicio súbito y de rápido progreso en hipocondrio derecho, con irradiación a zona lumbar del mismo lado, asociado a síntomas vaso vágales. Se da manejo primario como urolitiasis.

Ante el deterioro clínico y los signos evidentes de peritonitis generalizada, el paciente es llevado a laparoscopia diagnóstica que requiere conversión a laparotomía por cirugía pediátrica. El hallazgo quirúrgico es úlcera duodenal perforada como causa del cuadro clínico. Este reporte pretende mostrar la experiencia de los casos clínicos en los que se da un error diagnóstico inicial e incluir a la ulcera duodenal complicada como diagnóstico diferencial.

Palabras clave: Abdomen agudo; Úlcera duodenal; Pediatría (DeCS).

Zarate-Suarez LA, Urquiza-Suárez YL, García CF, Padilla-Mantilla DA, Mendoza MC. [Abdomen agudo quirúrgico, úlcera duodenal perforada en un adolescente: reporte de caso]. Rev. Fac. Med. 2018;66(2):279-281. English. doi: http://dx.doi.org/10.15446/revfacmed.v66n2.59798.

Introducción

Acute abdominal pain (AAP) is a frequent reason for consultation in pediatrics, is difficult to diagnose and constitutes a medical emergency. Semiologically, its onset may be sudden and insidious, and may progress rapidly or intermittently. It is associated with alterations in intestinal motility, oral intolerance and systemic symptoms such as fever.

The causes of AAP may be inflammatory, ischemic or obstructive, and include closed or penetrating abdominal trauma. Clinical diagnosis should be timely to avoid complications that endanger the patient's life, since incarcerated inguinal hernias and testicular and gynecological pathologies are entities that may present similar clinical characteristics of extra abdominal origin.

Clinical case

A 14-year-old adolescent with no relevant history attended the General Medicine Service due to abdominal pain of 20 minutes of evolution, of sudden onset and rapid progress, located in the hypochondrium and right iliac fossa, irradiated to the ipsilateral lumbar area, associated with emesis, diaphoresis and hypotension. Physical examination revealed mucocutaneous pallor, pain and abdominal guarding in right hemiabdomen with positive costovertebral angle tenderness.
Initially, medical management was directed to treat possible urolithiasis. Paraclinical examinations showed mild leukocytosis with neutrophilia, while abdominal ultrasound described anechoic free fluid in the right iliac fossa that did not rule out an appendiceal process. Renal etiology was ruled out.

The patient was assessed by pediatric surgery after eight hours due to persistent pain, generalized involuntary guarding and peritoneal irritation. A peptic ulcer was suggested and endoscopy of the upper digestive tract and H2 antihistamine were requested. An emergent surgery was performed considering the clinical deterioration of the patient, signs of shock and generalized peritonitis.

Management

A diagnostic laparoscopy was performed, obtaining the following findings: seropurulent fluid with duodenal and biliary content of 100cc, perforation on the anterior wall of the pyloric region of about 0.8cm in diameter (Figure 1), localized serositis, edema and fibrin. Due to technical difficulties, the procedure was converted to mid-suprainfraumbilical laparotomy, and dieresis by planes until the cavity, revision of the entire duodenum, perforation raffia with absorbable suture (vicryl 3) omentum patch, cavity washing and cleaning, synthesis by planes with absorbable suture (vicryl) 0) and skin with PDS 4.0 were performed without complications.

