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Revista *de la* Facultad *de* Medicina

Journal of the Faculty of Medicine

Rev. Fac. Med. 2020Año 72, Vol. 68, No. 1

UNIVERSIDAD
NACIONAL
DE COLOMBIA

ISSN *0120-0011*
e-ISSN: *2357-3848*
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Revista *de la* Facultad *de* Medicina

EDITORIAL
DOI: https://doi.org/10.15446/revfacmed.v68n1.86482

The COVID-19 pandemic

Introducción

I open this note with some alarming figures: as of May 26, 2020, over 5 635 000 people have become infected and nearly 350 000 have died from the new coronavirus (COVID-19) worldwide.[1] Meanwhile, in Colombia, there are already 21 981 people infected and 750 deaths from this disease, that is, a 3.4% mortality rate.[2]

COVID-19 is an infectious disease caused by a new coronavirus strain. Most people infected with COVID-19 will develop a mild to moderate respiratory illness and recover without the need for hospital care. However, the disease can significantly affect older people and those with underlying diseases such as diabetes, chronic respiratory diseases, cancer, obesity, and cardiovascular disease,[3] and it could even lead to death, which undoubtedly places a burden on health systems, particularly on intensive care units (ICUs).

Currently, no health system in the world has sufficient capacity to treat these patients in their ICUs and intermediate care units nor the necessary staff (doctors, nurses, and respiratory therapists) and equipment (ventilators and monitors). In other words, no country is prepared to face a pandemic of these dimensions, basically because the measures to be taken require having massive economic resources available, as well as the cooperation of a supportive and responsible community. Both requirements, together, will make it possible to achieve complete isolation of the population, which is the only effective action known to date to reduce the spread of the virus. However, achieving this also requires that governments, on the one hand, implement equity measures that meet the basic needs of a large part of the population and, on the other, inject considerable resources into health systems so that healthcare institutions and staff can serve as many people as possible under the best biosecurity conditions.

According to the Asociación Colombiana de Sociedades Científicas (Colombian Association of Scientific Societies),[4] there are approximately 12 000 ICU beds in Colombia. Even so, only 5 300 have ventilators, 80% of them are usually occupied, and only 10-15% are fully isolated. This means that the country would only have about 750 ICU beds to deal with the COVID-19 pandemic.

On January 11, when the first death from pneumonia secondary to the new coronavirus was reported in Wuhan, a highly technological and populous city located in central China, this disease seemed a distant problem. Furthermore, when quarantine was declared in that city 12 days after the first death, many considered it an arbitrary measure that would have severe economic and social repercussions.

At this time, when the pandemic continues to spread at an alarming rate, the world must learn from the experience of countries such as China and Japan. These countries, in addition to abiding by the decisions taken by their governments (in the first case because of their authoritarian regime and in the second case because of their cultural tradition), faithfully adopted the following health measures:

Containment phase: frequent hand washing, physical distance of at least 1.5 meters, limitation of crowding in public places (no more than 10 people), and implementation of isolation protocols that included the closure of schools, colleges, universities, bars, entertainment sites, among others.

Mitigation phase: when the virus began to circulate in the population (not airborne but through contact routes), the decision was more drastic: people's mobility was completely limited and maximum willingness to comply with the measures was requested.

Also, the experience of South Korea should be considered. It is a powerhouse that exports and markets —among other products— ventilators, monitors, and other medical supplies, which the entire world is now requiring. There, authorities made a wise decision and initiated fast and creative actions against this virus because an uncontrolled pandemic can overflow and collapse any health system; therefore, this situation must be dealt with promptly. Thus, the South Korean authorities, knowing that RNA viruses, like the coronavirus, reproduce mainly in the respiratory tract and

have a high rate of transmission and mutation, decided to apply a *bali-bali* (quick-quick) strategy: more than 20 000 daily rapid tests were performed (in less than 5 minutes) for free in the largest cities of the country. These tests were randomly performed to pedestrians, drivers, students, employees, among others, which allowed identifying early a large number of people infected and put them in quarantine for 15 days, thus controlling the disease. By May 26, 2020, that country had reported 10 806 confirmed cases, 11 225 recovered patients, and 269 deaths, data that undoubtedly confirm an effective control of the pandemic.[5]

In the April editorial of the New England Journal of Medicine, Dr. Harvey Fineberg,[6] concerned about the unfortunate decisions of President Donald Trump in view of the imminent mortality of a large number of Americans from COVID-19, proposed six goals that the U.S. presidency should develop to deal with this pandemic successfully. These goals can be replicated in other countries according to their local characteristics:

1) *Establish unified command.* The President should appoint a commander that reports directly to him. This person should have the same powers to mobilize the resources necessary to overcome this pandemic. Moreover, each governor should designate one commander per state with the same authority because the variation of the pandemic phases in different regions will make it possible to focus actions in specific places and times target and redirect limited supplies to where they are most needed, and learn from experience as the situation progresses.

2) *Make millions of diagnostic tests available.* If millions of these tests are performed within two weeks, it will be possible to identify and trace the infected people and isolate them preventively; this was the key to the good results obtained in South Korea. Without diagnostic tests, the extent of the outbreak cannot be traced, so research laboratories and test collection and analysis centers need to be mobilized across the country to better screen the population.

3) *Supply health workers with sufficient personal protective equipment and provide hospitals with the necessary equipment to cope with the massive increase in critically ill patients.*

4) *Differentiate the population into five groups and treat accordingly.* It is necessary to establish: 1) confirmed cases, 2) suspected (symptomatic) cases, 3) persons exposed to the virus, 4) persons who are not known to have been exposed or infected, and 5) persons who have recovered and are now immune. Regarding the first two groups, these people should be separated from the general population in facilities temporarily fit for this purpose (e.g., hotels, stadiums, etc.). In turn, patients in critical condition or at high risk should be hospitalized.

5) *Inspire and mobilize the public.* In this all-out battle, everyone has a role to play, and virtually everyone wants to play it. Everyone, without exception, must commit since we are all responsible for each other. We can all help reduce the risk of exposure and help friends and neighbors in these times of crisis.

6) *Learn while doing through real-time, fundamental research.* Clinicians and researchers require better predictors to determine which pre-existing conditions make patients with COVID-19 more likely to deteriorate or who may die from the disease. Decisions on public health actions and the restart of the economy must be guided by science because if we know for sure how many people have been infected and if they are now immune, we can determine whether it is safe for them to return to their jobs. If this science-driven approach is implemented, all types of businesses, including airlines and restaurants, can reopen, which in turn will allow us to resume our normal activities gradually.

In conclusion, not having lived through or contemplated the ravages of a health emergency such as the current pandemic is no reason to enter into despair and fear. Instead, it should strengthen and motivate us all to work together and bring out the best of humanity to overcome this situation.

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Rev. Fac. Med. 2020 Vol. 68 No. 1: 9-13

rfm
Revista *de la* Facultad *de* Medicina

ORIGINAL RESEARCH
DOI: http://dx.doi.org/10.15446/revfacmed.v68n1.71744
Received: 16/04/2018 **Accepted:** 05/06/2018

Differences in pain measurement between nurses and physicians in a teaching hospital

Diferencias en la medición del dolor entre enfermeros y médicos en un hospital universitario

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Abstract

Introduction: In clinical practice, the administration of opioid analgesics depends on pain intensity records from nurses because they are responsible for determining the severity of the patient's complaints; however, discrepancies regarding pain measurement are often observed between physicians and nurses, which can lead to an inadequate use of analgesics.
Objective: To carry out a comparison of pain intensity measurements made by staff physicians and nurses in a teaching hospital during the first 24 hours of hospital stay of patients with movement-related pain.
Methods and methods: Retrospective, cross-sectional study. Data were obtained from the pharmacy database and medical records (opioids prescribed for 1 month, pain intensity, and medication management). The medical records of 634 in patients who were prescribed at least 1 dose of an opioid analgesic were reviewed.
Results: The average pain score provided by physicians (5.4/10; SEM=0.17) was significantly higher than the average pain score reported by nurses (3.5/10; SEM=0.15) ($p<0.05$). The intra-class correlation coefficient was 0.371 (95%CI: 0.138-0.563), indicating poor agreement between measurements.
Conclusion: A poor agreement between pain measurements made by physicians and nurses during the first 24 hours of hospital stay was found. Bearing in mind that pain measurement is essential for achieving an appropriate treatment, the jointly provision of pain management education programs to doctors and nurses should be considered, so that they assess pain intensity similarly, thus improving the management of inpatients and their quality of life.
Keywords: Analgesics, Opioid; Prescriptions; Pain Management (MeSH).

Moyano-Acevedo JR, Molina-Arteta BM, Matute-Gonzales E, Camargo-Sánchez L. Differences in pain measurement between nurses and physicians in a teaching hospital. Rev. Fac. Med. 2020;68(1):9-13. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.71744.

Resumen

Introducción. En la práctica clínica, la administración de analgésicos opioides depende de los registros de intensidad de dolor realizados por los enfermeros, ya que estos son los responsables de determinar la intensidad de las quejas de los pacientes. Sin embargo, a menudo se observa que existen discrepancias entre médicos y enfermeros profesionales respecto a la medición del dolor, lo que puede llevar a un uso inadecuado de analgésicos.
Objetivo. Comparar las intensidades de dolor de pacientes con dolor asociado al movimiento y registradas por médicos y enfermeros de un hospital universitario durante las primeras 24 horas de hospitalización.
Materiales y métodos. Estudio retrospectivo de corte trasversal. La información se obtuvo de las historias clínicas y de la base de datos de la farmacia del hospital (opioides prescritos por 1 mes, intensidades de dolor y uso de medicamentos). Se revisaron las historias clínicas de 634 pacientes a los que se les recetó al menos 1 dosis de opioide durante su estancia hospitalaria.
Resultados. El puntaje promedio de dolor registrado en el grupo de médicos fue significativamente mayor (5.4/10, SEM=0.17) que el registrado en el grupo de enfermeros (3.5/10; SEM=0.15) ($p<0.05$). El coeficiente de correlación intra-clase fue 0.371 (IC95%: 0.138-0.563), lo que indica una pobre concordancia entre las mediciones de médicos y enfermeros.
Conclusiones. Se observó una pobre concordancia entre la medición del dolor realizada por los enfermeros y los médicos del hospital. Teniendo en cuenta que la medición del dolor es fundamental para lograr un tratamiento adecuado, debe considerarse ofrecer programas de educación en manejo del dolor a médicos y enfermeros de manera conjunta para que su medición sea uniforme, lo que mejorará el manejo de los pacientes hospitalizados y, por tanto, su calidad de vida.
Palabras clave: Analgésicos opioides; Prescripciones de medicamentos; Manejo del Dolor (DeCS).

Moyano-Acevedo JR, Molina-Arteta BM, Matute-Gonzales E, Camargo-Sánchez L. [Diferencias en la medición del dolor entre enfermeros y médicos en un hospital universitario]. Rev. Fac. Med. 2020;68(1):9-13. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.71744.

Introduction

Many barriers prevent proper pain management, including poor pain measurement from health care professionals.[1] However, most data show that assessing pain is imperative for achieving good outcomes[2,3] and that it is necessary for choosing a treatment and evaluating its efficacy in the clinical setting. In other words, an effective treatment depends on proper evaluation.

In routine clinical practice, inpatients are asked about the intensity of their pain upon admission, during their stay at least once a day, and upon discharge from their hospital stay; the nurse in charge carries out this process. Analgesics are prescribed after the treating physician measures pain. The multidisciplinary approach to patient care requires agreement between the measurements provided by both professionals. However, said measurements may be misleading if the people involved have different perceptions about pain intensity of the patient.

According to the relevant literature, training received by physicians and nurses in pain management is deficient.[4,5] Previous studies have shown that there are significant differences in pain intensity assessment between doctors and nurses, and that said differences may lead to inadequate treatments because the interventions, for example, increase or reduce dosages of analgesics often based on the pain reports obtained from the nursing records. It should be noted that pain is not always measured and that this lack of reporting may also result in inadequate treatments.[6]

Contemporary analgesia takes into account many aspects that can generate pain, but the most important analgesic goals are those associated with painful movement,[7] given that its inadequate management may result in late recovery of mobility or previous functional status.

The presence of diverse types of pain is still problematic for many people around the world. For example, several studies report that 75% of the patients feel moderate/extreme pain during the immediate post-surgical period.[8,9] In low and middle-income countries, the prevalence of unspecified chronic pain ranges from 13% to 49.4%.[10] In Colombia, according to the 2014 National Pain Survey, the intensity of chronic pain was severe in 41% of the respondents, and 30% of those suffering from chronic pain did not receive treatment for it.[11] Furthermore, chronic pain affects people of all ages, and there are even studies on this type of pain in adolescents.[12]

The objective of the present study was to carry out a comparison of pain intensity measurements made by staff physicians and nurses in a teaching hospital during the first 24 hours of hospital stay of patients with movement-related pain.

Materials and methods

This is a retrospective and cross-sectional study on the pain measurements reported by physicians and nurses over a one-month period in patients hospitalized in a university hospital that serves most medical and surgical specialties. According to a hospital policy, pain must be assessed during the hospital stay (admission and follow up). To this end, a form that includes the following opioid analgesics is used: hydromorphone, morphine, and tramadol; parenteral pethidine; transdermal and parenteral fentanyl; and oral codeine, hydrocodone, methadone, and oxycodone.

Routine treatment of pain in patients hospitalized in this teaching hospital includes multimodal analgesia based on non-steroidal anti-inflammatory drugs, paracetamol, and short-acting opioids through different routes of administration and based on the therapeutic guidelines considered as most appropriate for each patient. At the end of the first 24 hours of hospitalization, each patient is asked about their level of pain while performing physical activity or moving their bodies (sitting or walking after surgery for the first time or upon admission to the floor in the case of non-surgical patients), using a scale from 0 to 10, being zero absence of pain and 10 the worst imaginable pain. The staff doctor and the nurse manager record these reports independently.

For this study, data on socio-demographic characteristics, clinical diagnosis, prescriptions, prescriber, opioid analgesic, and pain (type, duration, and intensity as recorded by the staff physician or graduated nurse) were retrieved from the electronic database of the hospital pharmacy and from the patients' medical records. The quality of the information collected was assured by training the team responsible for this task by conducting a pilot study and by double-checking the information. In case of disagreement regarding the data collected, the researchers who reviewed the databases resolved them through consensus.

This retrospective study was conducted in a 190-bed teaching hospital. The study population consisted of 634 patients who were hospitalized for surgical and non-surgical treatment and who were prescribed at least 1 dose of opioid analgesic (codeine, hydrocodone, hydromorphone, fentanyl, methadone, morphine, oxycodone, pethidine, or tramadol). Patients who were not prescribed any of these opioids, as well as pediatric (younger than 18 years old) and obstetric patients, were excluded.

No experiments on human or animal subjects were performed. This study was approved by the institutional ethics committee through Minutes n° CCEI-1647-2011 (24/10/2011). Likewise, the principles of the Declaration of Helsinki[13] and the regulations of Resolution 8430 of 1993 for conducting health research in humans were followed.[14]

Statistical analysis

A descriptive analysis was conducted using measures of central location and dispersion for continuous variables, and the Student's t test was used to compare continuous variables. Mean, standard deviation (σ), and maximum and minimum values were calculated for quantitative variables. If variables were not distributed symmetrically, the median and interquartile ranges were calculated. Qualitative variables were expressed as absolute percentages and relative frequencies. The chi-square test was used to compare proportions and to estimate the intra-class correlation coefficient. Analyses were performed for a 2-sided type I error level of 0.05 using the statistical package R.

Results

As mentioned above, the study population consisted of 634 hospitalized patients, of which 387 (61.9%) were female. Regarding age ranges, 354(55.5%) were 18 to 50 years old, 169 (26.7%) 51-70, and 111 (17.%) were

older than 70 years old. The most frequent diagnoses were diseases of the musculoskeletal system (n=100), trauma in different body regions (n=94), non-specific systemic symptoms (n=8), digestive system disorders (n=70), genitourinary system diseases (n=57), and neoplasms (n=51).

Distribution of pain intensity measurements

Physicians recorded the pain intensity measurements on admission of 349 patients (55.1%), while nurses did so in 275 patients (43.4%). It should be noted that in 10 patients (1.5%) it was not possible to determine who did this assessment. It was found that, on average, physicians rated pain intensity significantly higher than nurses: the physicians' mean intensity was 5.45/10 (σ: 0.17) (95%CI: 5.13-5.78), while the nurses' mean pain intensity was 3.55/10 (σ: 0.15) (95%CI: 3.25-3.86). The intra-class correlation coefficient was 0.371 (95%CI: 0.138-0.563), indicating poor agreement between pain measurements made by physicians and nurses. Opioids were prescribed for the treatment of acute pain in 578 (91.1%) patients, chronic pain in 35 (5.5%), and cancer pain in 17 (2.7%). Finally, their prescription was not undetermined in 4 cases (0.6%).

Prevalence of pain

On a scale from 0 to 10, the scores of the 349 patients whose pain intensity was measured by doctors on admission were as follows: 73 (20.9%) reported a 0-2 score; 94 (26.9%), a 3-5 score; and 182, (52.15%) reported severe to unbearable pain (≥6) (Figure 1).

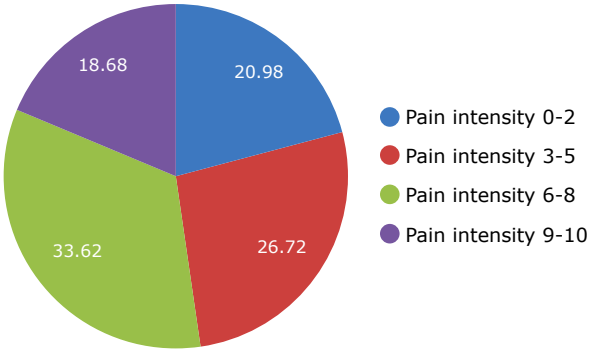

Figure 1. Distribution of first pain intensity (%) assessment by physicians in 349 patients.
Source: Own elaboration

On the other hand, the following scores were found for the 275 patients whose pain intensity measurement on admission was performed by nurses: 120 (43.6%) reported a score 0-2; 84, (30.5%) said their pain was 3-5; and 71 (25.7%) reported they were experiencing severe to unbearable pain (≥6) (Figure 2).

Opioids used for managing severe pain (visual analog scale score, >6/10) were tramadol (43.0%), morphine (35.8%), hydromorphone (12.6%), fentanyl (5.3%) and pethidine (3.3%).

According to the medical records, pain was classified based on the duration of the symptoms as acute (n=578), chronic (n=35), cancer pain (n=17), and undefined (n=4). Limbs were the body part in which pain was most frequently located (Figure 3).

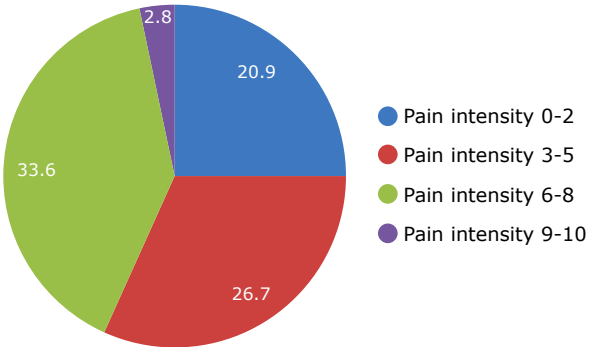

Figure 2. Distribution of first pain intensity (%) assessment by nurses in 275 patients.
Source: Own elaboration.

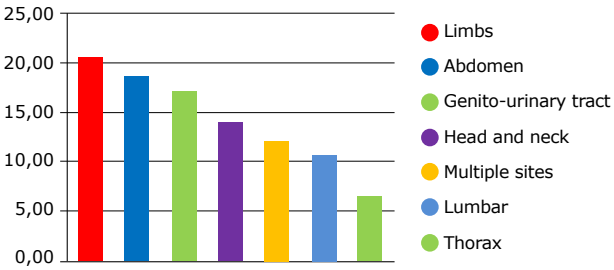

Figure 3. Pain location during the worst pain intensity according to the patients' medical records.
Source: Own elaboration

Discussion

This study reports several relevant findings. One of them is the disagreement in pain intensities reported by each professional group, which reaches a significant difference of 1.5/10 (σ: 0.2). This difference is particularly marked during the worst moment of pain, and is potentially linked to analgesics prescription: some patients may not receive analgesics because the nursing group does not deem them necessary, or may receive them because doctors consider that pain intensity ranges from severe to unbearable. These disagreements in the measurement of pain intensity have been previously documented and the result is poor pain management.[15]

Pain affected most patients admitted to the hospital, but pain relief in this setting was inadequate. In fact, in the sample studied here, 25% to 47% patients presented severe to unbearable pain during their hospital stay, that is, after undergoing triage. The most influential factor to this situation may be the lack of systematic pain measurement, which may require a personal or institutional improvement process, as previously reported in other scenarios.[16] In this research, pain intensity was reported in only 55.1% of the patients seen by doctors and in 43.4% of the patients seen by nurses. Background and personal conditions, in addition to pain education, make a difference in pain measurement and treatment.[17]

Another relevant finding was the need to improve pain control through a better evaluation of the intensity assessment made by physicians and nurses and better prescription practices of opioid analgesic treatment after assessing the reports of patient pain. Only just over half of patients had their pain intensity assessed by their physician and even less by nurses. It should be noted

that, in patients with severe pain, tramadol, an analgesic comparatively less potent than other opioids, was the drug most frequently prescribed, indicating that the intensity of pain was not a variable that defined the selection of the opioid to be prescribed.

In daily practice, nurses play an essential role in pain measurement because they tend to have more contact with patients than physicians. However, this study detected lack of measurements by nurses; both physicians and nurses should assess the pain of their patients. The lack of correlation between the rating of pain intensity by the nurses and physicians may reflect the lack of a systematic approach to pain measurement and suggests the need for unified training for both professional groups, which may lead to better accessibility to timely pain measurement and efficient analgesic administration. Effective physician-nurse communication may help build strong professional relationships, keep things working, and make people feel included.

In the hospital setting, measurement of pain intensity could give way to more effective treatments.[18] As mentioned before, pain documentation needs to be improved through institutional educational programs for nurses and doctors, accompanied by pain monitoring and treatment. Therefore, postoperative pain measurement and treatment remain a priority challenge for physicians and nurses.

In addition to pain measurement, this research focused on opioid analgesics because they are essential in the pharmacological management of severe pain. In fact, their use can be increased or reduced according to the intensity of pain. Although it may seem redundant, it is worth stressing that these drugs have an essential role in pain management, although opiophobia has been identified as a barrier to proper pain control.

Face-to-face education, as well as other educational initiatives,[19] can modify professional behavior[20] and improve the process of drug prescription for patients with severe pain and their adherence to management guidelines, while preventing abuse and drug addiction.[21] The results of this study describe the patterns of prescription and this knowledge may encourage hospitals to provide prescribers with friendly face-to-face education as a first step to achieve a similar assessment of pain intensity by physicians and nurses.

Conclusion

Bearing in mind that pain measurement is essential for providing an appropriate treatment, the jointly provision of pain management education training programs for both doctors and nurses should be considered, so that they assess pain intensity similarly, thus improving the management of inpatients and their quality of life.

Conflicts of interest

None stated by the authors.

Funding

None stated by the authors.

Acknowledgments

None stated by the authors.

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rfm
Revista *de la* Facultad *de* Medicina

ORIGINAL RESEARCH
DOI: http://dx.doi.org/10.15446/revfacmed.v68n1.73180
Received: 28/06/2018 **Accepted:** 03/11/2018

Systematic review and comparative analysis of pediatric nutrition screening tools validated in Europe and Canada

Revisión sistemática y análisis comparativo de las herramientas de tamizaje nutricional en pediatría validadas en Europa y Canadá

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Abstract

Introduction: Nutritional screening is a useful tool for determining the risk of hospital malnutrition; therefore, reviewing the guidelines on its use in the pediatric population is of great importance.
Objective: To provide recommendations on the use of nutrition screening tools validated in Canada and Europe in the Colombian pediatric population.
Materials and method: A systematic review was conducted using the PRISMA methodology. The quality of the evidence found in the review was assessed using the U.S. Preventive Services Task Force (USPSTF) tool, which was established by the Canadian Task Force on the Periodic Health Examination for assessing preventive actions.
Results: Fifteen studies were included in the review as they met the inclusion criteria. In addition, 7 nutrition screening tools were identified (PYMS, iPYMS, PeDiSMART, PNR, STAMP, PMST and STRONGkids). According to guidelines of the European Society for Clinical Nutrition and Metabolism, the PYMS, iPYMS and STRONGkids tools simultaneously assess prognostic variables such as current nutritional status, stability, expected improvement or worsening of the condition, and the influence of the disease process in nutritional deterioration. Regarding concurrent validity, data analysis shows that PYMS, iPYMS and PMST have sensitivities >85%, and that PYMS has a specificity >85%. In terms of reproducibility, PEDISMART, STRONGkids, STAMP and PYMS have an acceptable interobserver agreement (k>0.41).
Conclusion: Based on the evidence found, which was analyzed in terms of prognostic variables, concurrent validity and reproducibility, the use of the PYMS tool in the clinical practice is suggested. In contrast, hospitals must assess the applicability of the STAMP and iPYMS tools.
Keywords: Review; Mass Screening; Malnutrition; Pediatrics; Hospitals (MeSH).

Vásquez-Cárdenas L, Pinzón-Espitia OL. Systematic review and comparative analysis of pediatric nutrition screening tools validated in Europe and Canada. Rev. Fac. Med. 2020;68(1): 14-23. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.73180.

Resumen

Introducción. El tamizaje nutricional es una herramienta efectiva que permite establecer el riesgo de desnutrición hospitalaria, por consiguiente es importante revisar las directrices respecto a su uso en pediatría.
Objetivo. Ofrecer recomendaciones sobre el uso de las herramientas de tamizaje nutricional validadas en Canadá y Europa en población colombiana.
Materiales y métodos. Se realizó una revisión sistemática siguiendo la metodología PRISMA. Para la evaluación de la calidad de la evidencia se utilizó la herramienta U.S Preventive Services Task Force, formulada para medir acciones preventivas por la Canadian Task Force on the Periodic Health Examination.
Resultados. Se incluyeron 15 estudios que cumplían los criterios de selección y se identificaron 7 herramientas (PYMS, iPYMS, PeDiSMART, PNR, STAMP, PMST y STRONGkids). Según los lineamientos de la Sociedad Europea de Nutrición Clínica y Metabolismo, la PYMS, la iPYMS y la STRONGkids evalúan simultáneamente variables pronósticas como estado nutricional actual, estabilidad, progresión esperada e influencia de la enfermedad. En cuanto a validez concurrente, el análisis de datos muestra que la PYMS, la iPYMS y la PMST tienen sensibilidades >85% y que la PYMS tiene especificidad >85%. Respecto a reproducibilidad, la PEDISMART, la STRONGkids, la STAMP y la PYMS tienen una concordancia inter-observadores aceptable (k>0.41).
Conclusión. Según la evidencia analizada en términos de variables pronósticas, validez concurrente y reproducibilidad, se sugiere el empleo en la práctica clínica de la herramienta PYMS, mientras que para el uso de la STAMP y la iPYMS las instituciones deben evaluar su aplicabilidad.
Palabras clave: Revisión; Tamizaje masivo; Desnutrición; Pediatría; Medicina hospitalar (DeCS).

Vásquez-Cárdenas L, Pinzón-Espitia OL. [Revisión sistemática y análisis comparativo de las herramientas de tamizaje nutricional en pediatría validadas en Europa y Canadá]. Rev. Fac. Med. 2020;68(1): 14-23. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.73180.

Introduction

In Colombia, the Ministry of Health has acknowledged, on the one hand, the impact that malnutrition has on health care and, on the other, the usefulness of nutritional screening to prevent and reduce the prevalence of malnutrition in hospitals.[1]

The American Dietetic Association defines nutritional screening as the "process of identifying characteristics known to be associated with nutrition problems. Its purpose is to pinpoint individuals who are malnourished or at nutritional risk."[2, p1] With this in mind, screening is considered as an indicator of quality of healthcare services in the hospital setting.[3,4] However, nutritional screening is not routinely applied in pediatric hospitals since there is no accepted screening tool for these patients, leading to an underestimation of hospital malnutrition.[5,6] Currently, malnutrition rates are still considerable in Europe and Canada, as well as in Colombia, with a prevalence in pediatric populations between 7% and 16.6% for acute malnutrition, and 2.5% and 22.4% for chronic malnutrition.[7-12]

The American Society for Parenteral and Enteral Nutrition defines malnutrition in pediatrics as "an imbalance between nutrient requirements and intake, resulting in cumulative deficits of energy, protein, or micronutrients that may negatively affect growth, development, and other relevant outcomes".[13, p19] It should be noted that while malnutrition harms hospitalized patients of all ages,[14] children are at greater risk[13] since it is associated with inadequate growth and development, poor school performance and possibly having long-lasting impacts in adulthood.[15]

Colombia currently has evidence of the need to make recommendations on tools that allow, first, to identify pediatric patients with malnutrition or at risk of malnutrition and, second, to do nutritional screening.[5] All this becomes relevant taking into account that children are a population that is vulnerable to hospital malnutrition due to their physiological characteristics since they have greater energy requirements due to other processes such as growth, development and the severity of diseases that require hospital admission (acute diarrhea, primary malnutrition, celiac disease, obesity, dyslipidemias, among others).[16,17] Therefore, this research work presents a literature review and comparative analysis of nutritional screening tools used in pediatrics and validated in Europe and Canada to provide a set of guidelines and recommendations to expand their use in Colombian institutions. It also seeks to improve, in the future, healthcare services and manage the prevalence of malnutrition in pediatric hospitals.

In summary, this review aims to find whether the institutional use of nutritional screening tools in pediatrics allows the timely identification of patients with malnutrition or at risk of malnutrition, as well as the timely referral of patients to nutritional therapy.

Materials and methods

The present investigation followed the PRISMA (Preferred Reporting Items for Sistematic Reviews and Meta-analyses) statement, which provides guidelines for conducting systematic reviews and meta-analyses of studies that evaluate health interventions in biomedical sciences.[18]

The PICO procedure (patient or problem, intervention, comparison and outcomes) was used to define the research question,[19] and also allowed defining the criteria for the selection of the studies.

The following types of articles were excluded: 1) those without available full texts; 2) those that were not original researches, that is, letters to the editor, book chapters, systematic reviews, case reports and position papers, and 3) those that evaluated only excess weight and included extensive nutritional assessment parameters (such as biochemical analysis), or that did not employ a method of comparison. In view of the above, and as shown in Figure 1, all original studies in English, French or Spanish published between 2002 and 2017 that validated a nutritional screening tool in Europe or Canada and had a method of comparison were included. The search was carried out in May 2017 on the PubMed, Cochrane, Embase, Global Health and Dissertations & Theses Global databases using the search equation (Nutritional Screening) AND (paediatric OR child) AND malnutrition AND hospital.

The checklist of items from the Cochrane Handbook was used for data extraction.[20] First, the screening tools found were analyzed according to the guidelines of the European Society for Clinical Nutrition and Metabolism (ESPEN) 2002,[21] which state that the use of these tools should consider 4 variables that impact nutritional risk: current nutritional status, stability, expected progression and influence of the disease. Moreover, it clarifies that the first 3 variables must be part of all the instruments, while the fourth is included depending on the relevance defined by each institution; each one must be assigned a score in order to quantify the degree of risk, thus allowing the choice of the appropriate path to follow according to the categories established in the care protocols.[21,22]

Regarding methodology, it has been established that the usefulness of screening tools is usually based on the aspects of predictive validity, concurrent validity, reproducibility and practicality.[23] For this reason, in this review the statistics issued by the studies that were carried out to validate the screening tools were analyzed; the selected parameters were sensitivity and specificity, contained in concurrent validity and reproducibility, respectively. Concurrent sensitivity was understood as the proportion of individuals at risk of malnutrition correctly identified by the screening tests and concurrent specificity was understood as the proportion of individuals not at risk correctly identified by the nutritional screening tool. Sensitivity and specificity, as well as reproducibility, corresponded to data calculated in each study considering the selected method of comparison.

Finally, the quality of evidence was assessed following the recommendations of the U.S Preventive Services Task Force, a tool developed by the Canadian Task Force on the Periodic Health Examination to evaluate preventive measures and to help researchers extract information from clinical studies in the form of evidence-based medicine recommendations.[24,25] To achieve this, the design of the studies analyzed was considered first in order to establish the level of certainty of each study; then, the nutritional screening tools with the same level of certainty were grouped and the degrees of the recommendations were established according to the level of certainty assigned and the net benefit (greater number of benefits over the number of harms) of their use (Table 1).

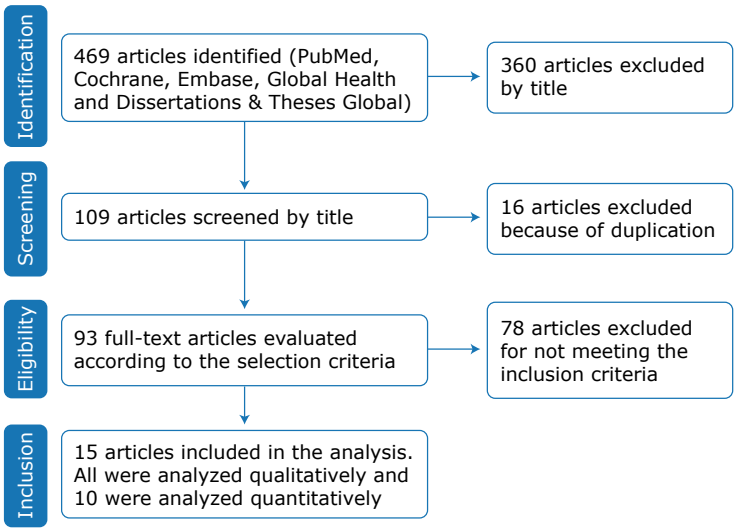

Figure 1. Flowchart of the selected articles.
Source: Own elaboration based on Hutton *et al.*[18]

Table 1. Degrees of recommendation according to level of certainty and net benefit.

Evidence	Net benefit of nutritional screening *				
Quality	Considerable	Moderate	Small	Null or negative	Insufficient evidence
Good	A	B	C	D	I
Moderate	B	B	C	D	I
Low	E	E	E	E	I

Level of recommendation	Suggestions for practice
A	To offer or provide this service.
B	
C	To offer or provide this service to selected patients based on individual circumstances.
D	To discourage the use of this service.
I	If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

* The net benefit of screening was measured in terms of concurrent validity (sensitivity) and reproducibility. The net benefit was deemed considerable when sensitivity values were >85%, moderate >75% and low >50%. The net benefit was deemed considerable with a value k>0.81, moderate with k>0.61 and low with k>0.41.
Source: Own elaboration based on Primo.[24]

Results

Search results

The search yielded 469 articles in the PubMed, Cochrane/EBM Reviews, Embase, Global Health and Dissertations & Theses Global databases. 360 studies were excluded according to their title, 16 because they were duplicated and 78 for not meeting the selection criteria —32 were conducted outside Canada or Europe, 27 did not evaluate any screening tool, 11 were secondary studies (reviews), 4 included adult patients and 4 were incomplete or in another language. The final sample consisted of 15 studies.

Table 2 compiles and integrates the information from the 15 studies included in the literature review according to the PICO characteristics of the research.[26-40] It should be noted that, although the search included original studies published between 2002 and 2017, the selected articles were released between 2010 and 2017 (67% of them were published between 2012 and 2017), thus indicating that the results are up-to-date. All studies were developed in European countries.

Table 2. PICO characteristics of the included studies.

Study	Country	n	Population (age)	Screening tool	Comparative	Conclusions
Thomas *et al.*[26] 2016	United Kingdom	300	0 to 17.6 years	STAMP, PMST, PYMS	WHO growth charts	The tools have low sensitivity, variable specificity and a positive predictive value <50%. They are difficult to interpret in an acute context.
Mărginean *et al.*[27] 2014	Romania	271	1 to 17 years	STRONGkids	WHO growth charts	The STRONGkids tool, modified by implementing serum protein levels, performed well in predicting malnutrition in a pediatric population treated at a hospital of Romania.
Karagiozoglou-Lampoudi *et al.*[28] 2014	Greece	Two cohorts: 161 y 500	1 month to 17 years	PeDiSMART, STRONGkids, STAMP, PYMS	WHO growth charts	PeDiSMART is applicable to all hospitalized patients of all ages, classified by bioelectric impedance and with electronic medical records. It also improves the effectiveness and reproducibility of the identification of pediatric patients with risk factors for malnutrition.
Spagnuolo *et al.*[29] 2013	Italy	144	1 to 18 years old	STRONGkids	Italynas growth charts	It is an easy to administer and highly sensitive tool, but it is not very specific. It can be used as a preliminary screening tool together with other clinical data to reliably predict the risk of malnutrition.
Huysentruyt *et al.*[30] 2013	Belgium	Two cohorts: 29 y 368	0 to 16 years	STRONGkids	WHO growth charts	This is a quick and easy to use screening tool with intra- and inter-observer reliability. It has good correlation with the weight-for-height z-score, but not with the height-for-age z-score.
Lama-More *et al.*[31] 2012	Spain	250	1 month to 18 years	STAMP y STAMPm	Charts from the Research Institute for Growth and Development in Spain	STAMP is a simple and useful tool for nutritional screening that would avoid the need to assess all patients on admission to detect those who are at risk.
Sikorová & Zavřelová[32] 2012	Czech Republic	130	2 months to 18 years	PNR, STAMP	Comparison between both tools	STAMP is a simple tool for early detection of risk of malnutrition that predicts better medium and high nutritional risk.
McCarthy *et al.*[33] 2012	United Kingdom	Two cohorts: 122 y 238	2 to 17 years	STAMP	Complete evaluation by professional	It is a quick and easy to use tool that does not require any previous knowledge, as only minimal training is necessary to implement it. It is reliable, compared to the results of a full nutritional assessment, to identify children at risk of malnutrition upon hospital admission.
Gerasimidis *et al.*[34] 2011	United Kingdom	1571	1 to 16 years	PYMS	Full professional evaluation	Regular clinical use of this tool seems to be feasible as it has outstanding performance in the identification of patients at risk of malnutrition and does not require a significant increase in staff or workload.
Gerasimidis *et al.*[35] 2010	United Kingdom	247	1 to 16 years	PYMS, STAMP	Full professional evaluation	PYMS is an acceptable screening tool to identify children at risk of malnutrition without producing an uncontrollable number of false positive cases.
Hulst *et al.*[36] 2010	Netherlands	424	1 to 18 years	STRONGkids	WHO growth charts	A significant relationship was found between having a 'high risk' score and a long hospital stay.
Galera-Martínez *et al.*[37] 2017	Spain	223	1 to 18 years	STAMP, STRONGkids	Growth charts for the Spanish population	Both tools are suitable for nutritional screening in settings where examiners have no previous experience in the field.

Table 2. PICO characteristics of the included studies. (Continued)

Study	Country	n	Population (age)	Screening tool	Comparative	Conclusions
Chourdakis *et al.*[38] 2016	12 European countries	2 567	1 month to 18 years	PYMS, STAMP, STRONGkids	WHO growth charts	The data obtained do not allow recommending the use of any of these screening tools for clinical practice.
Ling *et al.*[39] 2011	United Kingdom	43	1 month to 18 years	STAMP, STRONGkids	WHO growth charts	Based on the results, it could be said that STAMP tends to over-diagnose nutritional risk in hospitalized children, while STRONGkids allows a more precise identification.
Milani[40] 2016	United Kingdom	Two cohorts: 210 y 187	0 and 12 months	iPYMS, STRONGkids	Subjective Global Nutritional Assessment	The diagnostic performance of iPYMS in both cohorts improved after raising the high-risk threshold from ≥2 to ≥3. iPYMS could work well in countries such as Iran, which have a history of high prevalence of malnutrition, and could be used by health staff to identify malnourished children.

STAMP: Screening Tool for the Assessment of Malnutrition in Paediatrics; STAMPm adaptation of the original STAMP tool, in which the UK growth charts were replaced by the Spanish growth charts; PMST: Paediatric Malnutrition Screening Tool; PYMS: Paediatric Yorkhill Malnutrition Screening; WHO: World Health Organization; STRONGkids: Screening Tool for Risk of Impaired Nutritional Status and Growth; PeDiSMART: Pediatric Digital Scaled Malnutrition Risk Screening Tool; PNR: Paediatric Nutritional Risk; iPYMS: Infant Paediatric Yorkhill Malnutrition Score; TPH: tertiary pediatric hospital; DGH: district general hospital.
Source: Own elaboration.

Description of the identified screening tools

Seven tools have been validated in European countries for the identification of pediatric patients at nutritional risk: Paediatric Yorkhill Malnutrition Screening (PYMS), Infant Paediatric Yorkhill Malnutrition Score (iPYMS), Pediatric Digital Scaled Malnutrition Risk Screening Tool (PeDiSMART), Paediatric Nutritional Risk (PNR), Screening Tool for the Assessment of Malnutrition in Paediatrics (STAMP), Paediatric Malnutrition Screening Tool (PMST) and Screening Tool for Risk of Impaired Nutritional Status and Growth (STRONGkids). All were designed to be used during hospital admission and, except for PNR, have the possibility of being used again after the first week of hospital stay.

Table 3 shows a comparison between the different nutritional screening tools, taking into account the four variables that must be incorporated to correctly identify the nutritional risk of hospitalized patients.[21,22]

Table 3. Comparison of screening tools according to the European Society for Clinical Nutrition and Metabolism guidelines.

Tool	Current nutritional status	Weight loss	Low intake	Severity of the disease	Others
STAMP	X		X	X	List of diseases
PMST	X		X	X	List of diseases
PYMS	X	X	X	X	
iPYMS	X	X	X	X	
STRONGkids	X	X	X	X	Symptoms and List of diseases
PNR			X	X	List of diseases
PeDiSMART	X		X	X	Symptoms

STAMP: Screening Tool for the Assessment of Malnutrition in Paediatrics; PMST: Paediatric Malnutrition Screening Tool; PYMS: Paediatric Yorkhill Malnutrition Screening; iPYMS: Infant Paediatric Yorkhill Malnutrition Score; STRONGkids: Screening Tool for Risk of Impaired Nutritional Status and Growth; PNR: Paediatric Nutritional Risk; PeDiSMART: Pediatric Digital Scaled Malnutrition Risk Screening Tool.
Source: Own elaboration based on Kondrup J *et al.*[21]

Concurrent validity and reproducibility

Considering the statistical data extracted from the included studies, concurrent validity and reproducibility were the basis of the analysis of the nutritional screening tools validity since they are commonly found in most studies. This allows comparing most of the identified nutritional screening instruments.

Table 4 presents the included studies that evaluate the concurrent validity of 5 pediatric nutritional screening tools (STAMP, PMST, PYMS, iPYMS and STRONGkids). In turn, Table 5 depicts the studies that included results on concordance among observers where it was considered sufficient for Kappa values >0.41.[41]

Table 4. Concurrent validity (sensitivity and specificity) of the screening tools.

Study	Sample	Screening tool	Method of comparison *	Concurrent sensitivity	Concurrent Specificity
Thomas *et al.*[26] 2016	300	STAMP	WHO growth charts	63.2%	36.3%
		PMST		94.4%	29.0%
		PYMS		26.1%	67.1%
Spagnuolo *et al.*[29] 2013	144	STRONGkids	Italian growth charts	71.0%	53.0%
Huysentruyt *et al.*[30] 2013	Dos cohortes: 29 y 368	STRONGkids	WHO growth charts	71.9%	49.1%
		STRONGkids		69.0%	48.4%
Lama-More *et al.*[31] 2012	250	STAMP	Spanish growth charts	90.0%	59.5%
McCarthy *et al.*[33] 2012	122	STAMP	Full nutritional assessment	77.0%	91.0%
	238	STAMP		70.0%	91.0%
Gerasimidis *et al.*[35] 2010	247	PYMS	Full nutritional assessment	85.0%	92.0%
		STAMP		81.0%	78.0%
Chourdakis *et al.*[38] 2016	2567	PYMS	WHO growth charts	92.7%	79.1%
		STAMP		76.3%	80.2%
		STRONGkids		45.0%	92.8%
Milani[40] 2016	210	iPYMS	Subjective pediatric global nutritional assessment	92.0%	76.0%
		STRONGkids		50.0%	94.0%
	187	iPYMS		98.0%	69.0%
		STRONGkids		44.0%	98.0%

STAMP: Screening Tool for the Assessment of Malnutrition in Paediatrics; PMST: Paediatric Malnutrition Screening Tool; PYMS: Paediatric Yorkhill Malnutrition Screening; STRONGkids: Screening Tool for Risk of Impaired Nutritional Status and Growth; iPYMS: Infant Paediatric Yorkhill Malnutrition Score; WHO: World Health Organization.
* Concurrent validity (sensitivity and specificity) was estimated and extracted from the primary studies.
Source: Own elaboration.

Table 5. Concordance (Kappa) between observers of the screening tools.

Reference	Sample	Screening tool	Observers	Kappa
Karagiozoglou-Lampoudi *et al.*[28] 2015	57	PeDiSMART	2 dieticians independent to the study	0.47
Huysentruyt *et al.*[30] 2013	368	STRONGkids	Nurses	0.61
Lama-More *et al.*[31] 2012	250	STAMP	2 nutrition specialists	0.85
McCarthy *et al.*[33] 2012	25	STAMP	Between clinical staff and a dietitian	0.88
	48	STAMP		0.92
Gerasimidis *et al.*[35] 2010	247	PYMS	Between nursing staff and 2 nutritionists	0.53
Galera-Martínez *et al.*[37] 2017	223	STAMP	Experts specialized in pediatric nutrition (physicians or dietitians) and non-specialized clinical staff	0.74
		STRONGkids		0.72

PeDiSMART: Pediatric Digital Scaled Malnutrition Risk Screening Tool; STRONGkids: Screening Tool for Risk of Impaired Nutritional Status and Growth; STAMP: Screening Tool for the Assessment of Malnutrition in Paediatrics; PYMS: Paediatric Yorkhill Malnutrition Screening.
Source: Own elaboration.

Levels of certainty of the studies

The level of certainty was estimated for 67% of the studies, as they included results assessing concurrent validity (in terms of sensitivity and specificity) and reproducibility (in terms of inter-observer agreement). The remaining 33% yielded other results such as predictive validity and intra-rater reliability, which were not analyzed because of the total number of articles with data, time and resources.[27,32,34,36,39]

Among the 10 studies for which the level of certainty was calculated, the Chourdakis *et al.*[38] study had the highest level of certainty, mainly because it was carried out in 12 countries throughout Europe with a sample of 2 567 patients and because the results were consistent. In contrast, the level of certainty of the study

by Thomas *et al.*,[26] which was carried out in the United Kingdom, was considered low, particularly because it was a unicenter research with convenience sampling and inconsistent results. The remaining 8 studies were classified at a moderate level since they were multicenter studies, with randomized, systematized or consecutive sampling and generally consistent results that allow, to some extent, the generalization of findings to clinical practice.[28-31,33,35,38,40]

Recommendations for the use of nutritional screening tools in pediatrics

Of the seven tools identified in this systematic review, quality assessment was only possible in six of them, namely, PYMS, iPYMS, STAMP, PMST, STRONGkids and PEDISMART. A complete quality analysis —i.e. concurrent validity and reproducibility— was conducted only for the STAMP, PYMS and STRONGkids, while in the case of iPYMS and PMST only concurrent validity was evaluated, and for the PEDISMART tool, only reproducibility was assessed.

The partial evaluation of the PEDISMART, PNR and iPYMS tools does not mean that they are not useful in other contexts or situations; it means that there is no information on the characteristics that were considered of greater relevance in those reviews. Table 6 presents recommendations for the use of validated nutritional screening tools in European children according to concurrent validity and reproducibility characteristics.

Table 6. Recommendation for the use of screening tools.

Tool	Features	Level	Suggestions
PYMS	Concurrent validity[35,38]	A B	Its use is recommended considering that there is enough evidence that PYMS is a tool with good concurrent validity; however, it should be noted that its reproducibility, according to the evidence, may be limited.
	Reproducibility[35]	C	
STAMP	Concurrent validity[26,31,33,35,39]	B I	Evidence shows that STAMP has moderate to substantial concurrent validity and reproducibility, so its use is recommended.
	Reproducibility[31,33,37]	B	
iPYMS	Concurrent validity[40]	B	iPYMS is recommended for screening, as it has moderate concurrent validity. No data on reproducibility are available.
STRONGkids	Concurrent validity[29,30,38,40]	C I	The STRONGkids tool can be used in settings where patients and the institution are likely to benefit. Even though its reproducibility is moderate, its concurrent validity is low.
	Reproducibility[37]	B	
PeDiSMART	Reproducibility[28]	C	Regarding this tool, evidence is limited, but it can be used in areas where its use is justified.
PMST	Concurrent validity[26]	I	The current evidence is insufficient to evaluate its usefulness.
Level of recommendation	Suggestions for practice		
A	To offer or provide this service.		
B			
C	To offer or provide this service to selected patients according to individual circumstances.		
D	To discourage the use of this service.		
I	If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.		

PYMS: Paediatric Yorkhill Malnutrition Screening; STAMP: Screening Tool for the Assessment of Malnutrition in Paediatrics; iPYMS: Infant Paediatric Yorkhill Malnutrition Score; STRONGkids: Screening Tool for Risk of Impaired Nutritional Status and Growth; PeDiSMART: Pediatric Digital Scaled Malnutrition Risk Screening Tool; PMST: Paediatric Malnutrition Screening Tool. Source: Own elaboration based on the information of the U.S. Preventive Services Task Force.[25]

Discussion

Description of the identified screening tools

Based on the ESPEN guidelines described in Table 3, only the PYMS tool for screening patients between 1 and 16 years of age hospitalized in floors and surgical areas, the iPYMS for the same type of population but under 2 years of age, and the STRONGkids for the same type of population with ages between 1 month and 18 years of age, evaluate all the variables that are considered to have a nutritional impact. To this end, they assess current nutritional status, weight loss, reduced intake and severity of disease (Table 2).[21]

Thus, the PYMS, iPYMS and STRONGkids tools can be considered as the most suitable tools for nutritional screening. However, these are not the only criteria that must be considered to state that a tool is appropriate since any screening tool can be used to identify children with or at risk of malnutrition, as long as the results translate into early intervention and improved clinical outcomes.

Concurrent validity and reproducibility

Nutritional screening is a tool that is classified into the same category of diagnostic tests, which means that it is an instrument that allows obtaining additional information about a patient in order to adequately define the care plan to be followed.[42] Moreover, the use of nutritional screening tools is relevant for care centers since their routine use allows the optimization of economic and human resources and the reduction of costs derived from hospital malnutrition.[21,43] In this sense, and given that a highly sensitive tool is designed to correctly detect a greater proportion of patients at real nutritional risk —i.e. those who require greater monitoring of their nutritional status—, the most important statistic is sensitivity.[44]

Although the screening tools were validated using different reference methods (Table 2), if sensitivity (ability to detect true positives) >85% is considered as acceptable, the PYMS, iPYMS and PMST tools may be the best options for screening, followed by STAMP with adequate but less consistent sensitivity according to the studies analyzed. However, if good specificity (ability to detect true negatives) is also considered as a desirable characteristic, only the PYMS tool meets these two characteristics of concurrent validity.[35,39]

It should be noted that these results are not consistent across studies,[26] partly because sensitivity and specificity tend to be inversely related.[45] In this regard, the meta-analysis by Huysentruyt *et al.,*[46] by including gold standards to validate the tools, shows that there is a marked variation among the studies included. Consequently, in order to have more consistent results, it is necessary to establish a gold standard to assess sensitivity and specificity and to obtain results with greater comparability between studies.