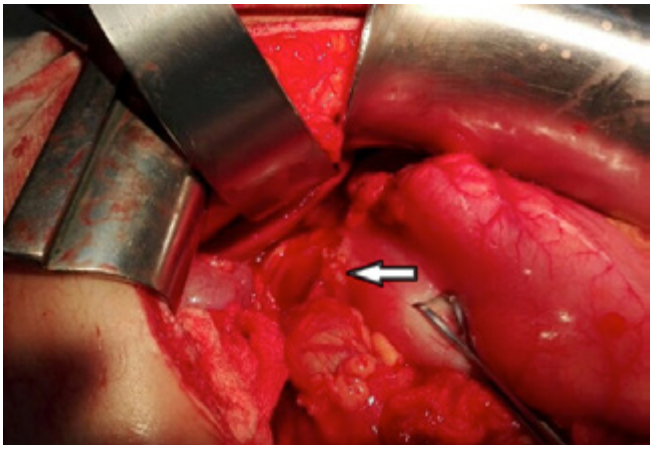

Figure 1. Intraoperative: Perforated duodenal ulcer on the anterior wall of the pyloric region.
Source: Own elaboration based on data obtained during the study.

Follow-up

The patient was transferred to the intensive care unit with proton pump inhibitor and antibiotics. After five days, intestinal restitution began and discharge was indicated without complications after eight days.

One month after discharge, an endoscopy of the digestive tract with biopsy was performed confirming the presence of *Helicobacter pylori*. Eradication treatment was indicated according to the guidelines established by the Colombian Society of Gastroenterology.

Discussion

AAP in pediatrics is a syndrome constituted by different pathologies that require timely diagnosis and emergent surgery for proper management. (1,2) This entity occurs between 5-15% of patients aged 5 to 15 years. (3) Clinical diagnosis is not easy to achieve, thus becoming a challenge for general practitioners in emergency services. Clinical manifestations are unclear and diagnostic aids are sometimes inconclusive or unspecific. (4) This situation causes a high percentage of diagnostic errors and masks abdominal surgical processes, as in the case of this patient, who was treated with complete analgesia because the first diagnostic impression was urolithiasis. The way to approach a child or adolescent and their family allows learning about the onset of symptoms and guide the diagnosis; in consequence, developing an adequate clinical history and a good physical examination is highly important. (5)

Bearing in mind that surgical abdominal pain may be caused by multiple causes, and that such causes vary according with pediatric age distribution, allows obtaining differential diagnoses to make relevant decisions (6,7) (Table 1).

The most frequent infectious cause in Colombia, according to the Colombian Society of Pediatrics, is acute appendicitis, prevalent in 25 cases per 10 000 school children and adolescents. (8,9) Traumatic causes are considered of great importance due to the increase in the last decades of child abuse and accident rates in the country. (10) In turn, obstructive causes are frequent in toddlers and preschool infants, as well as poor rotation, intussusception, Meckel's diverticulum and bowel volvulus, among others. (11)

Table 1. Distribution of AAP causes according to age ranges in pediatrics.

Neonates to preschoolers	Preschoolers to school children	Adolescents
Incarcerated inguinal hernia	Acute appendicitis	Acute appendicitis
Intussusception	Trauma	Pancreatitis
Bowel volvulus	Bowel obstruction by adhesion	Complicated duodenal ulcer
Intestinal malrotation	Parasitosis	Cholecystitis
Complicated Meckel's diverticulum	Neoplasms	Acalculous cholecystitis
Congenital anomalies	Testicular torsion	Bowel obstruction by adhesion
Trauma	Ovarian torsion	Trauma
		Ovarian torsion

Source: Own elaboration based on Reust & Williams. (9)

The initial approach to a patient with acute abdominal pain should begin with a general assessment of the child, including appearance, food intake, diuresis and level of activity, through eye contact or interviewing a relative. Special attention should be paid to abdominal pain history, which should include associated symptoms, previous episodes of abdominal pain, and pain intensity. Some of the clinical manifestations that lead to suspect AAP are absence of bowel sounds, bilious vomiting, involuntary abdominal guarding, rebound tenderness, abdominal rigidity and fever, when it appears after the onset of abdominal pain and emesis. Acute chronic intermittent abdominal pain is less likely to be related to a surgical cause than to a first episode of acute pain. (9)