Reproducibility was also assessed, as good agreement between raters in a nutritional screening tool is desirable. The results showed that the PeDiSMART, STRONGkids, STAMP, and PYMS tools have acceptable inter-observer agreement when assessing reproducibility across a broad spectrum of health professionals (Table 5). This is relevant given that a good nutritional screening tool should require little training of clinical staff to complete the instrument and should be quick to use and interpret thanks to a simple scoring system.[23]

Recommendations for use

Table 6 presents recommendations for the use of the PYMS, STAMP, iPYMS, STRONGkids, PeDiSMART and PMST tools according to desirable characteristics such as concurrent validity and reproducibility. Nevertheless, it should be remembered that these are not the only characteristics to consider; ease of use, the time required, and predictive validity should also be considered,[23] although that was not the case of this paper due to the limited information available. Even so, it is expected that the results reported here will help health staff choose the best option for nutritional screening in pediatrics from the tools available for implementation in institutional protocols.

The present review is limited by geographical demarcation to only Canada and Europe, so this work should be complementary to other reviews carried out outside the proposed context.[22,47] Another limitation is that this study focuses on screening tools that determine the risk of malnutrition; however, these tools can be modified (especially the current nutritional status variable) to detect overweight, which can also have negative consequences in hospitalized children.

On the other hand, although the quality of the included studies was evaluated, bearing in mind that this review aims to summarize the available evidence, it is not exempt from the systematic errors of the designs of the original studies; therefore, the work was carried out according to the PRISMA statement to include all the available studies and minimize selection bias.[48,49] Finally, due to the lack of international consensus on the definition of malnutrition, there is no standard reference for assessing the validity of nutritional screening tools with the same method; this makes the results of the tools closely linked to the classification of malnutrition in each study. Therefore, once a universal diagnosis for malnutrition is established, it is expected that tool validation studies will yield more consistent results.

Conclusions

Currently, in Colombia there are no recommendations on the use of nutritional screening tools in pediatrics due to the lack of consensus on which is the most appropriate tool to be used in this population, especially considering the difficulties for their possible validation and comparison. The studies included here demonstrated that, with respect to concurrent validity and reproducibility, the PYMS, iPYMS and STAMP tools offer greater certainty and net benefit; however, based on the findings of this review, PYMS could be used in clinical practice, while each institution should make an assessment to consider the use of STAMP and iPYMS.

Conflicts of interest

None stated by the authors.

Funding

None stated by the authors.

Acknowledgements

None stated by the authors.

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rfm
Revista *de la* Facultad *de* Medicina

ORIGINAL RESEARCH
DOI: http://dx.doi.org/10.15446/revfacmed.v68n1.74383
Received: 21/08/2018 **Accepted:** 21/11/2018

Use of non-pharmacological interventions during urinary catheter insertion for reducing urinary tract infections in non-immunocompromised adults. A systematic review

Intervenciones no farmacológicas durante la inserción de un catéter urinario permanente para reducir las infecciones en adultos inmunocompetentes. Revisión sistemática

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Abstract

Introduction: Catheter-associated urinary tract infections (CAUTI) account for up to 30% of hospital -acquired infections. In this regard, several studies have reported the use of non-pharmacological interventions during urinary catheter insertion aimed at reducing the occurrence rate of CAUTI.
Objective: To assess the safety and effectiveness of non-pharmacological interventions during urinary catheter insertion aimed at reducing the risk of contracting infections in non-immunocompromised adults.
Materials and methods: A literature review was conducted in the MEDLINE, Embase, and LILACS databases. Only randomized clinical trials comparing the use of non-pharmacological interventions to placebos, pharmacological interventions, or no intervention during catheter insertion were included.
Results: Eight studies were retrieved (8 718 participants). Based on the evidence found in the review (low-quality and very low-quality evidence according to the GRADE system), using non-pharmacological interventions reduces the frequency of asymptomatic bacteriuria episodes (RR 0.67, 95%CI 0.48-0.94; 7 studies) or mild adverse events (RR 0.84, 95%CI 0.74-0.96; 2 studies), but does not reduce the occurrence rate of symptomatic urinary tract infections (RR 0.90, 95%CI 0.61-1.35; 4 studies) or improves quality-of-life scores (MD –0.01 EQ-5D scale; 95%CI (-0.03)-(0.01), 1 study).
Conclusion: The use of non-pharmacological interventions during urinary catheter insertion does not pose any risk at all. Instead, it could help reduce the occurrence rate of infections associated with this procedure, such as asymptomatic bacteriuria and mild adverse events. However, there is very little evidence (in fact, low and very low-quality evidence) to make conclusions on the effectiveness of these interventions.
Keywords: Early Medical Intervention; Urinary Catheterization; Urinary Tract Infections; Cross Infection (MeSH).

Sáenz-Montoya X, Grillo-Ardila CF, Amaya-Guio J, Muñoz-Vesga J. Use of non-pharmacological interventions during urinary catheter insertion for reducing urinary tract infections in non-immunocompromised adults. A systematic review. Rev. Fac. Med. 2020;68(1):24-33. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.74383.

Resumen

Introducción. La infección asociada al catéter urinario es responsable de hasta un 30% de las infecciones nosocomiales. Al respecto, se ha descrito el uso de intervenciones no farmacológicas durante la inserción del catéter urinario para reducir la frecuencia de infecciones asociadas.
Objetivo. Evaluar la seguridad y la efectividad de intervenciones no farmacológicas durante la inserción del catéter urinario diseñadas para reducir el riesgo de infección en adultos inmunocompetentes.
Materiales y métodos. Se realizó una búsqueda en las bases de datos MEDLINE, Embase y LILACS. Se incluyeron ensayos clínicos aleatorizados que compararan el uso de intervenciones no farmacológicas con el uso de placebos, el uso de intervenciones farmacológicas o la ausencia de intervención durante la inserción del catéter.
Resultados. Se encontraron ocho estudios (8 718 participantes). Con base en la evidencia encontrada (baja y muy baja calidad según la clasificación del sistema GRADE), el uso de intervenciones no farmacológica reduce la frecuencia de bacteriuria asintomática (RR 0.67; IC95%: 0.48-0.94; 7 estudios) o de eventos adversos menores (RR 0.84, IC95%: 0.74-0.96; 2 estudios), pero no disminuye la tasa de infecciones sintomáticas del tracto urinario (RR 0.90; IC95%: 0.61 a 1.35; 4 estudios), ni mejora las puntuaciones de calidad de vida (escala MD -0.01 EQ-5D, IC95%: (-0.03)-(0.01), 1 estudio).
Conclusión. El uso de intervenciones no farmacológicas durante la inserción del catéter urinario no supone riesgo alguno y sí podría ayudar a disminuir la frecuencia infecciones asociadas a este procedimiento, tales como la bacteriuria asintomática y eventos adversos menores; sin embargo, hay poca evidencia, y de baja o muy baja calidad, para llegar a conclusiones sobre su efectividad.
Palabras clave: Intervención médica temprana; Cateterismo urinario; Infecciones urinarias; Infección hospitalaria (DeCS).

Sáenz-Montoya X, Grillo-Ardila CF, Amaya-Guio J, Muñoz-Vesga J. [Intervenciones no farmacológicas durante la inserción de un catéter urinario permanente para reducir las infecciones en adultos inmunocompetentes. Revisión sistemática]. Rev. Fac. Med. 2020;68(1):24-33. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.74383.

Introduction

Catheterization is a common procedure that consists of the insertion of a latex, polyurethane, or silicone tube into the bladder to drain its contents.[1] Urinary catheters can be indwelling or placed intermittently depending on the indications and the patient's condition. Intermittent catheters are inserted every 6 to 8 hours,[2] while indwelling catheters are inserted for a period of time greater than 24 hours, and are usually connected to a collection bag.[3] Indwelling catheterization is typically used in patients with pathologies such as prostatic hyperplasia, neurogenic bladder, urinary retention, severe urinary incontinence, as well as critically ill patients[4] and those with pressure ulcers in the sacral region, or with contaminated perineal lesions associated with incontinence.[5]

Urinary catheterization is a minor procedure undertaken in up to 25% of all hospitalized patients.[6] It carries substantial risks and causes high morbidity and mortality secondary to bacteremia, as well as longer hospital stays and higher resource consumption.[7] Catheter-associated urinary tract infection (CAUTI) accounts for up to 30% of health-care associated infections.[7] In Latin America, CAUTI is the third leading cause of nosocomial infections and its incidence is estimated at 8.9 cases per 1 000 days of exposure to this device.[6] In Colombia, the estimated prevalence is 12% to 45%, which makes it one of the top five infections reported in the country.[6] In Bogotá, a prevalence of 16.1% was reported for the 2012-2013 period, with an incidence rate of 3.9 cases per 1 000 days of exposure.[6]

Since urinary catheterization carries substantial risks, multiple interventions have been described with the aim of reducing the occurrence of infectious processes. Non-pharmacological interventions include staff training in catheter insertion and care.[8] Access to guidelines and algorithms allows standardizing interventions that avoid variability among healthcare staff and guide the timely removal of unnecessary catheters.[7,9] Hand washing before and after catheter insertion and manipulation reduces non-saprophytic microflora without affecting the saprophytic microflora of the skin.[5,7] Using an aseptic technique, sterile equipment and supplies during the preparation of the catheter insertion area and during the insertion, using barrier measures such as sterile gowns and gloves;[10] and the use of antiseptics for cleaning the urinary meatus help reduce microbial load and the entrainment of microorganisms.[5,11]

In addition, the lubricant applied prior to insertion contributes to bladder neck relaxation, facilitating the passage of the catheter, and also prevents urethral trauma, false passages and pain.[10] Inserting a catheter of the smallest possible size can minimize urethral trauma and lead to a more effective drainage,[5,12] while using a closed drainage system makes it more difficult for microorganisms to colonize the urethral meatus intraluminally.[13]

Regarding pharmacological interventions, silicone catheters are recommended for patients requiring a long-term urinary catheter and in those with frequent obstruction of the device.[7] Antimicrobial-coated catheters are used in patients with a CAUTI that does not decrease with the application of primary strategies. Finally, the consumption of blueberries,[14] lactobacilli[15] and Chinese herbal medicines[14] has also been proposed to prevent urinary infections.

Since the use of catheters in clinical practice is heterogenous and considering the frequency of adverse events and the appearance of infections associated with their insertion and use, this systematic review seeks to assess the effects of non-pharmacological interventions aimed at reducing the probability of CAUTI in the adult population. This will help develop policies designed to standardize the care of adult patients with urinary catheterization.

Materials and methods

The report was developed following the recommendations suggested by the Cochrane Handbook (CHB)[16] and in accordance with the PRISMA statement.[17] Review methods were established before conducting the literature search, which is detailed at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017051553. Ethical approval was not required because this is a secondary study.

An attempt was made to identify as many relevant randomized controlled trials (RCTs) as possible, regardless of their language of publication. To this end, the Information Specialist of The Cochrane STI Group was contacted to conduct a complete search strategy, which was constructed using controlled vocabulary and text terms. The search was conducted in the MEDLINE, EMBASE, and LILACS databases. Grey literature was also consulted through the references listed in the included studies. The search was updated to September 30, 2016 (available at: https://www.crd.york.ac.uk/PROSPEROFILES/51553_STRATEGY_20161121.pdf) and citations were exported to EndNote version X6 (Thomson Reuters, New York, NY, USA). All published RCTs were included with no language restrictions.

The participants in the trials were non-immunocompromised men and non-pregnant women that required an indwelling urinary catheter as part of their inpatient or outpatient medical treatment. Indwelling urinary catheters are as those inserted for at least 24 hours in the urinary tract. The intervention of interest was the use of any non-pharmacological intervention during catheter insertion versus the use of placebo, or pharmacological interventions, or no intervention.

The primary outcomes were symptomatic urinary infection, time elapsed until the first episode of urinary infection, recurrent infection, bacteremia, asymptomatic bacteriuria, and major adverse effects associated with the intervention. The main secondary outcomes were satisfaction of participants, quality of life, mild adverse events, and cost-effectiveness of the intervention.

First, two authors (XSM and CFGA) selected the studies individually, and then, through consensus, they made the final selection of studies to be included in the systematic review. In addition, the other two authors (JAG and JLMV) assessed the risk of bias of the included RCTs using the tool suggested in the CHB:[16] sequence generation and allocation concealment,

blinding of participants, incomplete outcome data, selective reporting, and other risks of bias. Disagreement was resolved by consensus among all authors. All domains were assessed as low, high, or unclear risk of bias. The GRADE system was used for rating the quality of the evidence.

Results are presented as risk ratios (RR) with 95% confidence intervals (CI) and mean differences. I^2 statistic and Chi^2 test values were used to assess statistical heterogeneity, which was considered relevant if the I^2 statistic was greater than 40% and if there was a low p-value (less than 0.10) in the Chi^2 test for consistency. Statistical analyses were performed using Rev Man,[18] with fixed-effect meta-analysis for combining data, unless there was substantial heterogeneity, while a random-effects model was implemented if there was clinical or significant statistical heterogeneity.

Results

The searches yielded 311 references, and 214 were screened after removing duplicates. Of those, the full texts of 30 references were reviewed. A total of 8 studies met the inclusion criteria;[19-26] 12 papers were excluded because they were not RCTs, 6 trials implemented a different intervention and finally, 4 studies recruited a different kind of population. The following PRISMA diagram illustrates the selection process (Figure 1). For excluded RCTs and the rationale for exclusion, see Appendix A.

The selected RCTs were published from 1985 to 2012 and recruited participants from Sweden, the United Kingdom, Hong Kong, New Zealand, the USA and Belgium; 2 of those studies were funded by the industry.[21,25] Retrieved studies involved 8 718 men and women with an age range between 20 and 95 years, who required long-term catheterization (>24 hours) during their hospital stay due to general,[20,24] cardiac,[22] orthopedic[25] or elective urologic surgery;[26] 3 studies did not include information in this regard.[19,21,23] The studies excluded patients with current or previous urinary tract infection, recent exposure to antibiotics, history of diabetes or pelvic radiotherapy, or with a recent illness (Table 1).

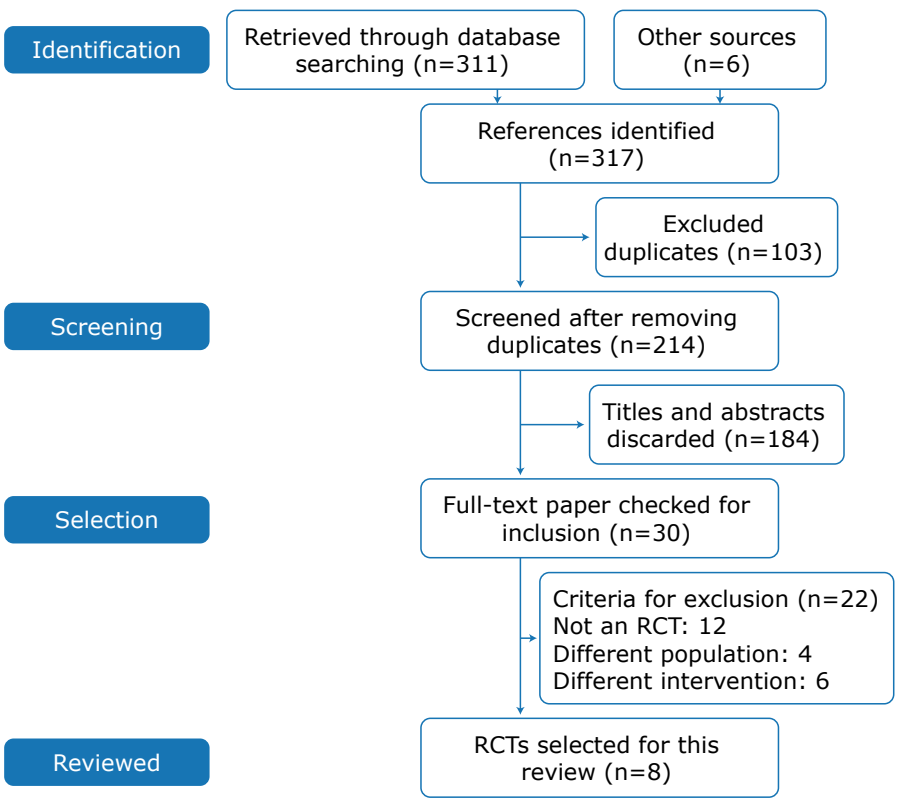

Figure 1. PRISMA flow chart.
Source: Own elaboration.

The intervention most commonly implemented was silicone-coated latex catheter in 5 studies;[21,23-26] 2 studies described sterile catheterization as the intervention;[19,20] and the remaining trials used non-coated silicone catheters.[22] The comparator in 6 studies was non-coated silicone urinary catheter[21-26] and in the other 2 it was clean/non-sterile catheterization technique.[19,20]

Sterile catheterization is the process of cleaning the urethral meatus utilizing an antiseptic aqueous solution and avoiding contact with the practitioner's gloves. The catheter is inserted following a non-touch technique and using forceps after lubrication with sterile lignocaine gel. On the other hand, participants assigned to non-sterile catheterization used sterile water and non-sterile gloves.[19,20]

Table 1. Main characteristics of the studies selected.

Author	Carappetti *et al.*19	Cheung *et al.*20	Liedberg & Lundberg *et al.*21	Nacey *et al.*22	Pickard *et al.*23	Riley *et al.*24	Stenzelius *et al.*25	Verleyen *et al.*26
Year	1994	2008	1990	1985	2012	1995	2011	1999
Study design	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT
Title	Randomized study of sterile versus non-sterile urethral catheterisation	Water versus antiseptic periurethral cleansing before catheterization among home care patients: a randomized controlled trial	Silver alloy coated catheters reduce catheter-associated bacteriuria	Catheter induced urethritis: a comparison between latex and silicone catheters in a prospective clinical trial	Antimicrobial catheters for reduction of symptomatic urinary tract infection in adults requiring short-term catheterisation in hospital: a multicentre randomised controlled trial	A large randomized clinical trial of a silver-impregnated urinary catheter: lack of efficacy and staphylococcal superinfection	Noble metal alloy-coated latex versus silicone Foley catheter in short-term catheterization: a randomized controlled study	Clinical application of the Bardex IC Foley catheter
Country	England	Hong Kong	Sweden	New Zealand	United Kingdom	Salt Lake City	Sweden	Belgium
Population		Elective surgery		Elective Cardiac surgery		Surgery or Internal Medicine	Elective orthopedic surgery	Elective urologic surgery
Age	22-91	mean 80.8	48-52	20-73	mean 59	mean 61.4	20-95	--
Number of participants	156	20	120	100	6 394	1 309	439	180
Intervention	Sterile catheterisation	Sterile catheterization	Silver coated latex catheter	Silicone catheter	Silver alloy-coated latex catheter	Silver coated silicone catheter	Noble metal alloy coated latex catheter	Silver-coated catheter
Comparison	Clean/ non-sterile catheterisation	Sterile water	Teflonised latex catheter	Latex catheter	PTFE-coated latex catheter	Silicone elastomer-coated latex catheter	Non-coated silicone catheter	Latex catheters
Primary outcomes	Bacteriuria	Symptomatic bacteriuria	Bacteriuria	Urethritis	Symptomatic CAUTI	Bacteriuria	Bacteriuria	Bacteriuria
Secondary outcomes	Costs				- Microbiologically confirmed symptomatic CAUTI - Quality of life - Catheter-related symptoms	Catheter-related symptoms	Catheter-related symptoms	Time to develop bacteriuria

RCT: Randomized controlled trial; PTFE: Polytetrafluoroethylene; CAUTI: Catheter-Associated Urinary Tract Infection.
Source: Own elaboration.

The included RCTs assessed at least one predetermined outcome, with some minor differences in the definition of the results between papers. A total of 7 studies reported bacteriuria as the primary outcome[19-21,23-26] using as threshold 10^5 colony-forming units (CFU) per milliliter (mL), except for one study[24] that defined a lower threshold (>1.000 CFU/mL). Three studies reported symptomatic urinary infection —defined as penile discomfort and purulent urethral discharge[22] reported by the patient or the caregiver—, bacterial colonization in urine,[20] or the presence of symptoms accompanied by antibiotic prescription.[23]

Urine specimens were collected at the time of catheterization,[19-21,25] at the time of catheter removal,[21,24,26] or within 7 to 14 days[20,23,25] after catheterization. The secondary outcomes reported by the trials were quality of life (EuroQol scale; EQ-5D),[23] mild adverse events,[24-26] and costs of the intervention.[19] For this study, data for primary outcomes (time elapsed until the first episode, recurrent urinary tract infection, bacteremia, or significant side effects), or the secondary outcome (patient satisfaction) were not collected. Finally, follow-up of participants ranged between 3 and 14 days,[19,21,25,26] 6 weeks,[23] or 6 months.[22]

According to the GRADE system, publications bias should be assessed using a funnel plot and asymmetry statistical tests if 10 or more studies are included in a systematic review or a meta-analysis; therefore, since only 8 studies were included in this review, a funnel plot was not required to assess publication bias. The RCTs included (n=8) had limitations regarding the use of risk of bias tools, which are detailed in Figure 2 and Appendix B. In

this regard, 4 trials[19,22,23,25] implemented a valid sequence generation method and 3 established an adequate allocation concealment process (Figure 2),[19,22,23,25] making selection bias unclear.

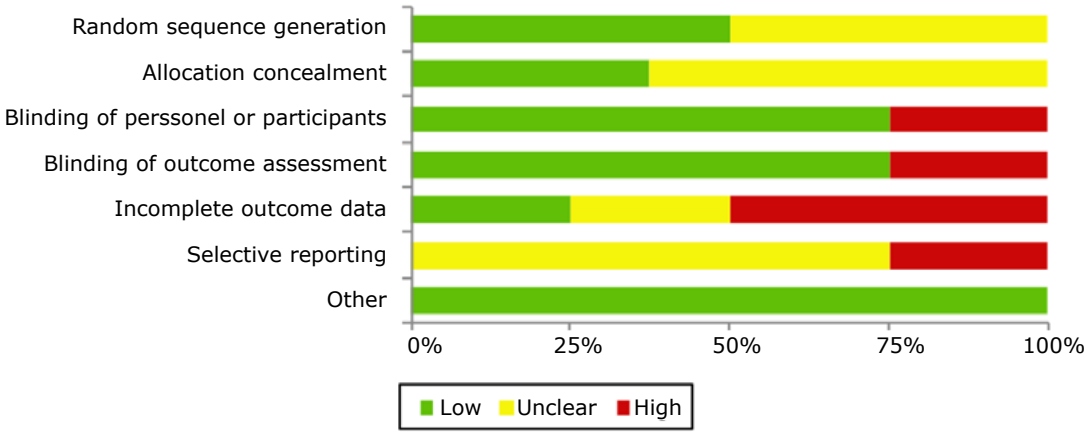

Figure 2. Risk of bias assessment of the included randomized clinical trials.
Source: Own elaboration.

Regarding blinding, 5 studies[19-21,24,26] did not report the method implemented. However, the studies were considered to be at low risk of detection and performance bias since the results were objectively appraised (i.e., culture) and, therefore, the lack of blinding is unlikely to affect confidence in the results. One study[22] was masked to the allocated intervention because of the similarity of the interventions, making performance and detection bias unlikely. Finally, [23,25] the participants of 2 trials were not masked to the intervention because of the distinctive appearance of the catheters; based on the subjective nature of some outcomes (i.e., mild adverse events of the intervention), these RCTs were considered as having high risk of performance and detection bias.

With respect to possible attrition bias, 2 RCTs[22,24] appropriately mentioned the exclusions (<20%) and the reasons were balanced between the arms, making incomplete outcome data bias unlikely. For 6 studies, trial protocols were not available and were assessed as having unclear risk of bias.[19-22,24,26] Finally, all RCTs were at low risk of other potential sources of bias. Table 2 presents a detailed description of the quality of the evidence.

Table 2. Quality of the evidence regarding non-pharmacological interventions at the time of insertion of an indwelling catheter for reducing urinary tract infection in non-immunocompromised adults.

Outcomes	Absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)
	Risk without any intervention	Any non-pharmacological intervention			
Symptomatic urinary infection	136/1000	123/1000 (83-184)	RR 0.90 (0.61-1.35)	4762 (4 RCTs)	VERY LOW *, †,‡
Asymptomatic bacteriuria	175/1000	117/1000 (84-164)	RR 0.67 (0.48-0.94)	5810 (7 RCTs)	LOW *,**
Mild adverse events after the intervention	193/1000	162/1000 (143-186)	RR 0.84 (0.74-0.96)	4157 (2 RCTs)	LOW *,††
Quality of life		MD - 0.01 (-0.03-0.01)	-	3672 (1 RCT)	LOW ‡,‡‡

RR: Relative risk.
* Two trials have high risk of detection, attrition and reporting bias.
† Heterogeneity I^2=63%.
‡ CI overlaps the line of no difference and failed to exclude appreciable benefit or harm.
** Relevant heterogeneity I2= 71%.
†† Heterogeneity I2=0%.
‡‡ High risk for detection, attrition, and selective reporting.
Source: Own elaboration.

Low-quality evidence showed that, compared to the control group, the use of non-pharmacological intervention does not seem to decrease the frequency of symptomatic urinary infections[20,22,23,25] (RR 0.90, 95%CI: 0.61-1.35; 4 762 participants, 4 RCTs; I2 statistic: 63%), or improve quality-of-life scores (MD –0.01 EQ-5D scale; 95%CI: -0.03 - 0.01, 1 RCT) (Figure 3). However, there was evidence of differences between groups in terms of asymptomatic bacteriuria episodes[19-21,23-26] (RR 0.67, 95%CI: 0.48-0.94; 5 810 participants,

7 studies; I2 statistic: 71%) (Figure 4) and the rate of mild adverse events[23,25] (RR 0.84, 95%CI: 0.74-0.96; 4 157 participants, 2 trials; I2 statistic: 0%) (Figure 5).

	Non-pharmacological intervention		Control		Risk Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H. Random 95%CI**
Cheung 2008	0	12	0	8		Not estimable
Nacey 1985	1	50	11	50	3.7%	0.99 [0.01, 0.68]
Pickard 2012	263	2097	271	2144	55.6%	0.99 [0.85, 1.16]
Stenzelius 2011	45	202	45	199	40.6%	0.99 [0.68, 1.42]
Total (95%CI)						
Total events	309					

Heterogeneity: Tau²=0.07: Chi²=5.47 df=2(P = 0.06): I²=63%
Test for overall effect: Z=0.49 (P=0.62)

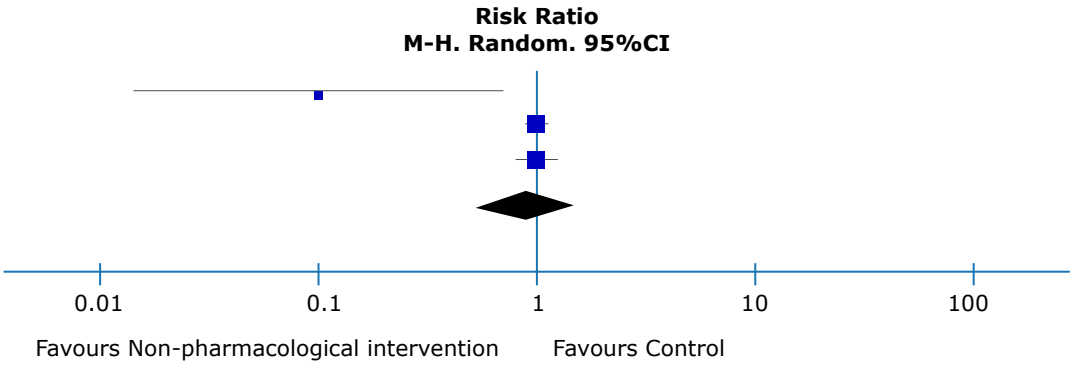

Figure 3. Symptomatic urinary infection as an outcome after performing any of the non-pharmacological interventions during catheter insertion.
Source: Own elaboration.

	Non-pharmacological intervention		Control		Risk Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H. Random 95%CI**
Carapeti 1994	7	12	0	8		Not estimable
Cheung 2008	0	50	11	50	3.7%	0.99 [0.01, 0.68]
Liedberg 1990	6	2097	271	2144	55.6%	0.99 [0.85, 1.16]
Pickard 2012	310	202	45	199	40.6%	0.99 [0.68, 1.42]
Riley 1995	85	745	73	564	23.7%	0.88 [0.66, 1.18]
Stenzelius 2011	3	202	11	199	5.7%	0.27 [0.08, 0.95]
Verleyen 1999	28	79	60	101	22.4%	0.60 [0.43, 0.84]
Total (95%CI)		**2957**		**2853**	**100.0%**	**0.67 [0.48, 0.94]**
Total events	439		498			

Heterogeneity: Tau²=0.10: Chi²=20.57 df=6(P=0.002): I²=71%
Test for overall effect: Z=2.31 (P=0.02)

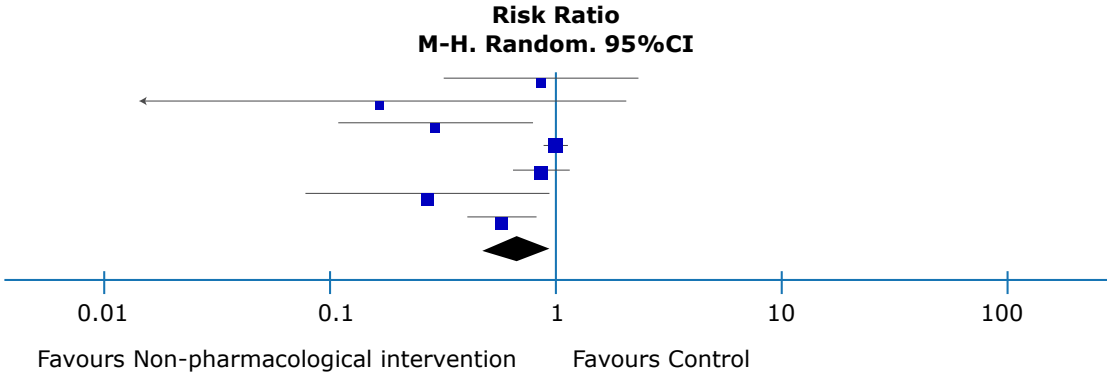

Figure 4. Asymptomatic bacteriuria as an outcome after performing any of the non-pharmacological interventions during catheter insertion.
Source: Own elaboration.

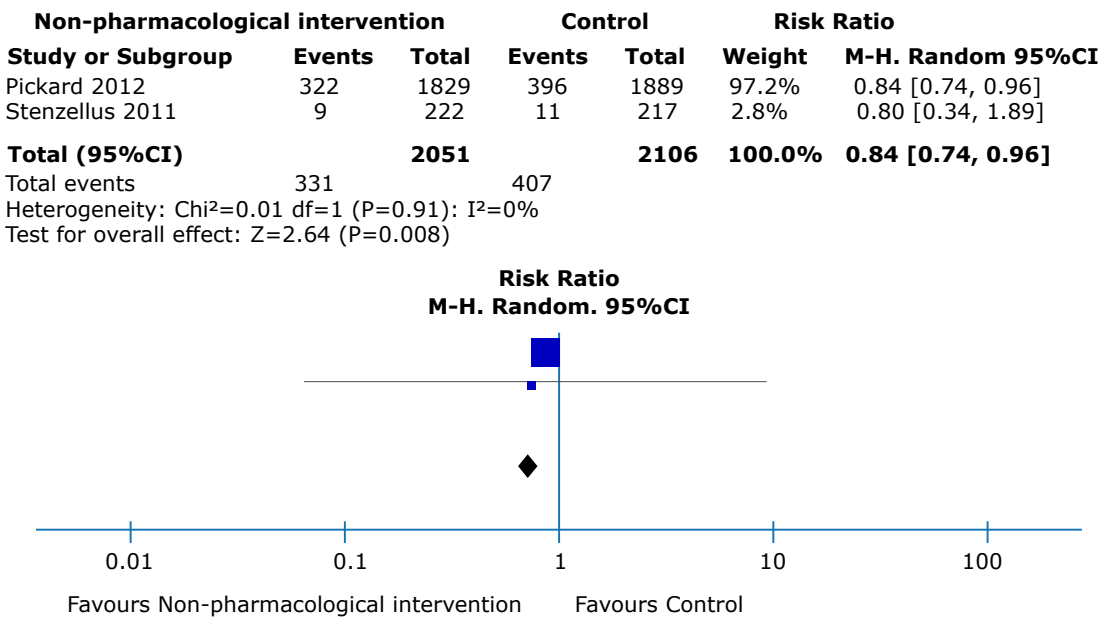

Figure 5. Mild adverse events as outcomes after performing any of the non-pharmacological interventions during catheter insertion.
Source: Own elaboration.

Carappetti *et al.* [19] measured resource and capital expenditure associated with the implementation of sterile interventions compared to clean catheterization. The recruited participants underwent preoperative urethral catheterization and the direct costs were estimated based on the supplies utilized: gloves, sterile gown, catheter pack, lignocaine gel, vaginal gel, sterile water, 10-milliliter syringes, catheter bag, Foley catheter, scrub solution, and skin preparation. Compared with clean catheterization, sterile technique doubled care-associated costs, as the total cost per participant was close to GBP 7.49 versus GBP 3.06, respectively, in 1994. This study did not assess indirect or long-term intervention-related costs.

To explore heterogeneity, a subgroup analysis was performed for the *asymptomatic bacteriuria* outcome. The tests for subgroup effect were not significantly different when the source of heterogeneity was explored (p=0.54, data not shown). Subgroup analyses did not explain the variability in the summary effect measures for the *asymptomatic bacteriuria* outcome, so these findings should be interpreted with caution. The outcomes *symptomatic urinary infection*, *time elapsed until the first episode of urinary tract infection* and *major adverse effects derived from the intervention* were not analyzed because of the sparse information provided by the RCTs included in the present review.

Discussion

This systematic review retrieved low-quality evidence to support the implementation of non-pharmacological interventions at the time of urinary catheter insertion to reduce the risk of infection in non-immunocompromised adults with indwelling catheterization. Regardless of the comparison, non-pharmacological interventions seem to reduce the frequency of asymptomatic bacteriuria episodes and the rate of mild adverse events.

One of the strengths of this systematic review is that its methodology was planned, developed and published at PROSPERO before conducting it, and all the methods that were established at that time were followed while doing the review, namely, a comprehensive literature search without language or date restrictions, two reviewers in charge of the selection of studies, data extraction and bias risk assessment using the tool suggested in the CHB;[16] evidence ranking by means of the GRADE approach; and the use of subgroup analyses and methods for statistical analysis.

One of the weaknesses of the present review is that the quality of the evidence found was very low according to the GRADE system; therefore, further research is highly likely to change the conclusions presented here. On the other hand, the RCTs included were heterogenous and publication bias was not assessed using a funnel plot due to the recommendation of the GRADE system regarding the detection of this type of bias when less than 10 studies are included in a meta-analysis or a systematic review.

There were no other systematic reviews evaluating the impact of non-pharmacological interventions for catheter insertion in cases of urinary tract infection that require long-term catheterization. Consistent with this review, a Cochrane review concludes that the use of silver-coated catheters reduces the frequency of asymptomatic bacteriuria, but the studies reviewed there only assessed short-term catheterization.[27]

Conclusion

Very low-quality evidence shows that non-pharmacological interventions at the time of urinary catheter insertion in non-immunocompromised adults could reduce the frequency of asymptomatic bacteriuria episodes and mild adverse events, without reducing the rate of symptomatic urinary infections or improving quality-of-life scores.

Conflicts of interest

None stated by the authors.

Funding

This study was financed through a HERMES grant (code 33595) awarded by the Faculty of Nursing of Universidad Nacional de Colombia, Bogotá Campus, as stated in Resolution 073 of 2016 (Act 11, May 12, 2016).

Acknowledgements

None stated by the authors.

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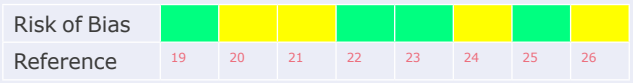
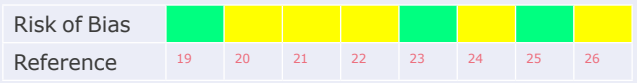
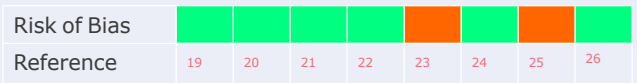
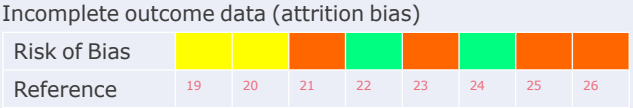
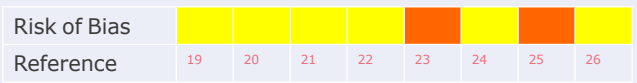
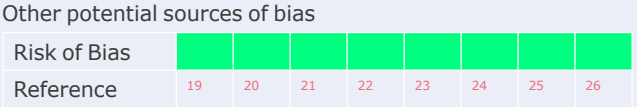
Supplemental Digital Content

Appendix A. Characteristics of the excluded studies.

Cooper FP, Alexander CE, Sinha S, Omar MI. Policies for replacing long-term indwelling urinary catheters in adults. Cochrane Database Syst Rev. 2014;(5):CD011115. http://doi.org/c9gx.	Non-randomized clinical trial.
Meddings J, Rogers MAM, Krein SL, Fakih MG, Olmsted RN, Saint A. Reducing unnecessary urinary catheter use and other strategies to prevent catheter-associated urinary tract infection: an integrative review. BMJ Qual Saf. 2014;23(4):277-89. http://doi.org/f5vn4j.	Different intervention. Interventions to reduce urinary catheter use.
Boettcher S, Brandt AS, Roth S, Mathers MJ, Lazica DA. Urinary retention: benefit of gradual bladder decompression - myth or truth? A randomized controlled trial. Urol Int. 2013;91(2):140-4. http://doi.org/f48r94.	Different interventions. Gradual decompression to prevent urinary retention.
Schumm K, Lam TB. Types of urethral catheters for management of short-term voiding problems in hospitalized adults. Cochrane Database Syst Rev. 2008;16(2):CD004013. http://doi.org/dg2bbk.	Non-randomized clinical trial.
Cardenas DD, Hoffman JM. Hydrophilic catheters versus non-coated catheters for reducing the incidence of urinary tract infections: a randomized controlled trial. Arch Phys Med Rehabil. 2009;90(10):1668-71. http://doi.org/cdcnqn.	Different population. Self-intermittent catheterization.
Al-Farsi S, Oliva M, Davidson R, Richardson SE, Ratnapalan S. Periurethral cleaning prior to urinary catheterization in children: sterile water versus 10% povidone-iodine. Clin Pediatr (Phila). 2009;48(6):656-60. http://doi.org/cms7ms.	Different population. Children.
Tenke P, Kovacs B, Bjerklund-Johansen TE, Matsumoto T, Tambyah PA, Naber KG. European and Asian guidelines on management and prevention of catheter-associated urinary tract infections. Int J Antimicrob Agents. 2008;31(Suppl 1):S68-78. http://doi.org/dkrrz2.	Non-randomized clinical trial.
Jahn P, Preuss M, Kernig A, Seifert-Hüehmer A, Langer G. Types of indwelling urinary catheters for long-term bladder drainage in adults. Cochrane Database Syst Rev. 2007;18(3):CD004997. http://doi.org/dq9w7t.	Non-randomized clinical trial.
Leone M, Perrin AS, Granier I, Visintini P, Blasco V, Antonini F, *et al.* A randomized trial of catheter change and short course of antibiotics for asymptomatic bacteriuria in catheterized ICU patients. Intensive Care Med. 2007;33(4):726-9. http://doi.org/drdxw3.	Different population. Participants with urinary tract infection.
Johnson JR, Kuskowski MA, Wilt TJ. Systematic review: antimicrobial urinary catheters to prevent catheter-associated urinary tract infection in hospitalized patients. Ann Intern Med. 2006;144(2):116-26. http://doi.org/gfxp8j.	Non-randomized clinical trial.
Leone M, Garnier F, Avidan M, Martin C. Catheter-associated urinary tract infections in intensive care units. Microbes Infect. 2004;6(11):1026-32. http://doi.org/ddg3wt.	Non-randomized clinical trial.
Webster J, Hood RH, Burridge CA, Doidge ML, Phillips KM, George N. Water or antiseptic for periurethral cleaning before urinary catheterization: a randomized controlled trial. Am J Infect Control. 2001;29(6):389-94. http://doi.org/ccqxp4.	Different population. Pregnant women.
Huth TS, Burke JP, Larsen RA, Classen DC, Stevens LE. Clinical trial of junction seals for the prevention of urinary catheter-associated bacteriuria. Arch Intern Med. 1992;152(4):807-12. http://doi.org/d25d75.	Different intervention. Junction seals to prevent infection.
Johnson JR, Roberts PL, Olsen RJ, Moyer KA, Stamm WE. Prevention of catheter-associated urinary tract infection with a silver oxide-coated urinary catheter: clinical and microbiologic correlates. J Infect Dis. 1990;162(5):1145-50. http://doi.org/cjqs9h.	Non-randomized clinical trial.
Cai T, Caola I, Tessarolo F, Piccoli F, D'Elia C, Caciagli P, *et al.* Solidago, orthosiphon, birch and cranberry extracts can decrease microbial colonization and biofilm development in indwelling urinary catheter: a microbiologic and ultrastructural pilot study. World J Urol. 2014;32(4):1007-14. http://doi.org/f6bwvd.	Different intervention. CISTIMEV PLUS after urinary catheter insertion.
Lam TB, Omar MI, Fisher E, Gillies K, MacLennan S. Types of indwelling urethral catheters for short-term catheterisation in hospitalised adults. Cochrane Database Syst Rev. 2014;23(9):CD004013. http://doi.org/f8mcww.	Non-randomized clinical trial.
Wilde MH, Fader M, Ostaszkiewicz J, Prieto J, Moore K. Urinary bag decontamination for long-term use: a systematic review. J Wound Ostomy Continence Nurs. 2013;40(3):299-308. http://doi.org/f4xtzg.	Non-randomized clinical trial.
Chung YC, Chen HH, Yeh ML. Vinegar for decreasing catheter-associated bacteriuria in long-term catheterized patients: a randomized controlled trial. Biol Res Nurs. 2012;14(3):294-301. http://doi.org/cgfkk2.	Different intervention. Rice vinegar after urinary catheter insertion.
Ching TY, Seto WH. Evaluating the efficacy of the infection control liaison nurse in the hospital. J Adv Nurs. 1990;15(10):1128-31. http://doi.org/brjnwf.	Cluster randomized clinical trial.
Burke JP, Garibaldi RA, Britt MR, Jacobson JA, Conti M, Alling DW. Prevention of catheter-associated urinary tract infections. Efficacy of daily meatal care regimens. Am J Med. 1981;70(3):655-8. http://doi.org/fvx23z.	Different intervention. Daily meatal care regimens after urinary catheter insertion.

Supplemental Digital Content

Appendix B. Summary of risk of bias according to the authors of this review for each included study

Random sequence generation (selection bias) 	Four trials[19,22,23,25] adequately reported the random sequence generation method by using a computer-generated randomization list or flipping a coin, making selection bias at entry unlikely. The remaining trials[20,21,24] did not report the random sequence generation method, making the risk of selection bias at entry unclear.
Allocation concealment (selection bias) 	Three studies adequately implemented an allocation concealment method by using sequentially numbered sealed envelopes,[25] a central randomization,[23] or flipping an unbiased coin,[19] making selection bias at entry unlikely. The other 5 trials[20-22,24,26] did not report the allocation concealment method used, so the risk of bias for this domain was deemed unclear.
Blinding (performance and detection bias) 	Five studies,[19-21,24,26] did not report the implemented methodology to blind study participants, outcome assessor and personnel from knowing what intervention was given to the participant. However, the studies were considered to be at low risk for performance or detection bias because the outcomes were objectively assessed (i.e., culture), so the lack of blinding would be unlikely to affect results. One study[22] was masked to the allocated intervention because of the similarities of each catheter, making performance and detection bias unlikely. Finally, in two trials,[23,25] participants, clinicians and trial team were not masked to the allocated intervention because of the distinctive characteristics of each intervention and based on the subjective nature of some outcomes (i.e., mild adverse events of the intervention). This study was considered to be at high risk of performance and detection bias.
Incomplete outcome data (attrition bias) 	Two trials[22,24] appropriately reported the attrition and exclusions at each stage; the reasons were balanced across groups and the level of missing data was not more than 20%, making attrition bias unlikely. Four studies[21,23,25,26] had a discontinuation rate and follow-up loss greater than 20%, so they were appraised as high risk of attrition bias. Finally, 2 trials[19,20] did not have enough information to permit judgment of "yes" or "no" (rated as unclear risk of bias).
Selective reporting (reporting bias) 	Some outcomes were not pre-specified in the protocol stage in two of the trials included,[23,25] but they were reported in the manuscript. These trials were considered to be at high risk of selective reporting bias. For 6 studies,[19-22,24,26] the trial protocol was not available, and it is unclear whether the published reports presented all the expected outcomes, including those that were pre-specified. The report had insufficient information to permit judgment of "Yes" or "No" (rated as unclear risk of bias).
Other potential sources of bias 	All retrieved trials seemed to be free from other sources of bias and were rated as low risk of bias for this domain.
	

rfm
Revista de la Facultad de Medicina

ORIGINAL RESEARCH
DOI: http://dx.doi.org/10.15446/revfacmed.v68n1.69885
Received: 19/01/2018 Accepted: 01/05/2018

Characterization of prenatal exposure variables in a group of children aged 0-5 years with congenital heart defect treated in Cali, Colombia. The importance of folic acid

Caracterización de la exposición prenatal de un grupo de niños de 0 a 5 años con cardiopatía congénita atendidos en Cali, Colombia. La importancia del ácido fólico

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Abstract

Introduction: Congenital heart defects (CHD) have an estimated prevalence of 4 to 9 cases per 1 000 births, and they have a significant impact on child morbidity and mortality. This prevalence variability has been attributed to regional differences in terms of genetic and environmental factors, among others.
Objective: To obtain data on prenatal exposure variables of patients with CHD treated in Cali, Colombia.
Materials and methods: A survey was administered to the mothers of 30 children aged 0 to 5 years with CDH treated in 2 health institutions of Cali, Colombia. The instrument was oriented to collect data on multiple prenatal exposure variables, and data collected were entered into an Excel database in order to analyze them using descriptive statistics.
Results: Several types of exposure potentially associated with having CHD were found, including altered body mass index, inadequate administration of folic acid, and being exposed to X-rays, vitamin A, alcohol and tobacco.
Conclusion: Insufficient or untimely administration of folic acid could facilitate the development of teratogenic effects of oxidizing agents. Therefore, education programs on the importance of a proper intake of folic acid and the risks derived from exposure to teratogenic agents during pregnancy should be provided to all pregnant women in Cali to reduce the incidence rate of CHD in the city.
Keywords: Congenital Heart Defects; Environmental Exposure; Congenital Abnormalities (MeSH).

Ramírez-Cheyne J. Characterization of prenatal exposure variables in a group of children aged 0-5 years with congenital heart defect and treated in Cali, Colombia. The importance of folic acid. Rev. Fac. Med. 2020;68(1):34-43. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.69885.

Resumen

Introducción. Con una prevalencia estimada de 4 a 9 casos por cada 1 000 nacimientos, las cardiopatías congénitas (CC) tienen gran impacto en la morbimortalidad pediátrica. La variabilidad de prevalencia se ha atribuido a diferencias regionales en cuanto a factores genéticos, ambientales, entre otros.
Objetivo. Obtener datos sobre variables de exposición prenatales de pacientes con CC atendidos en Cali, Colombia.
Materiales y métodos. Se aplicó una encuesta a las madres de 30 pacientes de 0 a 5 años con CC atendidos en 2 clínicas de alta complejidad (tercer y cuarto nivel) de Cali. La encuesta estaba orientada a múltiples variables de exposición y la información recolectada fue digitalizada en una base de datos en el programa Microsoft Excel para hacer un análisis estadístico descriptivo.
Resultados. Se evidenciaron varias exposiciones potencialmente asociadas a CC, tales como índice de masa corporal alterado, administración inadecuada de suplementos de ácido fólico y exposición a vitamina A, rayos X, alcohol y cigarrillo.
Conclusión. El consumo insuficiente o inoportuno de ácido fólico podría facilitar la generación de efectos teratogénicos de sustancias oxidantes. Por lo tanto, se debe educar a las mujeres de Cali sobre la importancia de una ingesta adecuada de ácido fólico y sobre los riesgos de la exposición a agentes teratogénicos durante el embarazo para reducir las tasas de incidencia de CC en esta ciudad.
Palabras clave: Cardiopatías congénitas; Exposición a riesgos ambientales; Anomalías congénitas (DeCS).

Ramírez-Cheyne J. [Caracterización de la exposición prenatal de un grupo de niños de 0 a 5 años con cardiopatía congénita atendidos en Cali, Colombia. La importancia del ácido fólico]. Rev. Fac. Med. 2020;68(1):34-43. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.69885.

Introduction

Congenital anomalies are found in 2-3% of newborns and constitute a major public health problem; in Colombia, the most common anomalies of this type include alterations of the limbs, central nervous system defects and congenital heart disease (CHD).[1] Given that CHD have the greatest impact, since 2010, pulse oximetry has been implemented in the U.S. as a routine screening method on all live newborns for early detection of congenital heart defects associated with hypoxia in the neonatal period.[2]

Some studies associate the occurrence of CHD with teratogenic agents,[3-5] and others, based on animal models extrapolated to humans, argue that the consumption of folic acid (also known as folate) during the first 3 weeks of pregnancy prevents heart disease caused by exposure to teratogens.[6-7] In this sense, it is known that initiating folic acid supplementation in humans one month prior to pregnancy reduces the incidence of neural tube defects by more than 70%;[8] furthermore, there is epidemiological evidence that supplementing mothers with this vitamin protects the babies against various types of CHD.[9]

The aim of this study was to obtain data on prenatal exposure variables of CHD patients treated in Cali, Colombia. Consequently, this research is the first step towards improving the understanding of the multiple factors related to CHD in the local context.

Materials and methods

A descriptive case series study was conducted using a random sample of 30 patients under 6 years of age with CHD treated in 2 institutions of Cali: DIME Clínica Neurocardiovascular (institution 1) and Clínica Versalles (institution 2). Isolated ductus arteriosus cases were excluded because only newborns without gestational age or disease status restriction were included in the study, as it is known that, regardless of exposure to other factors, gestational age and the presence of respiratory distress syndrome can affect ductal closure.[10]

Patients treated between September 2014 and November 2015 were selected for this study. In the case of institution 1, which is a reference center for the diagnosis and management of cardiovascular diseases, the database of echocardiograms performed there was reviewed and the mothers of CHD patients born in the past 5 years were contacted by phone to invite them to participate in the study; calls were made in chronological order, that is beginning with the patient most recently treated. Once the mother agreed to participate, an appointment was made with her and the patient to formally carry out the informed consent process and administer the survey to the mother.

In order to select the patients in institution 2, which is a tertiary care center with the highest number of births in the city, all the care staff of the Obstetrics Service and the Newborn Intensive Care Unit were informed of the study, so that when new cases of newborns with CHD confirmed by echocardiogram were diagnosed, they informed the study staff, who also asked daily if there were any new cases, thus allowing an active search. When the CHD were confirmed, the informed consent process and the mother's survey were formally conducted. No patients were captured by screening with pulse oximetry.