Duodenal peptic ulcer (DPU) is relatively rare in pediatrics. In Colombia, an incidence rate of 4.4 per 10 000 children has been reported. (12) It is classified into primary and secondary; primary ulcers present along with infection by H. pylori, bacteria related to socioeconomic conditions and found in 2/3 of the world population, in 80% of the adults of developing countries. (13,14) In Japan, a 20-year follow-up study was conducted with a sample of 52 patients, of whom 90% were adolescents with acute abdominal pain, predominantly

male, with family risk factors for DPU such as smoking, alcohol consumption, use of chronic drugs, and in all cases *H. pylori* infection was identified as the main cause. (15)

Secondary ulcers are related to causes such as burns, exogenous drugs (NSAIDs or steroids), stress, hypergastrinemia, causes of central origin due to trauma or neoplasms, low weight and prematurity in neonates, and gastrin hypersecretion of parietal cells due to maternal or spontaneous influence. The latter has been reported in isolation in these age ranges. (16,17)

It should be borne in mind that other ulcers may be silent until they manifest as a perforation with shock in patients with acute abdomen, since laparotomy is the only diagnosis method of this disease, as in the case presented here. (18,19)

Conclusions

Complicated duodenal peptic ulcer should be considered in differential diagnoses of acute surgical abdomen in children and adolescents. In Colombia, a developing country with a high rate of *H. pylori* infection, its existence is well documented except for pediatrics. For this reason, it is important to promote prevalence studies in the Colombian population that allow developing eradication protocols to avoid complications.

Conflicts of interest

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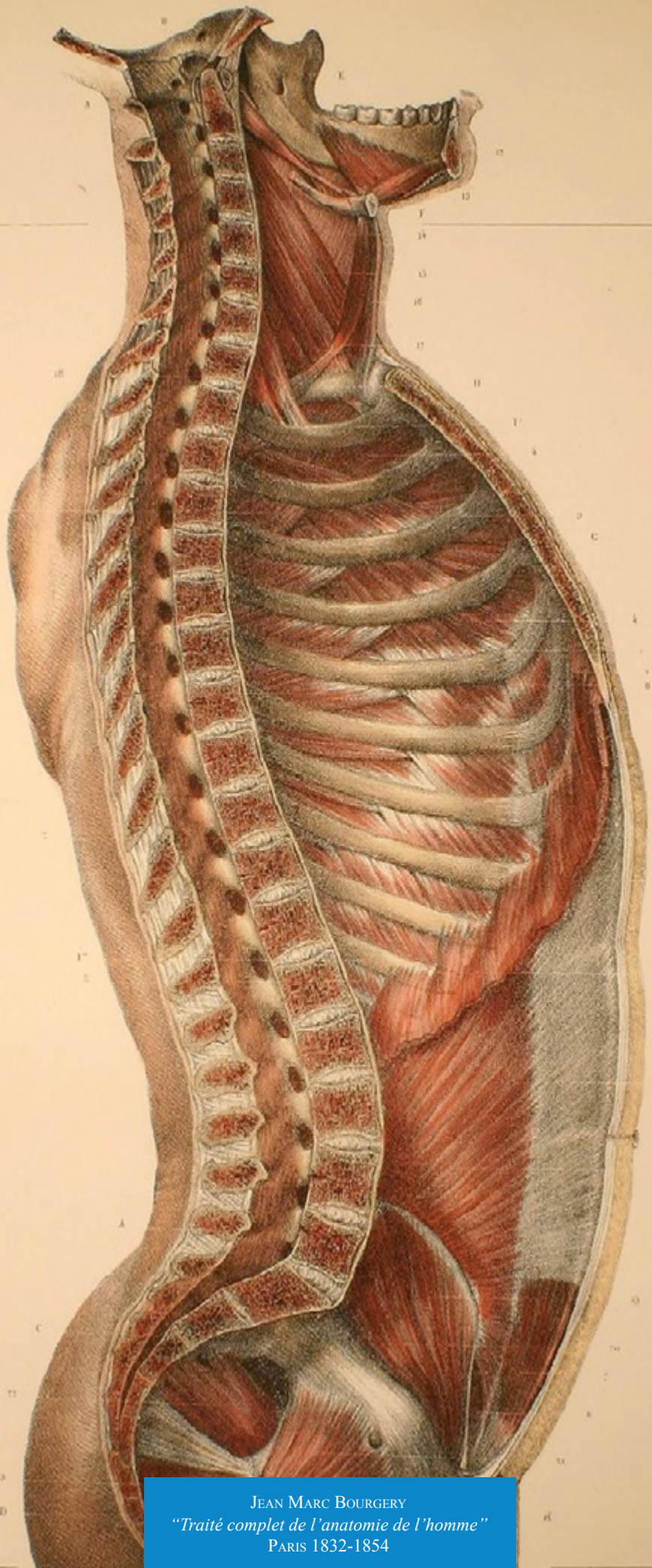
References