The administered survey was an extensive instrument of more than 90 pages, validated in previous original studies and designed by the research groups Congenital and Perinatal Malformations, Medical Genetics and Dysmorphology (MACOS by its acronym in Spanish) and Epidemiology and Population Health (GESP by its acronym in Spanish). It sought to find out multiple socio-demographic and exposure variables such as drinking water, medicines, cigarettes, alcohol and other psychoactive substances, as well as the history of diseases and X-ray studies. At this point, it is worth noting that there may be memory bias when answering this type of survey.

The collected data were digitized in a Microsoft Excel sheet and a univariate and bivariate descriptive statistical analysis was performed using relative frequency distributions (%) presented in tables to describe the exposure characteristics found.

This study was approved by the Institutional Committee for the Review of Human Ethics of the Faculty of Health of the Universidad del Valle by means of approval act No. 04013 of April 5, 2013. Moreover, the principles of the Declaration of Helsinki[11] and the regulations of Resolution 8430 of 1993 of the Colombian Ministry of Health were followed.[12]

Results

Socio-demographic characterization

Of the 30 cases, 24 were captured in institution 1 and 6 in institution 2. The births took place in 13 health institutions, mostly in the Hospital Universitario del Valle and the Clínica Versalles, which means that 16 of the patients were born in one of these 2 institutions.

The sample studied was composed of 19 boys (63.33%) and 11 girls (36.67%). Regarding health insurance, 46.66% of the mothers were enrolled in the subsidized regime and 53.33% in the contributory regime, and 56.66% of them lived in Cali during the periconceptional period (3 months before and 3 months after the approximate date of conception or fertilization) (Table 1).

Among the mothers who lived in Cali during their periconceptional period, most resided in the central and eastern areas (Aguablanca district): 23.5% in commune 14 and 17.6% in commune 9; the remaining mothers lived in different communes during this period, that is, they were distributed without constituting aggregates. Both institutions where the study was conducted are in commune 2.

Table 1. Socio-demographic characteristics of the study cases.

Characteristics		n (%)
Sex	Women	11 (36.67%)
	Men	19 (63.33%)
Place of residence during the periconceptional period	Cali	17 (56.66%)
	Outside Cali	13 (43.33%)
Health Care System	Contributive	16 (53.33%)
	Subsidized	14 (46.66%)

Source: Own elaboration.

Characterization of the exposure

20 of the 30 pregnancies were not planned, and, on average, the mothers found out about their status during the 7th week. An average of 8 prenatal check-ups was obtained, and ultrasound studies detected some fetal structural abnormality in only 2 cases; no invasive prenatal diagnostic study was performed for any of these cases. In a third case, the ultrasound reported a placental abnormality.

Table 2 shows and describes the types of heart disease found in the patients included in the series, while Tables 3, 4 and 5 summarize the most relevant maternal exposures found in the research.

Table 2. Characterization of the patients included in the research.

Case	Age at study entry	Heart disease	Associated abnormalities
1	1 day	Transposition of the great arteries	None
2	4 months	Double atrioventricular canal, single ventricle, transposition of the great arteries	Complete situs inversus, intestinal malrotation
3	2 months	Tricuspid insufficiency	None
4	7 days	Tetralogy of Fallot, patent ductus arteriosus, interatrial communication and hypoplasia of the valve, trunk and branches of the lungs	None
5	1 day	Ventricular septal defect	Right preauricular sinuses, abnormal hand and foot dermatoglyphics, clinodactyly, hypoplasia of the middle phalanx of the fifth digit of the left hand
6	1 day	Ventricular septal defect, patent foramen ovale	Down facies (Down syndrome confirmed by karyotype)
7	5 days	Left lower pulmonary vein stenosis, ventricular septal defect, patent ductus arteriosus	Low-set ears, over-folded ears, prominent antihelix, hypoplastic helix crus, protruding cheekbones, microstomia, hands in trisomy, prominent heel (trisomy 18 confirmed by karyotype)
8	1 day	Complete atrioventricular canal	None
9	20 days	Patent ductus arteriosus, patent foramen ovale, mild to moderate mitral regurgitation, mild tricuspid regurgitation	None
10	2 days	Tricuspid atresia, right ventricular hypoplasia, pulmonary atresia	None
11	2 months	Truncus arteriosus	Hirsutism (on the face, back and limbs), absent earlobe, wide nasal bridge, micrognathism, micropenis.
12	22 days	Double outlet right ventricle, severe pulmonary stenosis, transposition of the great arteries	None
13	5 days	Atrioventricular valve dysplasia, moderate tricuspid regurgitation, situs inversus	None
14	1 month	Dysplastic pulmonary valve with insufficiency and stenosis	None
15	6 months	Ostium secundum atrial septal defect, patent ductus arteriosus	Epicanthal fold, short nose, smooth philtrum, anteverted nostrils
16	1 year	Ventricular septal defect, patent foramen ovale	Down facies (Down syndrome confirmed by karyotype), hypothyroidism
17	1 month	Tetralogy of Fallot	Low-set ears, myelomeningocele, hydrocephalus, shortening of the second left metatarsal bone, abnormal dermatoglyphics
18	4 years	Interatrial communication	Esophageal atresia, neonatal teeth (two incisors), big, protruding ears
19	4 years	Double superior vena cava system, persistent left superior vena cava, dilated coronary sinus	Café-au-lait spots (one spot of 5cm in the lower right quadrant of the abdomen)
20	2 years	Ventricular septal defect	Delayed psychomotor development, bilateral hydronephrosis, protuding forehead, arched eyebrows
21	2 years	Subvalvular aortic stenosis, tricuspid but functionally bicuspid aortic valve, aortic vascular ring in the descending thoracic aorta without coarctation	None

Table 2. Characterization of the patients included in the research. (continued)

Case	Age at study entry	Heart disease	Associated abnormalities
22	1 month	Single atrioventricular connection through a central atrioventricular valve, double-outlet right ventricle, blood vessels in abnormal position, right ventricular hypoplasia, right anterior aorta and left posterior pulmonary aorta, interatrial communication, single atrium, lack of interventricular septum, dilated left ventricle, hypoplastic pulmonary artery, patent ductus arteriosus, single atrioventricular valve, right aortic arch, tricuspid pulmonary atresia with severe infundibular and pulmonary stenosis	Right isomerism, esophageal atresia
23	1 day	Ostium secundum atrial septal defect, moderate mitral regurgitation	Frontal hemangioma extending towards the right eye, anteverted nostrils, inverted nipples, megabladder, bilateral hydronephrosis, large, thick-walled, partitioned bladder mass, anasarca, anal atresia, urethral meatus agenesis, probable urogenital sinus, lumbar hemivertebra
24	2 days	Right ventricle hypoplasia,pulmonary atresia	None
25	2 years	Supracardiac pulmonary anomalous venous connection, interatrial communication, persistent left superior vena cava.	Café au lait spot on right shoulder with a diameter of 3cm, short nose, barely visible nasal tip, anteverted nostrils, long philtrum, protruding cheekbones, left cryptorchidism
26	5 years	Ventricular septal defect, interatrial communication, pulmonary stenosis	Seizures, repeated respiratory infections, strabismus, flattened cervical vertebrae, delayed psychomotor development, self-injury (of the tongue), dolicocephaly, big ears, thick lips, pectus excavatum, right cryptorchidism, hypotonia
27	4 years	Tetralogy of Fallot, mild stenosis at the origin of the right pulmonary branch	Atopic dermatitis, mild y-shaped syndactyly between toes 2 and 3, including penis.
28	2 years	Pulmonary stenosis, patent foramen ovale	Neonatal jaundice, wide nose, small café-au-lait spots
29	2 years	Ebstein anomaly, tricuspid insufficiency	Left pyelectasis, two café-au-lait spots <1cm on the abdomen
30	2 years	Coarctation of the aorta, interatrial communication	Agenesis of the corpus callosum

Source: Own elaboration.

Table 3. Periconceptional exposures found in this study.

Case	Exposure in the 3rd month before conception	Exposure in the 2nd month before conception	Exposure in the 1st month before conception	Exposure in the 1st month after conception	Exposure in the 2nd month after conception	Exposure in the 3rd month after conception
1	None	Warfarin	Alcohol (beer, rum, aguardiente, whisky)	Acetaminophen, warfarin, alcohol (beer, rum, aguardiente, whisky)	Warfarin, alcohol (beer, rum, aguardiente, whisky)	Warfarin, alcohol (beer, rum, aguardiente, whisky)
2	Smoker at home	Smoker at home	Smoker at home	Smoker at home	Acetaminophen, smoker at home	Smoker at home
3	NPH and aspart insulin, smoker at home	NPH and aspart insulin, smoker at home	NPH and aspart insulin, smoker at home	NPH and aspart insulin, smoker at home	NPH and aspart insulin, smoker at home	NPH and aspart insulin, smoker at home
4	Contraceptive injection, smoker at home	Contraceptive injection, smoker at home	Contraceptive injection, smoker at home	Contraceptive injection, metoclopramide, acetaminophen	Contraceptive injection	Contraceptive injection
6	None	Acetaminophen	None	Alcohol (beer)	None	Acetaminophen
7	None	None	None	Aspirin, metoclopramide	Aspirin, metoclopramide	Aspirin

Table 3. Periconceptional exposures found in this study. (continued)

Case	Exposure in the 3rd month before conception	Exposure in the 2nd month before conception	Exposure in the 1st month before conception	Exposure in the 1st month after conception	Exposure in the 2nd month after conception	Exposure in the 3rd month after conception
10	None	None	None	None	None	Acetaminophen, metoclopramide
11	None	None	None	Acetaminophen	Acetaminophen, alcohol (rum, aguardiente, whisky)	None
12	Acetaminophen	Acetaminophen	Acetaminophen	Acetaminophen	Acetaminophen	Acetaminophen
13	Alcohol (beer), marihuana, smoker at home	Alcohol (beer), marihuana, smoker at home	Alcohol (beer), marihuana, smoker at home	Alcohol (beer), marihuana, smoker at home	Levothyroxine, Alcohol (beer), marihuana, smoker at home	Levothyroxine, marihuana, smoker at home
14	Smoker at home, alcohol (beer, rum, aguardiente, whisky)	Smoker at home, alcohol (beer, rum, aguardiente, whisky)	Acetaminophen, smoker at home, alcohol (beer, rum, aguardiente, whisky)	Acetaminophen, omeprazole, smoker at home, alcohol (beer, rum, aguardiente, whisky)	Acetaminophen, omeprazole, smoker at home	Smoker at home
15	Smoker at home	Smoker at home	Smoker at home	Smoker at home	Acetaminophen, smoker at home	Smoker at home
17	None	Smoker at home	Smoker at home	Smoker at home	Smoker at home	Smoker at home
18	None	None	None	Acetaminophen	Acetaminophen	Levothyroxine
19	Alcohol (beer), smoker at home	Alcohol (beer), smoker at home	Alcohol (beer), smoker at home	Acetaminophen, smoker at home	Ovules, acetaminophen, smoker at home	Smoker at home
20	Acetaminophen	Acetaminophen	Acetaminophen	None	None	None
21	Acetaminophen, smoker at home	Acetaminophen, smoker at home	Acetaminophen, smoker at home, alcohol (beer, rum, aguardiente, whisky)	Acetaminophen, metoclopramide, smoker at home, alcohol (beer, rum, aguardiente, whisky)	Smoker at home, misoprostol	Smoker at home
22	None	None	None	Alcohol (whisky cream)	None	None
24	None	None	None	None	None	Acetaminophen
25	None	Acetaminophen	Acetaminophen	Acetaminophen, alcohol (beer)	None	None
27	None	None	None	None	Acetaminophen	Acetaminophen
28	Smoker at work	Smoker at work	Smoker at work	Acetaminophen, smoker at work	Acetaminophen, smoker at work	Acetaminophen, smoker at work
29	None	None	None	None	Magnesium sulfate, acetaminophen	Magnesium sulfate, acetaminophen

Source: Own elaboration.

Table 4. Maternal diseases and pregnancy exposures.

Disease/exposure	n (%)
Pregestational diabetes	1 (3.33%)
Gestational diabetes	1 (3.33%)
Chronic hypertension	1 (3.33%)
Gestational hypertension	3 (10%)
Hypothyroidism	1 (3.33%)
Hypoglycemia	1 (3.33%)
Pregestational Body Mass Index >24.9	10 (33.33%)
Pregestational body mass index <18.5	1 (3.33%)
X-rays without protection	4 (13.33%
Folic acid supplementation: absent or initiated after the first month of pregnancy	18 (60.0%)
Vitamin A	1 (3.33%) (exposure during the second and third trimesters of pregnancy)
Warfarin	1 (3.33%)

Source: Own elaboration.

Table 5. Non-therapeutic maternal exposures.

Exposure	n (%)
Active smoking	0 (0%)
Passive smoking	11 (36.66%)
Alcohol *	9 (30%)
Marihuana *	1 (3.33%)
Misoprostol	1 (3.33%)
Untreated river water	3 (10%)
Consumption of boiled river water	4 (13.33%)
Consumption of untreated well water	2 (6.66%)

* The questionnaire included the quantification of alcohol and marijuana consumption; however, the mothers did not remember or could not specify the amount.

Source: Own elaboration.

Discussion

Socio-demographic aspects

41% of the mothers who lived in Cali during their periconceptional period resided in communes 14 and 9, which are composed of neighborhoods in strata 2 and 3 (Table 6).

In commune 14, 68.4% of the houses are classified as stratum 1 and 31.6% as stratum 2; 17.7% of office machinery factories (telephones, computers, printers, photocopiers, video projectors, guillotines, etc.), 11.8% of automotive industries and 10.7% of electricity, gas and water suppliers of the city are located in this place. Some of its main problems are the lack of adequate green areas and environmental education programs, and inadequate solid waste disposal.[13]

Table 6. Socioeconomic strata in Colombia according to the National Administrative Department of Statistics.

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

Source: Elaboration based on the data by National Administrative Department of Statistics.[14]

On the other hand, the commune 9 is characterized because 10% of the households are stratum 1, 20% are stratum 2, and 70% are stratum 3. This place concentrates 32.69% of the recycling centers and 25% of the tanneries and centers of preparation of leathers (footwear) of the city.[13]

These findings explain the need for a specific and detailed analysis of risk factors associated with congenital anomalies in these geographical areas.

Exposure aspects

An unplanned pregnancy increases the chances of risk exposure during the periconceptional period, as a woman who is not aware of her condition continues to engage in behaviors she might not have if she knew. In addition, late pregnancy awareness does not allow for the timely consumption of the necessary micronutrients. In this study, 66.66% of the pregnancies were unplanned.

Quality of prenatal care

The mothers assisted, on average, to 8 prenatal checkups, which is an acceptable number. All of them underwent at least 1 obstetric ultrasound, although this examination only detected anomalies in 3 cases; thus, considering that ultrasound findings in one of the cases revealed a placental anomaly, only 2 patients were diagnosed with fetal structural anomalies. It should be noted that the 2 mothers diagnosed with fetal structural anomalies belong to the contributory regime, which means that some fetal structural anomaly was detected in 12.5% of the mothers in the contributory regime and none in the mothers enrolled in the subsidized regime. This may suggest that there is less access to timely and quality ultrasound for the mothers in the latter, as previously reported.[15]

Maternal hypertension

Chronic maternal hypertension has been associated with CHD (OR: 1.81, 95% CI: 1.61-2.03),[16] specifically with ventricular septal defects, common atrioventricular

canal defect and truncus arteriosus. It has been found that there is increased prevalence of non-critical CHD in children of women who develop preeclampsia after the 34th week, and that the prevalence of critical and non-critical heart disease increases in children of women who develop preeclampsia before the 34th week.[17] Significant associations between maternal hypertension and CHD in general have been observed for treated (RR: 2, 95% CI: 1.5-2.7) and untreated patients (RR: 1.4, 95% CI: 1.2-1.7), as well as for hypertension (RR: 1.8, 95 CI%: 1.5-2.2).[18]

This study found that 4 of the mothers had hypertension: 1 of them had chronic hypertension and her child presented tricuspid insufficiency, while the other 3 mothers had gestational hypertension with onset before the 34th week and their children presented syndromic cardiopathies.

Maternal diabetes

It is well known that the incidence of congenital abnormalities, including heart disease, is high in children of diabetic mothers.[5] Traditionally, it was thought that this increased risk was limited to patients with diabetes at the time of conception; however, it has been suggested that hyperglycemia caused by gestational diabetes may also influence cardiac development, which has been particularly associated with abnormalities such as patent ductus arteriosus, pulmonary stenosis and interventricular septal hypertrophy.[19] Likewise, Ornoy[20] proposes hyperglycemia-induced oxidative stress as a teratogenic mechanism of maternal diabetes.

This study also found that 2 of the mothers had diabetes: the first, mother of a patient with isolated tricuspid insufficiency, had preconceptional type 1 diabetes —which is associated with CHD (OR: 4.65, 95%CI: 4.13-5.24),[16] specifically coarctation of the aorta,[4] while the second, mother of a patient with Ebstein's anomaly and tricuspid insufficiency, had gestational diabetes. It is noteworthy that alterations in the tricuspid valve were observed in 3 of the 4 cases of maternal hypertension and in the 2 cases of gestational diabetes.

Maternal thyroid disease

Studies such as Liu *et al.*[16] have associated thyroid disorders with CHD (OR: 1.45, 95%CI: 1.26-1.67). In the present investigation, 1 of the mothers had hypothyroidism and her child (case 18) presented ventricular septal defect.

Maternal hypoglycemia

In animal models, hypoglycemia has been found to be potentially teratogenic during embryogenesis.[8] This study found that 1 of the mothers had hypoglycemia and her child had subvalvular aortic stenosis, tricuspid (but functionally bicuspid) aortic valve and aortic vascular ring in the descending thoracic aorta without coarctation.

Maternal body mass index

Previous studies have reported an association between maternal body mass index (BMI) and the occurrence of CHD; in general, the higher the BMI, the higher the OR for CHD.[21] Low maternal weight, on the other hand, appears to increase the risk for aortic stenosis.[22]

This study found that 10 of the mothers started the pregnancy with BMI above normal values (>24.9) and 1 with BMI lower than normal values (<18.5), which may indicate that BMI alterations are an important factor for the development of heart disease in the study population.

Exposure to X-rays

It has been found that the risk of inducing embryonic death or congenital anomalies after irradiating a newly fertilized egg with the usual range of doses used in diagnostic radiology is very low compared to the spontaneous risks. However, these findings are not considered a reason not to take precautions when possible, in part due to the possibility of epigenetic alterations.[23] In this sense, Ornoy[20] proposes that the teratogenic mechanism of ionizing radiation is the induction of oxidative stress.

This research found that 4 of the mothers underwent x-ray studies during pregnancy without protection, and that 3 of these children had non-syndromic heart disease and 1 had syndromic heart disease.

Exposure to tobacco

Mothers who smoke during the first trimester have been reported to be at increased risk of having children with CHD (OR: 1.16, 95%CI: 1.08-1.24). A dose-dependent effect and a very strong association have also been observed in some specific defects such as pulmonary valve disease, pulmonary artery anomalies and isolated interatrial communication.[24] In this sense, passive periconceptional exposure to tobacco has been established as an independent risk factor for heart disease[25,26] and the teratogenic mechanism of tobacco is the induction of oxidative stress.[20]

None of the mothers in this study smoked during pregnancy, so there appears to be an awareness of the potential dangers of smoking among them, but this was not the case for passive smoking exposure, as 36.66% of them were exposed.

Exposure to alcohol

Maternal alcohol consumption is known to cause multiple birth defects included in fetal alcohol syndrome (FAS), among them, heart disease. Only 10% of those affected with alcohol embryopathy meet all the criteria for FAS, while the remaining 90% fall somewhere else on the spectrum.

Multiple studies have shown that maternal alcohol consumption increases the risk of CHD[3,16,27] and teratogenic mechanisms include disruption of midline expansion;[28,29] apoptosis and alteration of neural crest and anterior precordal mesoderm cell migration;[30-32] disruption of several signaling pathways such as shh, fgf8, foxa2 and goosecoid;[29,33] and induction of oxidative stress.[20,34] This study found that 30% of the mothers consumed some alcohol, perhaps indicating a lack of awareness that there is no safe time or dose for alcohol consumption during pregnancy.

Folic acid intake

Folate is necessary for the synthesis of purines and pyrimidines, and therefore, it is important for proper cell proliferation. This micronutrient is also necessary for the synthesis of S-Adenosyl methionine, the main donor of methyl groups, and for adequate epigenetic regulation.[35,36]

It is well known that starting folic acid supplementation 1 month before pregnancy reduces over 70% of neural tube defects.[8] Worldwide, it is recommended that all women who may become, plan to become, or are pregnant take a daily supplement of 0.4mg to 0.8mg (400-800µg) of this vitamin.[37]

On the other hand, by using animal models extrapolated to humans, it has been found that the consumption of folic acid during the first 3 weeks of pregnancy prevents heart disease due to teratogenic exposure.[6,7] There is epidemiological evidence in humans that maternal folate supplementation is associated with a significant decrease in the risk of CHD (RR: 0.72; 95%CI: 0.63-0.82).[9]

This study found that only 10% of mothers started folic acid supplementation 1 month before conception, 30% during the first month of pregnancy, 36.66% after the first month, 16.66% did not receive supplementation and 6.66% took some multivitamin after the first month of pregnancy. The methodology used does not allow stating that the folate consumed did not have a protective effect against congenital anomalies. However, it showed that a high percentage (60%) of mothers did not consume it in the way recommended to generate a protective effect against neural tube defects nor in the way theoretically suggested by animal studies to achieve a protective effect against heart disease. Thus, although 83.34% of mothers received folic acid supplementation, it could only have a potential protective effect against neural tube defects and heart disease in the 10% who initiated it 1 month before conception, and it only had a potential protective effect against CHD in the 30% who initiated it during the first month of conception.

It is very interesting that the teratogenic mechanism of several of these factors (diabetes, X-rays, cigarettes, alcohol) is the generation of oxidative stress, since insufficient or inappropriate consumption of folic acid, which has an antioxidant action, may facilitate teratogenesis by these factors.

Vitamin A intake

The teratogenic effect of retinoic acid —a vitamin A derivative— on cardiovascular morphogenesis has been demonstrated in animal models at both higher[38,39] and lower than normal doses.[40,41] In this study, 6.66% of the mothers took a multivitamin and were unaware of its vitamin A content, and even 3.33% claimed to have specifically consumed vitamin A. In this regard, there is a need to raise awareness of the risk of excessive supplementation and the need to discuss micronutrient intake with the physician.

Use of warfarin

Exposure to warfarin between the 6th and 9th week of pregnancy results in hypoplasia of the nasal bone; depressed nasal bridge; deep depression between the nose wings and nasal tip; punctate calcifications of the epiphysis of the axial skeleton, proximal femur, and calcaneus bone (which disappear after the first year); hypoplastic distal phalanges that look like inverted triangles; low birth weight; and sometimes CHD. Moreover, exposure between the 14th and 20th week produces microcephaly, hydrocephaly, Dandy-Walker malformation, agenesis of the corpus callosum, cerebellar degeneration, seizures, spasticity, intellectual disability, language disorders, optic atrophy, cataracts, microphthalmia, Peters anomaly, intrauterine growth restriction and scoliosis.[8]

This study found a mother exposed to warfarin since the 9th week; her child presented with non-syndromic transposition of the great arteries and none of the other characteristics of fetal warfarin syndrome. Thus, it is evident that there is a need to educate medical personnel about drug teratogenesis and pharmacological alternatives in order to obtain therapeutic effects with drugs without teratogenic potential.

Use of misoprostol

Prenatal exposure to misoprostol in the first trimester of pregnancy for abortion purposes has been associated with Moebius sequence, limb defects, among other congenital anomalies.[42] For example, Pachajoa *et al.*[43] reported a case of prenatal exposure to misoprostol in which the newborn presented CHD.

This study found a mother exposed to this drug in the second month of pregnancy, with a child that had subvalvular aortic stenosis, tricuspid but functionally bicuspid aortic valve and aortic vascular ring in the descending thoracic aorta.

The limitations of this research include that the sample used was small and the methodology employed has risk of memory bias. In addition, exposures were evaluated only through questions to the patients' mothers and reviews of available medical history at the time of evaluation, while no laboratory exams were performed to determine exposures.

Conclusions

This case series presents several prenatal exposures associated with potential risk for CHD, such as maternal diabetes, vitamin A intake, undergoing unprotected x-ray studies, altered pregestational BMI, alcohol consumption, passive smoking and inadequate folic acid supplementation.

Insufficient or untimely intake of folic acid could facilitate the generation of teratogenic effects of oxidizing substances. Therefore, women in Cali should be educated about the importance of adequate folic acid intake and the risks of exposure to teratogenic agents during pregnancy.

Prenatal detection of congenital defects, including heart disease, was low (10%), which highlights the need to implement neonatal CHD screening with pulse oximetry.

Conflicts of interest

None stated by the authors.

Funding

This work was financed with resources from the Universidad del Valle.

Acknowledgements

To Universidad del Valle, Clínica Neurocardiovascular DIME and Clínica Versalles.

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rfm
Revista de la Facultad de Medicina

ORIGINAL RESEARCH
DOI: http://dx.doi.org/10.15446/revfacmed.v68n1.71589
Received: 08/04/2018 Accepted: 06/07/2018

Cumulative incidence of lethal congenital anomalies in Peru

Incidencia acumulada de anomalías fetales incompatibles con la vida en Perú

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Abstract

Introduction: Lethal congenital anomalies (LCA) are anomalies associated with early stillbirth or newborn death. Currently, there are no data on the incidence of LCAs in Peru.
Objectives: To estimate the cumulative incidence of LCAs in Peru, the Department of Lima, and six hospitals located in the city of Lima (Peru), and to describe the characteristics of LCA cases reported between 2012 and 2016 at Instituto Nacional Materno Perinatal (INMP), located in Lima, Perú.
Materials and methods: Cumulative incidence of LCAs in Peru was determined based on the cases reported in a five-year period, which varied depending on data accessibility (2011-2015 and 2012-2016). In addition, the medical records of neonates with LCA registered at INMP were reviewed to identify the characteristics of these cases.
Results: Cumulative incidence of LCAs in Peru was 0.89 cases per 10 000 newborns, while at INMP it was 7.19 cases. Out of 48 newborns with LCAs treated at INMP during the study period, 54.2% were born with neonatal depression, and 83.3% died during their hospital stay.
Conclusion: Cumulative incidences of LCAs reported here (Lima, Department of Lima, and Peru) were lower than those described by international epidemiological surveillance systems, which might be caused due to shortcomings related to the registration of these cases in the health institutions and records analyzed here.
Keywords: Congenital Abnormalities; Perinatal Mortality; Fetal Mortality (MeSH).

Taype-Rondan A, Zafra-Tanaka JH, Guevara-Ríos E, Chávez-Alvarado S. Cumulative incidence of lethal congenital anomalies in Peru. Rev. Fac. Med. 2020;68(1):44-50. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.71589.

Resumen

Introducción. Las anomalías fetales incompatibles con la vida (AFIV) son aquellas que se asocian con la muerte temprana del feto o del recién nacido. En la actualidad, se desconoce la magnitud de este problema en Perú.
Objetivos. Estimar la incidencia acumulada de AFIV en Perú, en el departamento de Lima y en seis hospitales de la ciudad de Lima, y describir las características de este tipo de anomalías reportadas entre 2012 y 2016 en el Instituto Nacional Materno Perinatal (INMP) de Lima, Perú.
Materiales y métodos. Se determinó la incidencia acumulada de las AFIV reportadas en un período de cinco años en Perú, el cual varió dependiendo de la disponibilidad de los datos (2011-2015 y 2012-2016). Además, se revisaron las historias clínicas de los neonatos con AFIV registradas en el INMP para obtener sus características.
Resultados. La incidencia acumulada de AFIV en todo el Perú fue de 0.89 por cada 10 000 recién nacidos y en el INMP fue 7.19. De los 48 recién nacidos con AFIV atendidos en el INMP, 54.2% nacieron con depresión neonatal y 83.3% fallecieron en el hospital.
Conclusión. Las incidencias acumuladas de AFIV encontradas fueron menores a las reportadas por los sistemas internacionales de vigilancia epidemiológica, lo que podría deberse a falencias en su registro en las instituciones de salud y registros analizados.
Palabras clave: Anomalías congénitas; Mortalidad perinatal; Mortalidad fetal (DeCS).

Taype-Rondan A, Zafra-Tanaka JH, Guevara-Ríos E, Chávez-Alvarado S. [Incidencia acumulada de anomalías fetales incompatibles con la vida en Perú]. Rev. Fac. Med. 2020;68(1):44-50. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.71589.

Introduction

According to the Sociedad Española de Ginecología y Obstetricia (Spanish Society of Gynecology and Obstetrics), lethal congenital anomalies (LCA) are "anomalies that are predictably/usually associated with the death of the fetus or newborn during the neonatal period."[1, p97] While most of these cases result in death before or immediately after birth, some children may live for days or even years.[2,3] Thus, studying the incidence of LCAs is highly relevant, considering that it may reveal possible teratogenic agents.[4]

Multiple epidemiological surveillance systems and other primary studies have assessed the incidence of LCAs, since many of them are compiled by the International Clearinghouse Centre for Birth Defects (ICBDSR), which includes information from 29 countries.[5] One of the largest and most organized surveillance systems is the European Surveillance of Congenital Anomalies (EUROCAT), which consists of 23 European countries that follow a standardized data collection methodology.[6]

In Latin America, most countries do not have surveillance systems for LCAs, but some studies have reported new cases of congenital anomalies.[7,8] The Latin American Collaborative Study of Congenital Malformations (ECLAMC) collects data from several sentinel hospitals in 7 South American countries (4 from Chile, 4 from Argentina, 4 from Brazil, 2 from Bolivia, 4 from Venezuela, 1 from Colombia and 1 from Peru), although they do not report incidences for each country.[9] The data reported for Peru are provided by the Hospital Nacional Edgardo Rebagliati Martins (HNERM), a Social Security (EsSalud) referral institution located in Lima that treats pregnant women who are employed or have a partner who is employed. The HNERM is a reference center since it attends the largest number of births in EsSalud.[10]

Estimates are that 945 children are born with LCAs in Peru each year;[11] however, few studies have delved into this figure: Velásquez-Hurtado *et al.*[12] evaluated the records of neonatal deaths in the provincial municipalities of Huánuco and Ucayali and reported 1 case of trisomy 18 among 11 441 births in 2011; del Aguila-del Aguila[13] reviewed the records of the neonatal service of EsSalud's Hospital III Iquitos and reported 4 cases of anencephaly among 2 982 births in 2014; finally, Mansilla-Gallegos[14] analyzed the records of neonates with chromosomopathies at the Cytogenetics Laboratory of the Hospital Nacional Edgardo Rebagliati Martins and reported 25 cases of trisomy 18 and 11 of trisomy 13 among 25 086 births in the period 2013-2015. These studies did not assess the characteristics of infants with LCAs.

The lack of information on the incidence of LCAs and their characteristics does not allow measuring their impact on the Peruvian context. Therefore, this study has 2 objectives: to estimate the cumulative incidence of infants with LCAs in 6 hospitals of Lima, in the department of Lima and throughout Peru over a 5-year period, and to describe the characteristics of the cases reported between 2012 and 2016 at the Instituto Nacional Materno Perinatal (INMP) of Lima. It should be clarified that the INMP was selected to make the specific characterization of the anomalies because it is the reference hospital of the Ministry of Health (MINSA) and the one that attends the largest number of births in the country.[15]

Materials and methods

Study design

A secondary data analysis was conducted to estimate the cumulative incidence of infants with LCAs in six hospitals of Lima, the department of Lima and throughout Peru. For its part, the INMP carried out a retrospective analysis of the medical records of neonates born with congenital anomalies to describe their characteristics.

Definition of LCA

According to SEGO, which proposes a list of 17 of anomalies (Table 1), LCAs are defined as conditions that, due to their severity, do not require evaluation by a clinical committee to determine its classification, since it would be considered as such anywhere in the world due to its poor prognosis.[1] However, since the records analyzed were based on the 10th revision of the International Classification of Diseases (ICD-10),[16] it was only possible to evaluate the 9 LCAs currently included in that classification. It should be noted that the term LCA has not yet been adopted by the Peruvian health system.

Table 1. List of lethal congenital anomalies according to the Sociedad Española de Ginecología y Obstetricia.

N	Diagnosis	ICD-10 Code	Evaluated in this study
1	Anencephaly/ Acephaly/Acrania	Q00.0	Yes
2	Holoprosencephaly	Q04.2	Yes
3	Renal agenesis, bilateral	Q60.1	Yes
4	Potter's syndrome	Q60.6	Yes
5	Thanatophoric short stature	Q77.1	Yes
6	Trisomy 18	Q91.0 - Q91.3	Yes
7	Trisomy 13	Q91.4 - Q91.7	Yes
8	Trisomy 9	Q92.0 - Q92.1	Yes
9	Triploidy and polyploidy	Q92.7	Yes
10	Hydranencephaly	-	No
11	Laryngeal atresia	-	No
12	Tracheal atresia	-	No
13	Agenesis of the diaphragm	-	No
14	Ectopia cordis	-	No
15	Pentalogy of Cantrell	-	No
16	Amniotic band syndrome	-	No
17	Limb-body wall complex	-	No

ICD-10: International Classification of Diseases, 10th revision.
Source: Elaboration based on the data of the Sociedad Española de Ginecología y Obstetricia [1] and the ICD-10.[16]

A newborn with LCA was that which had one of the 9 LCA diagnoses contemplated in the ICD-10. Anomalies that were not coded in the ICD-10 were not included in the study as it was not possible to identify them. Cumulative incidence was used as a unit of measurement; it was estimated by dividing the number of reported LCA cases by the number of live births in the period studied, which, for accessibility reasons, varied as follows: from 2011 to 2015 in the Hospital Nacional Arzobispo Loayza (HNAL), the Hospital Nacional Docente Madre Niño San Bartolomé (HONADOMANI) and the records from Peru and Lima, and from 2012 to 2016 in the Hospital Nacional Cayetano Heredia (HNCH), the Hospital María Auxiliadora (HMA), theHospital Nacional Sergio E. Bernales (HNSEB) and the INMP.

Procedures

Information on the incidence of the 9 LCAs contemplated in the ICD-10 was collected over a 5-year-period for all of Peru, the department of Lima, 5 hospitals in Lima and the INMP from three sources:

For all of Peru and for the department of Lima. This information was requested from the MINSA's Public Information Access System (SAIP),[15] which obtains its data from the hospital discharge records of the ministry's level II and III centers and merges them into the central statistics office. It should be noted that only the main diagnosis of each patient's epicrisis is found in these records. In addition, the total number of births reported to MINSA for all of Peru and the department of Lima was requested in order to calculate incidences.

For hospitals in Lima. This information was requested from the SAIP for each of MINSA's Level III hospitals in Lima, and only five responded: the HNCH, the HNAL, the HMA, the HONADOMANI and the HNSEB. Only the main diagnosis of the epicrisis of each newborn is found in these records. In addition, the number of births reported by each of the hospitals assessed was requested in order to calculate incidences.

For the INMP. The INMP's Statistics and Information Office was asked for the hospitalization databases of its neonatal service, in which the ICD-10 codes of each newborn born in that hospital were recorded, including stillborn children. After identifying the neonates with any of the 9 LCAs described in the ICD-10, a manual review of their medical records was performed to corroborate the diagnoses and extract the demographic and maternal/perinatal characteristics.

Variables

The main variable considered for the present study was the presence of any of the LCAs evaluated as described above. In the specific case of INMP, other variables collected during the review of medical records were: mother's age, gestational age at birth using the Capurro test (full term ≥37 weeks of gestation), type of delivery (vaginal or cesarean), neonatal depression (score <7 on the Apgar score 5 minutes after birth), sex of the newborn, hospitalization and death during the hospital stay.

Statistical analysis

Central tendency measures were used for the presentation of the results: dispersion for quantitative variables, and relative and absolute frequencies for qualitative variables. The analysis was done using Stata v14.0 (Stata Corp, College Station, TX, US).

Ethical considerations

This study followed the ethical principles outlined in the Declaration of Helsinki.[17] The research was based on secondary database analysis of, which were analyzed respecting privacy.

The protocol of the present study was approved by the INMP's Institutional Committee of Ethics through letter No. 0213-2017-DG-N°-083-OEAIDE/INMP of September 20, 2017.

Results

According to data provided by the SAIP for the periods studied (2011-2015 and 2012-2016), an incidence of 0.89 cases per 10 000 newborns was reported for Peru, 1.26 cases per 10 000 newborns for the department of Lima, and between 0.00 and 7.39 cases per 10 000 newborns for the 5 hospitals in the city of Lima from which data were obtained. Likewise, when evaluating INMP data, an incidence of 7.19 LCA cases per 10 000 newborns was obtained. The most frequent anomaly in this institution was anencephaly, followed by trisomy 18; no cases of bilateral renal agenesis, thanatophoric dysplasia, trisomy 9 or triploidy were reported (Table 2).

Sixty-six medical records of neonates with ICD-10 codes associated with some LCA were entered in the hospitalizations database of the INMP's neonatology service. However, a review of the medical records found that 18 had no diagnosis compatible with this type of anomalies, for a final count of 48 cases. After assessing the characteristics of the final sample, it was found that 20 infants died immediately after birth and the remaining 28 were hospitalized. In the end, 40 died in the hospital and no information was obtained on the survival of the remaining 8 once they were discharged (Table 3).

Discussion

The incidence of LCAs in Peru, the department of Lima, and 5 hospitals in Lima was established according to records provided by the SAIP, and the neonatal database of the INMP. The most frequent LCA was anencephaly, followed by trisomy 18. No cases of bilateral renal agenesis, thanatophoric dysplasia, trisomy 9 or triploidy were found.

Table 2. Incidence of lethal congenital anomalies per 10 000 births throughout Peru, in the department of Lima and six hospitals in the city of Lima.

Diagnosis	Peru * (2011-2015)	Department of Lima (2011-2015)	HNAL (2011-2015)	HONADOMANI (2011-2015)	HNCH (2012-2016)	HMA (2012-2016)	HNSEB (2012-2016)	INMP (2012-2016)
	n (Incidence)	n (Incidence)	n (Incidence)	n (Incidence)	n (Incidence)	n (Incidence)	n (Incidence)	n (Incidence)
Anencephaly/ Exencephaly/ Acrania	163 (0.71)	72 (1.02)	11 (5.42)	1 (0.29)	2 (0.91)	7 (1.81)	-	24 (3.59)
Trisomy 18	29 (0.13)	11 (0.16)	-	2 (0.59)	-	-	-	12 (1.80)
Alobar holoprosencephaly	-	-	1 (0.49)	1 (0.29)	-	1 (0.26)	-	6 (0.90)
Potter's syndrome	-	-	-	1 (0.29)	1 (0.46)	-	-	5 (0.75)
Trisomy 13	13 (0.06)	6 (0.08)	3 (1.48)	1 (0.29)	-	-	-	1 (0.15)
Bilateral renal agenesis	-	-	-	-	-	-	-	-
Thanatophoric dysplasia	-	-	-	-	-	-	-	-
Trisomy 9	-	-	-	-	-	-	-	-
Triploidy	-	-	-	-	-	-	-	-
Total	205 (0.89)	89 (1.26)	15 (7.39)	6 (1.76)	3 (1.37)	8 (2.07)	0 (0.00)	48 (7.19)
Newborns during the period	2 307 247	707 696	20 301	34 156	21 961	38 585	24 520	66 771

HNAL: Hospital Nacional Arzobispo Loayza; HONADOMANI: Hospital Nacional Docente Madre Niño San Bartolomé; HNCH: Hospital Nacional Cayetano Heredia; HMA: Hospital María Auxiliadora; HNSEB: Hospital Nacional Sergio E. Bernales; INMP: Instituto Nacional Materno Perinatal.
* Peru: figures for all of Peru.
Source: Own elaboration.

Table 3. Characteristics of neonates born with lethal congenital anomalies at the Instituto Nacional Materno Perinatal. 2012-2016.

Diagnosis	n	Mother's age	Gestational age at birth	Cesarean section delivery	Neonatal depression	Female sex	Hospitalized *	Immediate death after birth	Death during hospital stay
		$\bar{x}\pm\sigma$	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Anencephaly/ Exencephaly/ Acrania	24	29.2±7.1	13 (54.2)	8 (33.3)	18 (75.0)	8 (33.3)	9 (37.5)	15 (62.5)	24 (100.0)
Trisomy 18	12	32.1±8.0	3 (25.0)	7 (58.3)	3 (25.0)	5 (41.7)	11 (91.7)	1 (8.3)	9 (75.0)
Alobar holoprosencephaly	6	22.3±4.6	5 (83.3)	2 (33.3)	2 (33.3)	3 (50.0)	4 (66.7)	2 (33.3)	1 (16.7)
Potter's syndrome	5	25.8±7.2	2 (40.0)	3 (60.0)	2 (40.0)	3 (60.0)	4 (80.0)	1 (20.0)	5 (100.0)
Trisomy 13	1	23.0	0 (0.0)	0 (0.0)	1 (100.0)	1 (100.0)	0 (0.0)	1 (100.0)	1 (100.0)
TOTAL	48	28.6±7.5	23 (47.9)	20 (41.7)	26 (54.2)	20 (41.7)	28 (58.3)	20 (41.7)	40 (83.3)

$\bar{x}$: mean; σ: standard deviation.
Source: Own elaboration based on the data obtained in the study.

Cumulative incidence of LCAs

The incidence of LCAs found in the records for Peru, for the department of Lima and for most of the hospitals evaluated was lower than that found in the INMP database. This may be explained by differences in the methodology used, since INMP data were obtained from the hospital database, while central and hospital reports were used for the other populations evaluated (Peru, Lima department, and the other hospitals) and they only included the main diagnosis recorded in the patient's epicrisis at discharge, which may not necessarily be a LCA.

Other explanations to this difference in the incidence would be that other medical centers refer pregnant women with fetuses diagnosed with some LCA to the INMP, thus increasing its numbers. This could also be associated with the fact that the INMP, which has the largest neonatology service of the country, has trained personnel and the necessary supplies to make an adequate diagnosis of LCA, which would be underdiagnosed in other places.

On the other hand, the incidence for Peru (0.89 LCAs per 10 000 births) was much lower than that reported by international surveillance systems such as EUROCAT,[6] the Latin American Collaborative Study of Congenital Malformations (ECLAMC),[9] the National Registry of Congenital Anomalies of Argentina (RENAC)[18] and the Mexican Program for Registration and Epidemiological Surveillance of External Congenital Malformations (RYVEMCE),[19] which had incidents between 6.60 and 14.53. Since there is no reason to assume that the incidence of LCAs in Peru is lower than in other countries, estimates are that the records provided by the SAIP underestimate the figure by about 90%.

All this is very concerning, since knowing the actual magnitude of the problem, detect clusters of cases, carry out studies of associated factors and evaluate the impact of preventive measures, such as the use of folic acid supplements to avoid neural tube defects, is only possible if LCAs are properly reported.[20] This could be achieved by adopting an anomalies surveillance system as is the case of other countries and regions.[6,9,18,19]

Regarding international surveillance systems, the incidence reported by EUROCAT was twice as high as that reported by ECLAMC, RENAC, RYVEMCE and INMP. The reason may be that EUROCAT reports congenital anomalies in hospitals of various European countries in a standardized manner, while the other systems tend to combine hospitals and have varying degrees of standardization in their reporting. It is also possible that population differences, such as maternal age at conception and the spread of prenatal diagnosis in Europe, make EUROCAT records larger than those of other surveillance systems. Table 4 presents the incidents found by the above-mentioned international surveillance systems.

Table 4. Comparison between studies on incidences of lethal congenital anomalies per 10 000 births.

Diagnosis	Peru (2011-2015)	INMP (2012-2016)	RENAC (2012-2015)	EUROCAT (2011-2015)	ECLAMC (2007-2011)	RYVEMCE (2007-2011)
Anencephaly/Exencephaly/ Acrania	0.71	3.59	2.75	4.04	5.79	3.58
Trisomy 18	0.13	1.80	1.13	5.67	1.32	0.67
Alobar holoprosencephaly	-	0.90	2.38	1.51	0.78	1.79
Potter's syndrome	-	0.75	-	1.22	-	-
Trisomy 13	0.06	0.15	0.40	2.09	0.57	0.56
Bilateral renal agenesis	-	-	0.43	-	-	-
Thanatophoric dysplasia	-	-	0.12	-	-	-
Trisomy 9	-	-	-	-	-	-
Triploidy	-	-	-	-	-	-
Total	0.89	7.19	7.21	14.53	8.46	6.60

INMP: Instituto Nacional Materno Perinatal; RENAC: National Registry of Congenital Anomalies of Argentina; EUROCAT: European Surveillance of Congenital Anomalies; ECLAMC: Latin American Collaborative Study of Congenital Malformations; RYVEMCE: Mexican Program for Registration and Epidemiological Surveillance of External Congenital Malformations. Source: Own elaboration.

Characteristics of newborns with LCA

When reviewing the medical records of infants with LCAs born at INMP, it was found that 4 out of 10 died before they could be hospitalized, either in the delivery room or in the newborn's immediate care area, and that a similar proportion died during hospitalization. It should be noted that this high mortality is to be expected for this type of anomalies

When the different types of LCAs are studied separately, it can be seen that survival at discharge is almost entirely attributable to cases of holoproscencephaly and trisomy 18. Previous studies have also found a high survival rate related to these pathologies in the first week (71% and 65%, respectively), which drops drastically after the first year (47% and 16%, respectively).[2] This relatively long survival could impact the mother and the rest of her family financially and mentally, and this should be evaluated in future studies.

Implications

Most newborns with LCAs die, and if they survive, the degree of disability is high. Although these types of anomalies are rare, they are highly relevant because of their potential impact on mothers' physical and mental

health, such as psychological reactions of hopelessness, sadness, or guilt.[21-23] The magnitude of these damages has not been adequately assessed in countries where termination of pregnancy due to LCAs is illegal, and more studies are needed in Peru to assess the consequences and effectiveness of preventive interventions —such as the use of folic acid supplements for the prevention of anencephaly[24] or appropriate counseling on the mother's age at conception as a risk factor for trisomy 13 or trisomy 18—[25] and recovery interventions —including psychological support to the woman during and after pregnancy and avoiding medical futility in these babies.

Limitations and strengths

The main limitation of this study was the use of a secondary database (SAIP) and clinical records for the collection of information, which prevents ensuring that all diagnoses are reported, or that all the reported diagnoses are entered into the databases of the centers from which the information was obtained. Furthermore, since these databases only included the LCAs covered by the ICD-10,[16] it was not possible to track the 17 LCAs proposed by SEGO;[1] therefore, the cumulative incidence of LCAs is expected to be underestimated.

Another limitation is that the SAIP may have duplicate data, i.e. some patients may have gone to more than one hospital. However, due to the high lethality of LCAs during hospitalization and the underreporting observed, this was considered unlikely.

This is the first study that describes the incidence and characteristics of LCAs in Peru, so it is a relevant source of information to understand the impact and consequences that these anomalies can have in the country.

Conclusion

Cases of LCAs were reported for Peru, the department of Lima and six hospitals in Lima. The most frequent LCA was anencephaly, followed by trisomy 18, while no cases of bilateral renal agenesis, thanatophoric dysplasia, trisomy 9 or triploidy were found. In general, the incidences of LCAs found in this study are lower than those reported by international surveillance systems, which may be explained by shortcomings in the reporting of medical centers and the records analyzed.

Conflicts of interest

None stated by the authors.

Funding

This study was funded by the Centro de la Mujer Peruana Flora Tristán and the Centro de Promoción y Defensa de los Derechos Sexuales y Reproductivos through the Save Abortion Action Fund (SAAF) project in coordination with the International Planned Parenthood Federation (IPFF).

Acknowledgements

To Dr. Luis Távara and Rossina Guerrero for their valuable comments and support during the development of this study, and to Dr. Sixto Sánchez and Stefan Escobar for their comments and suggestions regarding the writing of the manuscript.

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rfm
Revista *de la* Facultad *de* Medicina

ORIGINAL RESEARCH
DOI: http://dx.doi.org/10.15446/revfacmed.v68n1.69979
Received: 24/01/2018 **Accepted:** 07/05/2018

Cardiovascular disease risk markers in children under 10 years of age and their relationship with serum concentrations of IGF-1, IGFBP-1, IGFBP-2 and IGFBP-3

Marcadores de riesgo cardiovascular en niños menores de 10 años y su relación con niveles séricos de IGF-1, IGFBP-1, IGFBP-2 e IGFBP-3

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Abstract

Introduction: Any type of nutritional imbalance experienced during childhood will affect the health of an individual, both in their childhood and their adulthood. Several studies have proved that there is an association between cardiovascular disease (CVD) risk and endocrine and lipid markers at early stages of life.
Objective: To establish the relationship between nutritional status (IGF-1 and serum levels of its binding proteins IGFBP-1, IGFBP-2 and IGFBP-3), and CVD risk markers in students aged 7 to 9 years.
Materials and methods: Cross-sectional observational study conducted in 84 children attending two schools from Bogotá D.C. and Soacha, Colombia, to identify the relationship between possible variations in CVD risk markers and nutritional status. Sexual development stage, lipid profile, anthropometric data, blood sugar levels and IGF-1 and IGFBP serum levels of all participants were measured. Statistical analysis was conducted using the Pearson's correlation coefficient, the analysis of variance (ANOVA), and the Kruskall-Wallis, Games-Howell and Dunnett's tests. The confidence interval and statistical significance were 95% and $p<0.05$, respectively.
Results: IGFBP-1 and IGFBP-2 levels proportionally decreased as weight increased. An inverse correlation between both proteins and triglyceride levels was found, as well as a direct correlation with HDL cholesterol levels.
Conclusions: Alterations in CVD risk markers can be identified during childhood. If said alterations are timely detected, it is possible to adopt preventive and therapeutic actions such as the promotion of public policies aimed at preventing childhood overweight and obesity, which in turn will reduce the risk of developing cardiovascular disease in adulthood.
Keywords: Nutritional Status; Insulin-Like Growth Factor Binding Protein 1; Insulin-Like Growth Factor Binding Protein 2; Insulin-Like Growth Factor Binding Protein 3; Pediatric Obesity; Dyslipidemias (MeSH).

Vera S, Figueroa T, Aranzalez LH, Mockus I. Cardiovascular disease risk markers in children under 10 years of age and their relationship with serum concentrations of IGF-1, IGFBP-1, IGFBP-2 and IGFBP-3. Rev. Fac. Med. 2019;68(1): 51-8. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.69979.