1. **Morrow S, Newman K.** Current management of appendicitis. *Semin. Pediatr. Surg.* 2007;16(1):34-40. http://doi.org/bcbjrt.
2. **Tamayo-Meneses L, Castillo-Loayza J.** Dolor abdominal agudo, síntoma indirecto de neumonía: a propósito de tres casos. *Cuad. Hosp. Clín.* 2006 [cited 2016 Oct 19];51(1):65-70. Available from: https://goo.gl/FY43vC.
3. **Árdela E, Domínguez F, Ansó S, Arce J.** Dolor abdominal en la edad escolar: Avances. *Bol. Pediatría.* 2000;40(173):147-157.
4. **Lin WC, Lin CH.** Multidetector computed tomography in the evaluation of pediatric acute abdominal pain in the emergency department. *Biomedicine (Taipei).* 2016;6(2):10. http://doi.org/cfpz.
5. **Nakayama DK.** Examination of the Acute Abdomen in Children. *J. Surg. Educ.* 2016;73(3):548-52. http://doi.org/f8k3qx.
6. **Coca-Robinot D, Liébana de Rojas C, Aguirre-Pascual E.** Abdominal emergencies in pediatrics. *Radiologia.* 2016;58(Suppl 2):80-91. http://doi.org/cfp2.
7. **García-Aparicio J.** Abdomen agudo en el niño. *Protocolos diagnóstico-terapéuticos de Urgencias Pediátricas SEUP-AEP.* Madrid: Hospital Infantil Universitario La Paz. Available from: https://goo.gl/5ZMQhB.
8. **Holguín D, Bautista, F, Fierro F, Holguín D, Rojas A.** Prevalencia del dolor abdominal agudo y sus manifestaciones en el paciente pediátrico. *Pediatría.* 2011;44(1).
9. **Reust CE, Williams A.** Acute Abdominal Pain in Children. *Am. Fam. Physician.* 2016;93(10):830-6.
10. **Gomes de Souza P, Ferreira AL.** Acute abdominal pain as a manifestation of physical violence in an infant: alert to pediatricians. *Rev. Paul. Pediatr.* 2012;30(4):608-12. http://doi.org/cjxh.
11. **Mazzi E.** Dolor abdominal en niños. *Rev. Soc. Bol. Ped.* 2013 [cited 2016 Oct 19];52(1):50-7. Available from: https://goo.gl/RRT6QM.
12. **Uribe-Garay C.** Enfermedad ácido-péptica. *CCAP.* 2014 [cited 2018 Jan 29];13(3):37–48. Available from: https://goo.gl/wkVogA.
13. **Malaty HM.** Epidemiology of Helicobacter pylori. *Best. Pract. Res. Clin. Gastroenterol.* 2007;21:205-14. http://doi.org/bb7xdt.
14. **Suebaum S, Michetti P.** *Helicobacter pylori* infection. *N. Engl. J. Med.* 2002;347:1175-86. http://doi.org/dq2t6t.
15. **Hua MC, Kong MS, Lai MW, Luo CC.** Perforated peptic ulcer in children: a 20-year experience. *J. Pediatr. Gastroenterol. Nutr.* 2007;45(1):71-4. http://doi.org/fq84jj.
16. **Amouei A, Ehsani F, Zarch MB, Tabatabaei SM, Ghodratipour Z.** Peritonitis Following Duodenal Ulcer Perforation in a Newborn: A Case Report. *J. Clin. Diagn. Res.* 2016;10(11):PD10-PD11. http://doi.org/cfp3.
17. **Trujillo M, García R, Sagaró E, Fragoso T, Lazo O, Borbolla E, *et al.*** Úlcera gastroduodenal en pediatría. *Rev. Gastroenterol. Perú.* 1997;17(2).
18. **Yildiz T, Ilce HT, Ceran C, Ilce Z.** Simple patch closure for perforated peptic ulcer in children followed by Helicobacter pylori eradication. *Pak. J. Med. Sci.* 2014;30(3):493-496. http://doi.org/cfp4.
19. **Yadav SK, Gupta V, El Kohly A, Al Fadhli W.** Perforated duodenal ulcer: A rare complication of deferasirox in children. *Indian. J. Pharmacol.* 2013;45(3):293. http://doi.org/cfp5.



Jean Marc Bourgery
"Traité complet de l'anatomie de l'homme"
Paris 1832-1854

LETTER TO THE EDITOR

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Teaching, research and scientific production. The three points of the triangle of quality in higher education

Docencia, investigación y producción científica. Tres puntas del triángulo de la calidad de la enseñanza superior

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Dear Editor:

While extending a warm greeting, we are writing to congratulate, through you, the authors of the article entitled "Scientific production in the Medicine Faculties of Colombia in the last 15 years". (1) In this work, the volume of scientific production of Colombian universities in the area of medicine during the past 15 years is determined by analyzing the SCOPUS database. (2) This type of studies is highly relevant today, if we consider that research is associated, now more than ever, with the quality of teaching (3) and that this can be indirectly measured through intellectual and scientific production. (4,5)

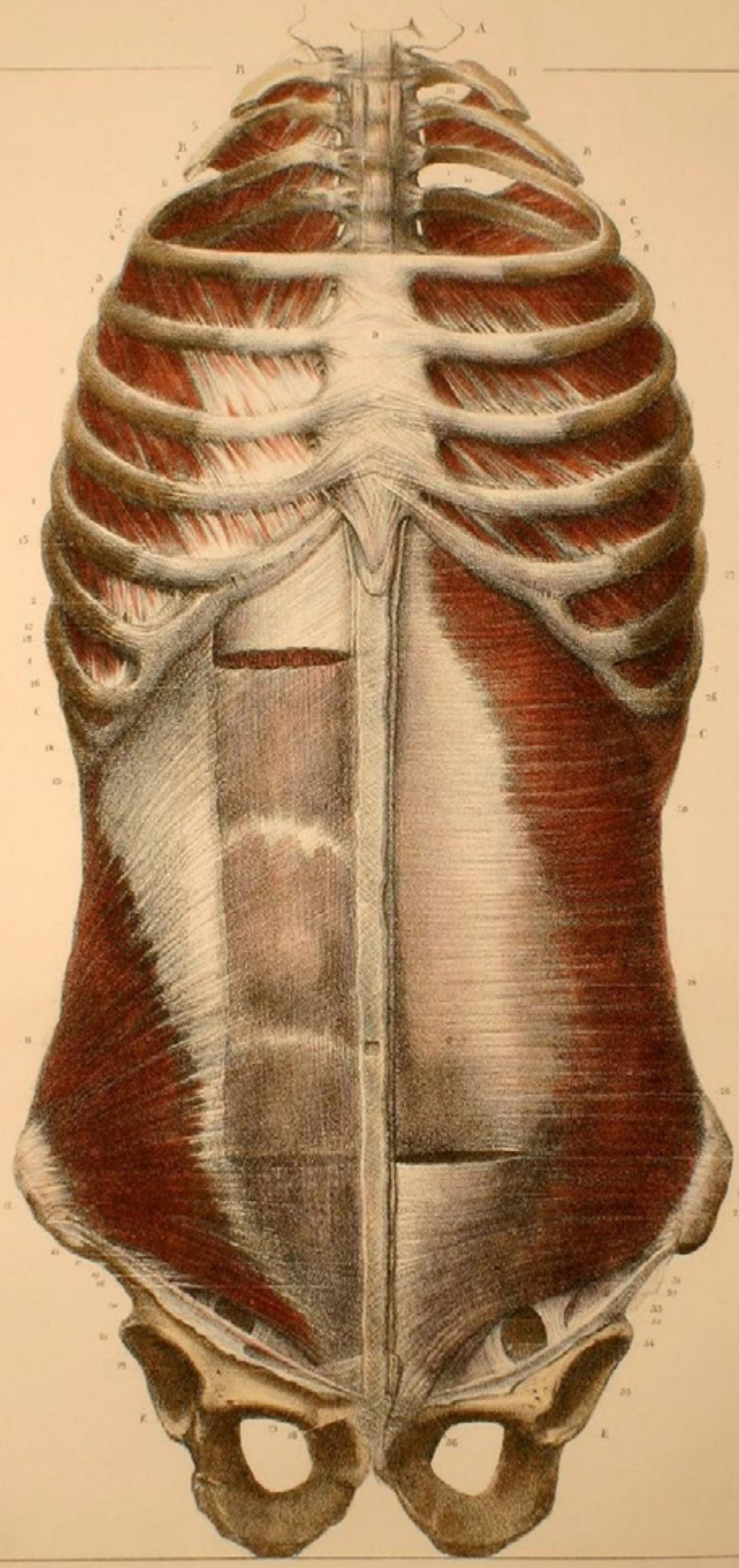
We think it is appropriate to add that one of the biggest obstacles to increasing scientific production in Latin American universities is writing scientific articles, as it is considered a part of research methodology in most of the countries of the region, although it is generally not addressed exhaustively or as an independent thematic unit. (6)