Resumen

Introducción. Los desequilibrios nutricionales en la infancia afectan la salud tanto en la niñez como en la adultez. Estudios previos demuestran la asociación de marcadores endocrinos y lipídicos con riesgo cardiovascular (RCV) desde edades tempranas.
Objetivo. Establecer la relación entre estado nutricional (niveles séricos de IGF-1 y sus proteínas enlazantes IGFBP-1, IGFBP-2 e IGFBP-3) y marcadores de RCV en estudiantes de 7 a 9 años.
Materiales y métodos. Estudio observacional comparativo transversal realizado en 84 niños de 2 colegios de Bogotá D.C. y Soacha, Colombia, para identificar la relación entre posibles variaciones de marcadores de RCV y estado nutricional. Se midieron los niveles de glucemia y niveles séricos de IGF-1 e IGFBP, el nivel de desarrollo sexual, el perfil lipídico y los valores antropométricos. Para el análisis estadístico se utilizaron el coeficiente de correlación de Pearson, un análisis de varianza (ANOVA) y las pruebas de Kruskal Wallis, Games-Howell y Dunnett. El intervalo de confianza fue del 95% y la significancia estadística, de $p<0.05$.
Resultados. La reducción en los niveles de IGFB-1 e IGFBP-2 fue directamente proporcional al aumento de peso. Por otra parte, se observó una correlación inversa entre ambas proteínas y concentraciones de triglicéridos, y una directa con los niveles colesterol HDL.
Conclusiones. Las alteraciones de marcadores de RCV se pueden identificar en la infancia. Si estas son detectadas a tiempo es posible adoptar medidas preventivas y terapéuticas como la promoción de políticas públicas dirigidas prevenir el sobrepeso infantil, lo que a su vez reducirá el riesgo de padecer enfermedades cardiovasculares en edades adultas.
Palabras clave: Estado nutricional; Proteína 1 de unión a factor de crecimiento similar a la insulina; Proteína 2 de unión a factor de crecimiento similar a la insulina; Proteína 3 de unión a factor de crecimiento similar a la insulina; Obesidad pediátrica; Dislipidemias (DeCS).

Vera S, Figueroa T, Aranzalez LH, Mockus I. [Marcadores de riesgo cardiovascular en niños menores de 10 años y su relación con niveles séricos de IGF-1, IGFBP-1, IGFBP-2 e IGFBP-3]. Rev. Fac. Med. 2019;68(1):51-8. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.69979.

Introduction

Childhood obesity and overweight are highly prevalent in Colombia. Currently, 1 out of every 6 children between the ages of 5 and 17 has one of these conditions,[1] situation that Fernández-Juan *et al.*[2] have reported on schoolchildren from Bogotá. Worldwide, several studies have discussed the relationship between childhood and adult lipid metabolism, and have reported that serum levels of total cholesterol, lipoproteins and body mass index (BMI) in children are predictors of cardiovascular disease (CVD) risk in adulthood.[3-5]

Delgadillo-Guerra & Romero-Hernández[6] report that alterations in glucose and insulin metabolism associated with dyslipidemia and changes in blood pressure are risk factors for the development of cardiovascular disease (CVD) and type 2 diabetes, conditions that can occur at an early age and persist into adulthood. In addition, insulin resistance (IR) and hyperinsulinemia are risk factors for metabolic syndrome (MS) in puberty.[7,8]

Considering the anabolic and mitogenic effects of insulin-like growth factor 1 (IGF-1) and its important role in development and growth, in recent years an association has been reported between this factor, as well as 3 of its binding proteins (IGFBP-1, IGFBP-2 and IGFBP-3), and the development of CVD.[9,10] It has also been suggested that the IGF/IGFBP axis may influence atherogenesis through the stimulation of vascular smooth muscle cells and foam cells proliferation, possibly by acting on lipid levels in blood and insulin sensitivity.[11]

IGF-1 is an effector hormone that is synthesized in multiple organs —especially the liver—, is essential for growth, and plays an important role in mediating growth hormone (GH) function;[9,12] it is also homologous to insulin and is capable of inhibiting proteolysis and stimulating glucose uptake, glycogen synthesis and lipogenesis.[13,14] In this regard, Mohanraj *et al.*[15] describe the relationship between obesity and circulating levels of IGFBP, while Akanji *et al.*[11] state that alterations in the IGF/IGFBP axis may increase the risk of CVD and that increased IGF-I is associated with premature atherosclerosis and increased risk of CVD.

IGFBP-1 is one of six binding proteins that regulates IGF-1 bioactivity. Its production in the liver is regulated by insulin.[16] Its plasma concentrations have been associated with metabolic, nutritional and anthropometric factors,[17] and its levels are inversely proportional to adiposity and IR.[18] Circulating concentrations of this protein are high during fasting, malnutrition and both types of diabetes, and are low in overweight cases.[19,20] There is also evidence that suggests that IGFBP-1 is a useful predictive marker of CVD risk given its relationship with BMI, circulating proinsulin levels, MS,[21] IR[11,17,22] and even fatty liver.[9,16]

On the other hand, IGFBP-2 is a biomarker that allows identifying IR and high CVD risk in adults. It is the most common IGFBP expressed during childhood and the main IGFBP produced by adipocytes. Recent studies have shown an inverse correlation between the circulating levels of this protein and adiposity. A similar correlation between IR and adiposity has also been described. Determining the levels of IGFBP-2 is useful in order to deepen understanding of the correlation between nutrition, growth, obesity and CVD risk.[23-25]

Regarding IGFBP-3 —protein synthesized mainly by the liver—, its circulating levels have been associated with CVD, obesity and IR. It has also been proven that it acts as an anti-inflammatory factor capable of inhibiting the pathway of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB).[15]

Mohanraj *et al.*[15] reported that proteolytic IGFBP-3 is positively correlated with adiposity parameters such as waist circumference (WC), BMI, fasting insulin and IR in overweight and obese population. Moreover, several studies have described an increase in IGF-1 and IGFBP-3 levels in overweight and obese adolescents.[15,19,20] This protein appears to have an antiproliferative action in vascular smooth muscle cells,[11] which inhibits the formation of atheromatous plaque.

With all this in mind, the aim of this study was to establish the correlation between nutritional status —determined by anthropometry and serum levels of IGF-1 and its binding proteins (IGFBP-1, IGFBP-2 and IGFBP-3)— and CVD risk markers in students aged between 7 and 9 years enrolled in 2 schools.

Materials and methods

Comparative cross-sectional observational study conducted in 84 children between 7 and 9 years of age to identify the correlation between possible variations in CVD risk markers and nutritional status.

This research was carried out during the second half of 2014 in a school located in Bogotá D.C. and another in Soacha, and was approved by the Ethics Committee of the Faculty of Medicine of the Universidad Nacional de Colombia by means of Minutes No. 75 of November 28, 2013. The study complied with all ethical aspects and followed the principles of the Declaration of Helsinki;[26] it was also classified as a minimal risk research according to Resolution 8430 of 1993[27] of the Colombian Ministry of Health. Both children and their guardians signed an informed consent

A non-probabilistic sample for convenience was selected; students enrolled at the Instituto Educativo Distrital Llano Oriental (Bogotá D.C.) and the Liceo Integral Los Alisos (Soacha) schools were included. The selection criteria were children aged between 7 and 9 years and 11 months, with no disease that could affect the results (diabetes, systemic arterial hypertension, hypoglycemia, hyperglycemia, hypercholesterolemia and growth hormone alteration), and children who had used medications in the last month. All the children were at stage 1 on the Tanner scale (no apparent sign of sexual maturation).

Weight was measured on a Tanita scale, with the participants barefoot and dressed in light clothing; height was determined using a dry stadiometer according to the recommendations of the World Health Organization's (WHO) growth pattern instructions for Colombia.[28] BMI or Quetelet index was defined as weight/height expressed in kg/m^2, and WC was measured in a horizontal plane halfway between the last right rib and the iliac crest using an inelastic fiberglass tape.

Blood samples were taken from the antecubital vein by venepuncture after 12 hours of fasting and centrifuged at 3 500 rpm for 5 minutes. The sera obtained were stored at -20ºC in order to measure blood glucose levels and lipid profile, and at -80ºC for determining IGF-1 and its 3 binding proteins.

Total cholesterol (total-c), triglycerides (TG), high-density cholesterol (HDL-c) and blood glucose were

measured using spectrophotometric enzymatic techniques; low-density cholesterol (LDL-c) was calculated using the Friedewald equation and non-HDL cholesterol (non-HDL-c) was defined as the difference between total-c and HDL-c. Serum levels of IGF-1, IGBP-1, IGFBP-2 and IGBP-3 were determined by double-binding enzyme immunoassay (ELISA) according to the manufacturer's instructions (DIAsource). This process was performed with the DS2/DSX automated equipment.

The WHO growth reference data for children and adolescents (2007) were used to interpret anthropometric variables as set forth in Resolution 2465 of 2016.[28] Moreover, weight/height, height/age and WC/age indicators were established and five subgroups with a similar number of children were formed: 1) low height-for-age and risk of low height-for-age, 2) eutrophic, 3) adequate weight and high WC, 4) overweight and 5) obese. WC in childhood was classified according to the percentiles established by McDowell *et al.*[29] and the lipid profile fractions were classified, as indicated by Bamba,[30] according to the National Heart, Lung, and Blood Institute (NHLBI) cholesterol screening guidelines and cut-off points,[30] which are also based on the National Cholesterol Education Program study.[31]

The statistical analysis was performed using the SPSS program version 18.0 after creating a database in Microsoft Excel 2013. The quantitative variables were mean, standard deviation of the mean, minimum and maximum values, percentiles and count of cases on which this calculation had been made; the frequency distributions of the continuous variables were represented in bar charts, box plots and histograms. Subsequently, an inferential statistic was made and anthropometric variables and lipid profile and glycaemia were described with means and standard deviation.

Pearson's correlation coefficient was used to identify the linear relationship between two quantitative variables. Furthermore, for non-homoscedastic lipid variables, the Kruskal-Wallis test was used to find significant differences between the nutritional status groups. Likewise, an analysis of variance (ANOVA) was used to compare the means of IGF-1, IGFBP-1, IGFBP-2 and IGFBP-3 between the groups according to the nutritional status of their members. On the other hand, pairwise comparisons were applied using the Games-Howell method, which assumes different variances, in order to complement the contrasts between the groups. In addition, groups were assessed according to the nutritional status of their members using the Dunnett's test, and significant results were obtained.

Results

The average age of the children was 8.2±0.7 years; 49% attended the Liceo Integral Los Alisos school and 51% the Instituto Educativo Distrital Llano Oriental school. Table 1 shows the anthropometric variables of the participants.

Table 1. Anthropometric, lipid profile and glycemic variables per nutritional classification group.

Variable	Eutrophic	Risk of underweight	Overweight	Obesity	High waist circumference
n	17	17	17	17	16
Weight (kg)	25.5±2.6	22.9±2.1	31.5±3.4	39.2±6.2	29.6±3.1
Height (cm)	126.7±4.7	122.3±6.0	128.0±6.5	133.8±5.0 *	132.4±5.2
BMI (kg/m2)	16.0±0.9	15.4±1.3	19.2±0.8	21.8±2.7	16.9±0.7
WC (cm)	56.0±1.5	54.0±3.9	65.0±3.7	73.5±8.4 *	63.5±3.7
Glycemia (mg/dL)	88.6±3.7	87.3±3.7	88.7±7.9	88.±6.5	85.4±4.9
Total-c (mg/dL)	151.9±23.9	156.4±26.8	168.4±29.9	160.7±27.0	166.8±28.0
HDL-c (mg/dL)	51.3±9.9	45.3±9.8	43.5±9.0	42.0±11.2 *	48.6±9.3
LDL-c (mg/dL)	87.5±19.9	94.0±20.5	105.3±24.0	96.0±17.6	100.6±24.4
TG (mg/dL)	65.3±17.5	84.8±23.5	98.0±29.4	109.5±72.4 *	87.6±33.7

BMI: body mass index; total-c: total cholesterol; HDL-c: HDL cholesterol; LDL-c: LDL cholesterol; TG: triglycerides; WC: waist circumference.
* Significant difference ($p<0.05$).
Source: Own elaboration.

The lipid profile of most children were within normal values (Table 1); however, a significant number had alarming (bordering) or elevated levels compared to the NHLBI recommended limits (Figure 1). All participants had blood glucose levels within the reference values.

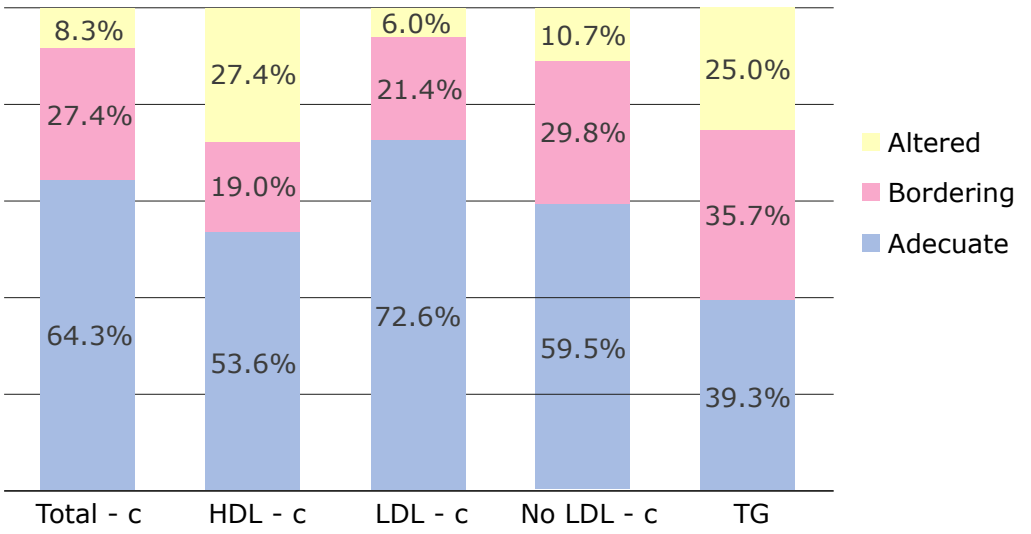

Figure 1. Percentage of children classified according to the National Heart, Lung, and Blood Institute's lipid profile cut-off points.
Total-c: total cholesterol; HDL-c: HDL cholesterol; LDL-c: LDL cholesterol; non-HDL-c: cholesterol no HDL; TG: triglycerides.
Source: Own elaboration.

After analyzing anthropometric variables and the lipid profile, a significant difference was found between children in the overweight, obesity and adequate weight groups with high WC compared to children in the eutrophic and at risk of underweight groups ($p<0.05$).

Moreover, 62% of children with excess weight had alterations of at least one variable of the lipid profile and 26.7% were in the bordering cut-off point, which would indicate that the lipid profile values of 88.7% of the participants in this group had alterations. These results could indicate the possibility of being at risk of CVD in the long term.

Also, using the Pearson's correlation coefficient, a direct association between IGF-1 and height was observed, while the ANOVA test, Kruskal Wallis' test and the medians allowed finding the inferences ($p<0.05$). The significant difference between individuals with adequate height and low height-for-age or at risk of low height-for-age was identified using the Dunnett's statistical method.

Figure 2 shows IGFBP-1 and IGFBP-2 serum levels according to the BMI classification. The lowest IGFBP-1 values were found in overweight individuals and those with a higher WC index; the lowest IGFBP-2 values were also found in overweight children.

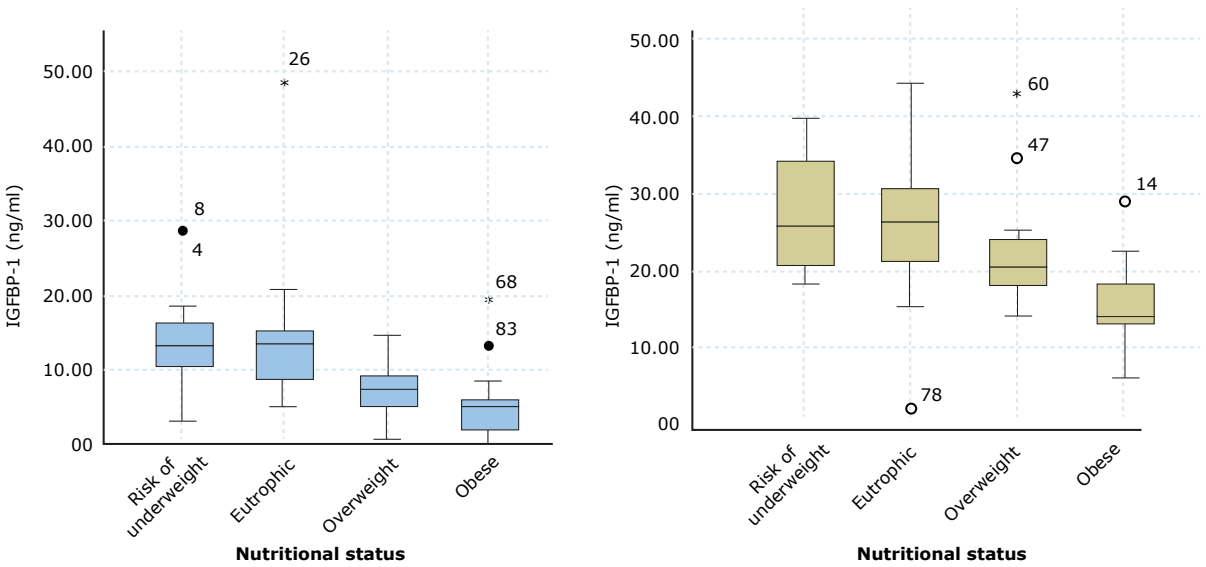

Figure 2. Box plot according to nutritional status and the IGFBP-1 and IGFBP-2 variables.
IGFBP-1: Insulin-like growth factor-binding protein 1; IGFBP-2: Insulin-like growth factor-binding protein 2
Source: Own elaboration.

With respect to IGFBP-1 levels, both the ANOVA test and the Games-Howell method established a significant difference between individuals with adequate BMI and those who are overweight or obese (p=0.000 and p<0.05, respectively). Likewise, the ANOVA analysis allowed evidencing that children with lower IGFBP-2 values were obese and overweight (p=0.001), while the Dunnett's test found that the highest statistical significance for IGFBP-2 is in the obese group.

The ANOVA analysis of the WC classification and the IGFBP-1 and IGFBP-2 levels revealed a significant difference (p=0.000), while the Games-Howell method identified that these proteins tend to decrease as the WC increases. On the other hand, IGFBP-3 did not show any significant difference according to nutritional status nor did it show any relationship with IGF-I levels.

The relationships between IGFBP-1 and IGFBP-2 levels and the lipid profile variables (Table 2) were evaluated, finding that both proteins are inversely correlated with TG concentrations and directly correlated with HDL-c values. Some variables were also compared between eutrophic and obese children (Table 3).

Table 2. Correlation coefficients between IGFBP-1 and IGFBP-2 and lipid profile variables.

Correlation		IGFBP-1	Total-c	HDL-c	LDL-c	TG
IGFBP-1 correlations	Pearson correlation	1.000	0.102	0.294	0.120	-0.339
	p-value		0.363	0.007 *	0.283	0.002 *
IGFBP-2 correlations	Pearson correlation	1.000	0.104	0.360	0.096	-0.352
	p-value		0.347	0.001 *	0.387	0.001 *

IGFBP-1: insulin-like growth factor-binding protein 1; IGFBP-2: insulin-like growth factor-binding protein 2; Total-c: total cholesterol; HDL-c: HDL cholesterol; LDL-c: LDL cholesterol; TG: triglycerides.

* Significant correlation (p<0.05).
Source: Own elaboration.

Table 3. Statistical summary of biochemical differences between eutrophic and obese children.

Characteristics of children	IGF-1	IGFBP-1	IGFBP-2	IGFBP-3	Total-c	HDL-c	LDL-c	TG
Eutrophic	244.9	14.4	266.5	3742.2	151.9	51.3	87.5	65.4
Obese	324.5	5.7	150.1	3605.1	160.7	42.5	96.3	109.5
p-value	0.035*	0.002 *	0.0000126 *	0.317	0.161	0.011 *	0.091	0.013 *

IGF-1: insulin-like growth factor 1, IGFBP-1: insulin-like growth factor-binding protein 1; IGFBP-2: insulin-like growth factor-binding protein 2; IGFBP-3: insulin-like growth factor-binding protein 3; Total-c: total cholesterol; HDL-c: HDL cholesterol; LDL-c: LDL cholesterol; TG: triglycerides.
* Significant difference (p<0.05) when assessing the assumption of equality of means for the variables.
Source: Own elaboration.

In each case, the hypothesis of equality of means was evaluated (p<0.05), finding that obese individuals had significantly lower IGFBP-1, IGFBP-2 and HDL-c levels compared to eutrophic individuals. In turn, significantly lower IGF-1 and TG levels were observed in the latter.

No strong association between IGF-1 and BMI or WC was observed. Furthermore, an inverse relationship between IGFBP-1 and IGFBP-2 serum levels and BMI was identified. Finally, it was observed an increase in TG levels and a decrease in HDL-c levels in eutrophic children as weight increases leading to overweight and obesity (Figure 3).

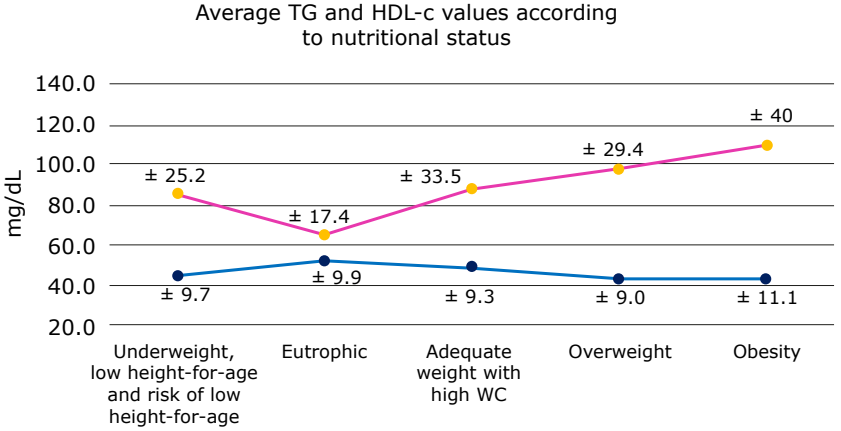

Figure 3. Mean values and standard deviation of TG and HDL-c for each nutritional status.
HDL-c: HDL cholesterol; TG: triglycerides; WC: waist circumference.
Source: Own elaboration.

A linear relationship between WC and IGFBP-1 and IGFBP-2 was identified using the Pearson correlation coefficient, which was confirmed with a Games-Howell statistical test. The average level of these proteins decreases as the WC of the individuals increases.

Finally, the relationship between TG and HDL-c was analyzed using the TG/HDL-c index; [32] the latter was >2 in 32 children, of whom 72% were in the high WC, overweight and obesity groups, suggesting a high risk of IR in this population.

Discussion

The results obtained show alterations in the lipid profile, particularly high concentrations of TG and low concentrations of HDL-c, which have been previously reported[33-36] and are constantly associated with future health risks. The most frequently reported risk factor for CVD is a decrease in HDL-c, which has protective functions at the endothelial level as it reduces the formation of foam cells and atheromatous plaques. Consequently, these alterations in early life are of particular concern, since they mean that individuals have a longer exposure time and, therefore, greater endothelial damage, which is considered a risk factor for IR in adolescents.

When analyzing the TG/HDL-c ratio, values >2 were observed, mostly in the overweight and obesity groups. In the study by Iwani *et al.,* [37] this indicator was significantly correlated with the value of the homeostatic model to assess IR (HOMA-IR) and WC, while the study by Soutelo *et al.* [32] established that it could facilitate timely decisions in health, even in children from 7 years of age.

IGF-1 was not related to BMI, but it was related to height when comparing the 5 study groups, finding lower levels in children with low height-for-age and at risk of low height-for-age compared to children with adequate height. Although IGF-1 secretion is stimulated by GH in all tissues, the response depends on nutritional status. In addition, this factor also stimulates cartilage growth; the synthesis of RNA, DNA and protein; and anabolic processes.[38,39] In this sense, IGF-1 plays a key role in growth, so there is a positive correlation between its circulating concentrations and the growth rate of children.[38]

When comparing obese children with eutrophic children, IGF-1 levels were elevated in the first group and also had a significant difference. Mohanraj *et al.* [15] and Park *et al.* [40] reported similar findings. Although obese individuals have lower GH production, their circulating IGF-1 concentrations were high, which could be explained by increased pre-adipocyte expression of IGF-1 and its receptor due to the effects of insulin and cortisol; thus, IGF-1 activates the proliferation of pre-adipocytes and their differentiation into adipocytes.[41]

IGF-1 production in response to an increased number of adipocytes may play a role in the decreased output of GH observed in patients who suffer from obesity.[20,42,43] However, this decrease in the secretion of this hormone is not associated with an alteration in the speed of growth, since obese children usually have a normal or even increased height for their age; for example, in this study, the obese group was 7cm taller than children of similar age with adequate weight.

There was no significant difference in IGFBP-3 levels according to the nutritional status; however, obese children had the lowest average IGFBP-3 compared to other nutritional statuses. This finding has been reported in other studies in which IGFBP-3 levels in obese children and adolescents were reduced[42] or did not change.[42,44,45] In Switzerland, Lewitt *et al.* [46] linked this decrease in total IGFBP-3 in obese adolescents to increased protease activity of IGFBP-3 and increased circulating fragments of IGFBP-3, and in the US, Mohanraj *et al.* [15] reported, on the one hand, the same situation in adolescents in whom circulating levels of total IGFBP-3 were low and, on the other, the presence of proteolytic fragments of IGFBP-3 in overweight and obese subjects.

The serum IGFBP-1 level observed in the children in this study was significantly lower in the obese than in the eutrophic children. Similar findings were reported by Martínez-de Icaya *et al.* [19] in Spain, Reinehr *et al.* [21] in Germany, Saitoh *et al.* [22] in Japan and Ricco *et al.* [44] in Brazil. Specifically in Spain, Martinez-de Icaya found in a group of 7-10-year-old children that overweight children had higher serum IGF-1 levels and lower serum IGFBP-1 levels compared to controls;[19] these findings in children with obesity are related to being more prone to IR.