The aforementioned work becomes even more important as it calls for the generation of research projects and the publication of their results. Therefore, the perspective of the authors towards encouraging research in students, at least implicitly, is remarkable. (7)

It is worth noting that by publishing this kind of research, the journal, as a host of scientific debate, fulfills the fundamental task of sustaining the notion of science as a social activity. In this context, it plays a key role for the interaction between researchers in order to address issues that, like the one described above, integrate scientific production, teaching and research as the points of the triangle of quality in higher education.

References

1. **Sánchez-Bello NF, Galván-Villamarín JF, Eslava-Schmalbach J.** Producción científica en las facultades de Medicina en Colombia en el periodo 2001-2015. *Rev. Fac. Med.* 2016;64(4):645-50. http://doi.org/cp56.
2. **Joshi MA.** Bibliometric indicators for evaluating the quality of scientifc publications. *J Contemp Dent Pract.* 2014;15(2):258-62. http://doi.org/bxgd.
3. **Brandao Z, de Carvalho CP.** Qualidade do ensino, balanço de uma década de pesquisas. *Educ. Soc. Campinas*. 2015;36(131):445-58.
4. **Salas-Perea RS.** La calidad en el desarrollo profesional: avances y desafíos. *Rev. Cubana Educ. Med. Super.* 2000;14(2):136-47.
5. **Eslava-Schmalbach J, Gaitán-Duarte HG, Escobar-Córdoba F.** Producción científica de las facultades de medicina en Colombia, 1940-2014. *Rev. Fac. Med.* 2014;62(3):363-7. http://doi.org/bhmv.
6. **Barbón-Pérez OG, Calderón-Tobar AR, Loza-Cevallos CA, Garcés-Viteri L, Fernández-Pino JW.** Algunos problemas de docentes universitarios en la elaboración de artículos científicos. *Actualidades Investigativas en Educación.* 2017;17(1):61-78. http://doi.org/cp57.
7. **Barbón-Pérez OG, Bascó-Fuentes EL.** Clasificación de la actividad científica estudiantil en la educación médica superior. *Educ Med.* 2016;17(2):55-60. http://doi.org/cp58.



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