Other relevant data reported in the present study were the relationships between IGFBP-1 and IGFBP-2 and the variables of the lipid profile. It was found that low levels of these proteins were associated with low levels of HDL-c and high levels of serum TG, which is similar to what was reported in adults by Ruan & Lai[13] and Heald *et al.* [47] These results suggest that low IGFBP-1 and IGFBP-2 levels may be associated with different factors that predispose to atherogenesis[13,48] and that low serum IGFBP-1 may be an early predictor of CVD in prepubertal obesity.[13,21]

Furthermore, this study found an inverse relationship between circulating IGFBP-2 levels and nutritional status. The lowest values were found in children diagnosed with obesity, which is consistent with previously reported data.[23,47,49,50]

IGFBP-2 has paracrine action and is the IGF-1 binding protein most expressed in the body and the main IGFBP secreted by white preadipocytes during adipogenesis.[23,24] The relationship found in the present study, between decreased circulating IGFBP-2 levels and overweight and obesity may be explained by an unfavorable secretion profile of this binding protein by adipocytes, which may be associated with increased leptin and decreased adiponectin levels.[49] In this regard, Hedbacker *et al.* [51] demonstrated that leptin increases liver transcription of IGFBP2 when administered peripherally or centrally in mice with lipodystrophy.

Conclusions

The presence of high levels of cholesterol and TG in children is a serious public health problem. In the present study, alterations in the lipid profile were evidenced in overweight and obese children, so early modifications in the metabolism regarding overweight and increased adiposity are recommended.

Excess weight was positively related to TG and negatively related to HDL-c. This fact is associated with an increased risk of developing CVD, so it is necessary to promote the implementation of physical activity and nutrition education programs in schools to improve eating

habits and the practice of physical activity in the child population.

In overweight children, there are alterations at the lipid and protein-binding level of insulin-like growth factors, which increase the risk of vascular disease in adulthood. Therefore, public health strategies should be established to prevent and treat excess weight in childhood, which in turn will reduce the risk of these diseases in adulthood.

Conflicts of interest

None stated by the authors.

Funding

This research was financed by the Master's Degree in Physiology and by the Universidad Nacional de Colombia through the DIB-Hermes-21970 and 21971 calls.

Acknowledgements

To the schools where the research was conducted and to their principals, boys, girls and parents, who allowed the development of the project.

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rfm
Revista *de la* Facultad *de* Medicina

ORIGINAL RESEARCH
DOI: http://dx.doi.org/10.15446/revfacmed.v68n1.71181
Received: 24/03/2018 **Accepted:** 14/06/2018

Knowledge about healthcare-associated infections in medical, bioanalysis and nursing students from a Venezuelan university

Conocimiento sobre infecciones asociadas a la atención de la salud en estudiantes de Medicina, Licenciatura en Bioanálisis y Licenciatura en Enfermería de una universidad venezolana

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Abstract

Introduction: Knowledge about healthcare-associated infections (HAIs) among health professionals is fundamental to reduce morbidity and mortality rates attributable to these infections.
Objective: To assess the level of knowledge on HAIs in final-year students enrolled in the School of Health Sciences of Universidad de Oriente, Venezuela.
Materials and methods: A descriptive study was conducted in a stratified random sample (n=98). A survey was administered to all participants in order to determine their knowledge about 3 specific areas: basics of HAIs, universal precautions and hand hygiene. Students who obtained an average score of 17.5 were considered as having an adequate level of knowledge about HAIs.
Results: Participants' average age was 24.9 years, and 74.9% were female. The average scores of nursing, medical and bioanalysis students were 18, 18.04 and 17.25, respectively; the total average score was 17.87. 59.2% of the respondents obtained a passing score. In terms of the 3 areas of knowledge assessed in the survey, most of the students obtained a failing score in basics of HAIs (n=78) and the Hand hygiene (n=76) components, while the majority (n=91) had a passing score in the Universal precautions area.
Conclusions: In general, all respondents have adequate knowledge about HAIs and their prevention. However, regardless of the academic program they were enrolled in, students showed a lack of knowledge regarding specific aspects of HAIs, such as the source of the microorganisms that cause these infections or the proper use of gloves, thus it is necessary that more attention is paid to these issues in their curricula.
Keywords: Cross Infections; Infection Control; Health Knowledge, Attitudes, Practice; Universal Precautions; Hand Hygiene (MeSH).

Guevara A, González O, Salazar P, Tedesco-Maiullari R, Gascón C. Knowledge about healthcare-associated infections in medical, bioanalysis and nursing students from a Venezuelan university. Rev. Fac. Med. 2020;68(1):59-65. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.71181.

Resumen

Introducción. El conocimiento acerca de las infecciones asociadas a la atención de la salud (IAAS) en profesionales en salud es fundamental para disminuir las tasas de morbimortalidad causadas por estas infecciones.
Objetivo. Evaluar el nivel de conocimiento sobre las IAAS en estudiantes del último año de la Escuela de Ciencias de la Salud de la Universidad de Oriente, Venezuela.
Materiales y métodos. Estudio descriptivo realizado en una muestra aleatoria estratificada (n=98). Se aplicó una encuesta para determinar los conocimientos de los participantes sobre 3 áreas específicas: generalidades sobre IAAS, precauciones universales e higiene de las manos. Se consideró que los estudiantes tenían un conocimiento adecuado si obtenían un puntaje promedio de 17.5.
Resultados. La edad promedio de los encuestados fue 24.9 años y el 74.9% fueron mujeres. En promedio, los estudiantes de Licenciatura en Enfermería, los de Medicina y los de Licenciatura en Bioanálisis obtuvieron 18, 18.04 y 17.25 puntos, respectivamente; el 59.2% de los respondientes aprobó la encuesta y el puntaje promedio total fue 17.87 puntos. En cuanto a las tres áreas de conocimiento evaluadas, la mayoría de estudiantes reprobó Generalidades sobre IAAS (n=78) e Higiene de las manos (n=76), mientras que la mayoría (n=91) aprobó Precauciones universales.
Conclusiones. En general, los estudiantes encuestados tienen un conocimiento adecuado de las IAAS y su prevención; sin embargo, independiente del programa académico, se evidenciaron deficiencias en aspectos puntuales del tema, tales como la fuente de los microorganismos causantes de las IAAS y el uso adecuado de guantes, por lo que es necesario que los currículos de estos programas profundicen más al respecto.
Palabras clave: Infección hospitalaria; Control de infecciones; Conocimiento; Precauciones universales; Higiene de las manos (DeCS).

Guevara A, González O, Salazar P, Tedesco-Maiullari R, Gascón C. [Conocimiento sobre infecciones asociadas a la atención de la salud en estudiantes de Medicina, Licenciatura en bioanálisis y Licenciatura en enfermería de una universidad venezolana]. Rev. Fac. Med. 2020;68(1):59-65. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.71181.

Introduction

Healthcare-associated infections (HAIs) are the most common adverse event in health care delivery and are of concern worldwide. The burden of HAIs is much higher in low- and middle-income countries than in high-income countries. These infections can occur while patients are being treated in any healthcare facility or even after discharge. They also include occupational infections contracted by healthcare personnel.[1]

The acquisition of HAIs may be associated with the lack of knowledge about certain infections among health care personnel or to practices that do not take into account preventive measures against them.[2,3] Institutions and governments in different countries have identified education as an important factor for prevention and control since poor knowledge in this regard is the main reason why professionals do not adhere to prevention measures in the future. [4,5] However, education is not the only aspect involved, because even though it increases knowledge, it does not necessarily increase the implementation of preventive and control measures. This also depends on factors such as the influence of co-workers or students, the workload and the availability of equipment, implements and sanitary facilities such as sinks with drinking water, paper towels, soap, among others.[3,5,6]

Studies conducted in different countries suggest that students of health science programs have insufficient knowledge of HAIs and their prevention;[7-13] this is mainly due to inadequate contents and training on these infections in the curricula of some universities.[5,11,12] In this sense, multiple authors have suggested that theoretical and practical contents on this matter should be strengthened[7,11,12,14-16] and that specific courses addressing HAIs and their prevention should be created.[13,17]

Two important aspects that should also be considered are the role of teachers in HAIs prevention training and their preparation for that. Teachers should not only act as educators, formally speaking, but should also act as role models and promoters of good clinical practices and serve as an example to their learners through the correct application (during teaching and daily clinical practice) of the measures and protocols established. Some research has found that teachers of different health science careers are not well prepared in HAIs and their prevention[18,19] and, therefore, they pass on wrong knowledge to their students and act as negative role models regarding their prevention by transmitting misconceptions or engaging in inappropriate practices.[18,20]

Students' knowledge about HAIs and their prevention is essential to reduce morbidity and mortality rates caused by these infections in professional practice. Given the above, universities must emphasize on raising awareness in future professionals about the spread of the infections to which they will be exposed in clinical practice.[7,16,21] Moreover, this knowledge must be strengthened once they start their working life, as it will allow them to improve their attitudes and practices regarding the prevention and control of HAIs.[22]

Due to the importance of this topic, this research aimed to evaluate the knowledge that medical, bioanalysis, and nursing students from a Venezuelan university have regarding HAIs and their prevention.

Materials and methods

Descriptive and cross-sectional study with field design carried out on a stratified random sample that included final year students of the medical, bioanalysis and nursing programs offered at the School of Health Sciences "Dr. Francisco Battistini Casalta" at the Universidad de Oriente, Bolívar Campus, in Venezuela.

Population and sample

The population consisted of 536 students: 284 from the medical program, 131 for the bioanalysis program, and 121 from the nursing program. Random stratified sampling was conducted, and each of the programs was considered as a stratum. The sample size and its distribution in the strata were estimated using the program for epidemiological data analysis EpiDat 4.1 (Xunta de Galicia/Pan American Health Organization). The estimation took into account the expected standard deviation (σ) according to previous studies that used the same methodology,[7,16] the correction of the sampling error by design effect, and absolute precision of 1.

The selected sample was proportionally distributed according to the size of each stratum. It was comprised of 98 students: 52 from Medicine, 24 from Bioanalysis and 22 from Nursing. Participants were randomly selected by the EpiDat program from the list of students in the population. All students selected agreed to participate in the study.

Data collection

To collect the data, a previously designed and validated survey was administered[7] to establish age, sex, and how information on HAIs and their prevention was acquired. Knowledge was investigated in 3 specific areas: basics of HAIs, universal precautions, and hand hygiene. The survey included 25 closed-ended questions with true/false responses, and each item answered correctly had a score of 1 point. The area basics of HAIs had 5 items, universal precautions had 12, and hand hygiene had 8.

Students who scored an average of ≥17.5 on the survey were considered as having adequate knowledge of HAIs and their prevention.[7,16] This same form of rating was applied to the different aspects evaluated; therefore, the minimum acceptable averages of correct answers by categories were: 3.5/5 for basics of HAIs, 8.4/12 for universal precautions, and 5.6/8 for hand hygiene.[16] Also, 4 questions inquired about the current definition of the HAIs, but the answers were not taken into account for the final rating of the survey.

Statistical processing

A bivariate analysis was performed. Statistical significance (p-value) was calculated using the chi-square test (X^2) for categorical variables and the analysis of variance (ANOVA) for continuous variables, with a 95% confidence interval. A logistic regression was done to identify independent factors associated with

acceptable knowledge about HAIs and their prevention. The considered variables were age, sex, and program, and the calculations were made with the program SPSS version 20; a value of $p \leq 0.05$ was considered statistically significant.

Ethical considerations

The research protocol was approved by the Bioethics and Health Biosafety Committee of the Complejo Hospitalario Universitario "Ruiz y Páez" in Ciudad Bolívar, State of Bolivar, Venezuela, through minutes number CHURP-CBBS-001-2017 of January 15, 2017. This research was developed in compliance with the ethical principles for the conduct of medical studies in human beings of the Declaration of Helsinki.[23] Respondents were informed of the purpose of the research and expressed their verbal and voluntary consent to participate in the study.

Results

In total, 98 students were interviewed, 74.5% female and 25.5% male, with an average age of 24.9 years (σ±2.3; range: 22-35). The average score obtained in the survey was 17.8 (σ±1.9; range: 11-23). When evaluating the knowledge about the areas studied, it was found that the average score in universal precautions was the only category above the passing score (Table 1).

The average score obtained according to the program was compared, finding that medical and nursing students have adequate knowledge about HAIs and their prevention, contrary to bioanalysis students; however, there were no statistically significant differences (ANOVA: F=1.4704; p=0.2350). Medical students obtained the highest average score in basics of HAIs and universal precautions. In contrast, nursing students had the highest average in hand hygiene (Table 1). Regarding universal precautions, statistically significant differences were found between the three groups (ANOVA: F=3.4486; p=0.0358). A Tukey HSD (honestly significant difference) post-hoc test also showed significant differences between medical students and bioanalysis students (p=0.0272).

59.2% of the respondents demonstrated adequate knowledge of HAIs and their prevention. However, when evaluating knowledge about the areas studied, it was found that most know the basic concepts of universal precautions (92.9%), but not of the basics of this type of infection (20.4%) or hand hygiene (22.4%) (Table 1).

Most nursing and medical students passed the survey, as opposed to the bioanalysis students; however, no statistically significant differences were found between the three groups (X^2=4.1798; p=0.1236). When considering each of the three areas evaluated separately, it was found that the majority of respondents failed in the basics of HAIs and hand hygiene (Table 1).

Table 1. Average score and percentage of passing students according to areas of knowledge studied and program.

	Overall	Program			p-value
		Medicine	Bioanalysis	Nursing	
Average score (±σ; Range)	17.8 (±1.9;11-23)	18.1 (±1.62;14-23)	17.3 (±2.35;11-21)	18 (±2.12;11-21)	0.235
Basics of HAIs (±σ; Range)	2.9 (±0.8; 1-5)	3.0 (±0.8;1-5)	2.9 (±0.8;2-5)	2.7 (±0.6;2-4)	0.265
Universal precautions (±σ; Range)	10.4 (±1.1;5-12)	10.6 (±0.9;7-12)	9.9 (±1.5;5-11)	10.5 (±1.1;7-12)	0.035
Hand hygiene (±σ; Range)	4.5 (±1.3;1-8)	4.4 (±1.1;3-7)	4.5 (±1.4;1-8)	4.8 (±1.5;2-7)	0.404
Number and percentage of passing students	58 (59.2%)	33 (63.5%)	10 (41.7%)	15 (68.2%)	0.123
Basics of HAIs	20 (20.4%)	15 (28.8%)	4 (16.7%)	1 (4.6%)	0.524
Universal precautions	91 (92.9%)	49 (94.2%)	21(87.5%)	21(95.5%)	0.494
Hand hygiene	22 (22.4%)	10 (19.2%)	5 (20.8%)	7 (31.8%)	0.483

σ: standard deviation; HAIs: Healthcare-associated infections.
Source: Own elaboration.

Most of the students stated that they had answered the survey based on the knowledge they acquired during their undergraduate studies. However, it is important to note that many participants also reported having obtained information from other sources (Figure 1).

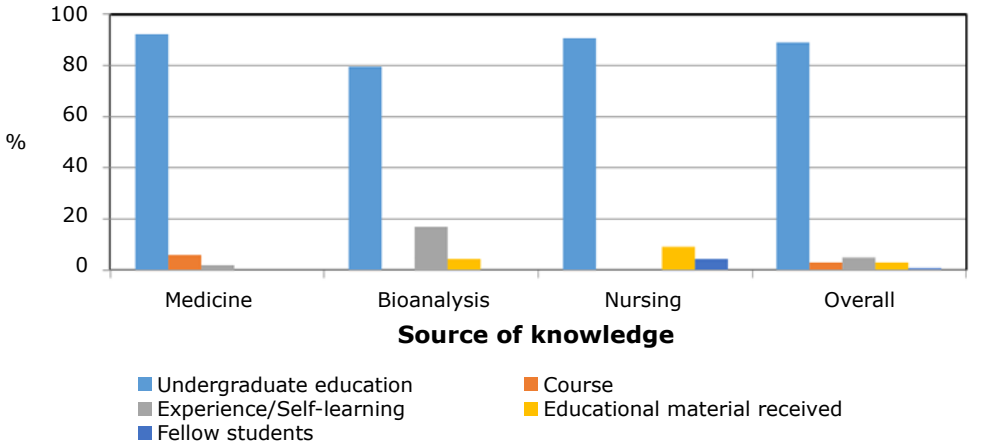

Figure 1. Source of knowledge about healthcare-associated infections and their prevention. Source: Own elaboration.

The average score for the questions on the current definition of HAIs was 2.9 (σ±1.01; range: 1-4). When evaluating this average according to each of the programs, it was found that bioanalysis students obtained 3.2 points (σ±0.8; range: 1-4); nursing students, 3.1 (σ±0.9; range: 1-4), and medical students, 2.8 (σ±1.1; range: 1-4). 77.6% of respondents correctly answered the question about the groups that are susceptible to contracting a HAI. In particular, nursing students were unaware that HAIs could develop up to 48 hours after hospital discharge or up to 3 months later if a device has been implanted in the patient. Also, a significant percentage of medical students are unaware that anyone in any health care setting is susceptible to acquiring one of these infections (Table 2).

Tables 3, 4, and 5 show the questions asked and the percentage of correct answers according to the areas evaluated and the program studied by the respondents.

Table 2. Percentage of correct answers in relation to the current definition of healthcare-associated infections.

Question	Correct answer	Overall	M	B	N
These are infections that occur only in hospitalized patients and appear 48 hours after admission.	F	64.3	57.7	70.8	72.7
These are infections that appear up to 48 hours after hospital discharge or up to 3 months after discharge if the patient has an implanted medical device or prosthesis.	T	73.5	73.1	83.3	63.6
These are infections that occur in any person, patient, healthcare worker or visitor who is in contact with healthcare facilities.	T	77.6	67.3	79.2	100
These are infections that occur in hospitals, long-term care facilities, community/outpatient facilities, home care settings, or community centers.	T	78.6	76.9	87.5	72.7

M: Medicine; B: Bioanalysis; E: Nursing; T: True; F: False.
Source: Own elaboration.

Table 3. Percentage of correct answers regarding the basics of healthcare-associated infections.

Question	Correct answer	Overall	M	B	N
The environment (air, water, inert surfaces) is the main source of bacteria responsible for HAIs	F	11.2	13.5	12.5	4.5
Older or very young age increases the risk of HAIs.	T	95.9	96.2	100	90.9
Invasive procedures increase the risk of HAI.	T	93.9	98.1	91.7	86.4
The prevalence of HAIs in Venezuela is unknown.	T	48	53.8	41.7	40.9
HAIs are responsible for approximately 10 000 deaths every year in Venezuela.	F	43.9	42.3	41.7	50

M: Medicine; B: Bioanalysis; E: Nursing; V: True; F: False; HAIs: Healthcare-associated infections.
Source: Own elaboration.

Table 4. Percentage of correct answers in relation to universal precautions.

Question		Correct answer	Overall	M	B	N
Universal precautions:	include recommendations to protect only the patients.	F	89.8	85.5	91.7	95.5
	include recommendations to protect patients and health workers.	T	96.9	96.2	95.8	100
	are applicable to all patients.	T	90.8	90.4	87.5	95.5
	are applicable only to health care workers who come into contact with body fluids.	F	81.6	86.5	75	77.3
Universal precautions recommend wearing gloves:	during all procedures.	F	11.2	15.4	4.2	9.1
	when there is a risk of contact with blood or body fluids	T	95.9	100	87.5	95.5
	when there is a risk of getting a cut.	T	92.9	98.1	87.5	86.4
	when health care workers have a skin injury.	T	95.9	98.1	91.7	95.5
When there is a risk of blood or body fluid splashes, health care workers should wear	mask only.	F	93.9	92.2	87.5	95.5
	eye protection only.	F	98	100	91.7	100
	gown only.	F	95.9	98.1	91.7	95.5
	mask, protective glasses and gown.	T	99	98.1	100	100

M: Medicine; B: Bioanalysis; E: Nursing; T: True; F: False.
Source: Own elaboration.

Table 5. Percentage of correct answers regarding hand hygiene.

Question		Correct answer	Overall	M	B	N
When is hand hygiene recommended?	Before or after touching a patient.	F	72.4	77.8	75	54.5
	Before and after touching a patient.	T	99	100	95.8	100
	Before patient contacts (i.e., after touching one patient and treating another).	T	89.8	92.6	83.3	90.9
	After removing the gloves.	T	84.7	79.6	91.7	86.4
What are the indications for using alcohol-based handrub or alcohol-glycerin solutions (on clean hands)?	Instead of traditional hand washing with soap and water (for 30 seconds).	T	31.6	25.9	25	50
	Instead of hand washing with antiseptic (for 30 seconds).	T	27.6	18.5	33.3	40.9
	Instead of surgical hand washing (for 3 minutes).	T	14.3	9.3	20.8	18.2
	Traditional hand washing with soap and water should be done before washing hands with alcohol-based handrub.	F	29.6	27.8	20.8	40.9

M: Medicine; B: Bioanalysis; N: Nursing; T: True; F: False.
Source: Own elaboration.

The logistic regression analysis showed that the probability of having adequate knowledge about HAIs and their prevention is statistically associated with studying Medicine, being this probability approximately 3 times higher than if studying Bioanalysis or Nursing (OR: 3.312; 95% CI:1.199-9.150; p=0.021). However, when considering each of the areas studied individually, no statistically significant relationship was found between age, sex, or program studied and having adequate knowledge.

Discussion

Throughout history, multiple investigations have been carried out in students and health workers to determine the degree of knowledge that they have about HAIs, as well as their attitude regarding the implementation of measures to prevent them, and the proper implementation of those measures when they have direct contact with patients. The results of those studies are divergent: some have reported insufficient knowledge of HAIs and their prevention,[8,9,11-13] while others report adequate knowledge with specific deficiencies,[7,10,14,16,17] which coincides with the findings of the present study.

Medical and nursing students had very similar average scores (higher in the latter group). This is consistent with some studies[7,10,16] but differs from others conducted in Namibia[17] and Albania,[15] where medical students had the highest passing scores.

In the present research, most of the respondents stated that they acquired knowledge about HAIs while they were studying in the university, which coincides

with the reports of other researchers.[4,7,11,14,15] However, self-learning was also reported as an important source of knowledge.[4,11,13] This is a relevant finding, as some authors argue that undergraduate education in developing countries does not often emphasize the potential risk of the spread of communicable infections from either the environment or from other patients or staff, and the corresponding preventive measures.[20,21,24] It should be noted that there is not a single course in the health sciences programs of the Universidad de Oriente that imparts the necessary knowledge about this type of infections. Many aspects of this topic are fragmented and dispersed across several courses, which make it challenging to integrate this knowledge and put it into practice during daily activities.

In general, the participants in the study know the definition of HAI; however, medical students had the lowest average score in this part of the survey, a finding that is consistent with other studies.[8,11] There is also a lack of knowledge, mainly among medical and nursing students, regarding the time from infection to onset of symptoms and the fact that HAIs may not only occur in patients. This information is relevant for making an accurate diagnosis of a HAI.[7]

The students surveyed showed insufficient knowledge about the general characteristics of HAIs, which differs from the reports of other authors.[10,15,16] It is noteworthy that many students believe that the primary source of HAI-producing microorganisms is the environment and do not conceive the hands as the main vehicle for the spread of pathogens, concepts that are fundamental to prevent these infections.[7,10,13,17] The lack of knowledge about the transmission mechanisms of microorganisms that produce HAIs indicates that there are significant gaps in the teaching given to the students.

Furthermore, the teachers of this same institution were also unaware of the role played by the hands of the staff in the onset of HAIs, as well as the impact of their hygiene on prevention.[19] Both students and teachers are unaware that in Venezuela, there are no statistical records on HAIs,[19] findings similar to those obtained in Italy[10] and France.[7]

The universal precautions category had the highest scores; however, the students of the three programs think that they should wear gloves when performing any procedure. This is consistent with what has been described in other works.[4,7,10,13,16,17] In this regard, the World Health Organization has recommended the use of gloves only in cases of possible contact with body fluids or secretions, either by direct contact with the patient or with contaminated surfaces.[1] The routine use of gloves as a preventative measure to avoid the spread of HAIs was introduced in the 1980s and early 1990s. However, it resulted in the misconception that gloves should be used for all activities and procedures involving contact with the patient.[25] Perhaps this belief rooted in the students is the product of their training, since this same flaw was observed in their teachers.[19]

Most respondents know when to perform hand hygiene, but few know when to use alcohol-based handrubs. This is a problem for the prevention of HAIs since adequate hand hygiene is considered a necessary measure to avoid the dissemination of pathogenic microorganisms that produce infectious diseases.[1,4,7,10,12,16,17] It is noteworthy that students are unaware that alcohol-based handrubs can be used for hand hygiene instead of washing with an antiseptic solution or that it is a substitute for surgical handwashing.[7,10]

This is the first research carried out in Venezuela that seeks to establish the knowledge that students from different health sciences programs have about HAIs and their prevention. Although this study is the first approximation to this issue, future research should assess the attitude, implementation and compliance with prevention measures, since these three aspects do not always go together.

Conclusion

Respondents have adequate knowledge of HAIs and their prevention, but the level of knowledge of bioanalysis students must be improved. In general, the students of the three programs have insufficient knowledge of specific aspects such as the source of the microorganisms that cause HAIs and the proper use of gloves and alcohol-based handrubs.

Conflicts of interest

None stated by the authors.

Funding

This research work was funded with resources from project CI-05040605-1963-15 of the Universidad de Oriente, Venezuela.

Acknowledgements

None stated by the authors.

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rfm
Revista *de la* Facultad *de* Medicina

ORIGINAL RESEARCH
DOI: http://dx.doi.org/10.15446/revfacmed.v68n1.70880
Received: 07/03/2018 **Accepted:** 04/07/2018

Anatomical features of bile ducts in a sample of Colombian corpses

Características anatómicas de las vías biliares en una muestra de cadáveres de población colombiana

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Abstract

Introduction: In comparison with other countries, studies on the anatomical characteristics of bile ducts in Colombian population are scarce.
Objective: To analyze the anatomical features of bile ducts in a sample of 60 gastrointestinal tracts obtained from Colombian cadavers.
Materials and methods: A cross-sectional, analytical and descriptive study was conducted. The bile ducts of 60 human digestive tracts were dissected and analyzed.
Results: According to the Blumgart's classification of the biliary tract anatomical variations, the following variations were found: Type A (78.3%), Type B (5%), Type C2 (3.3%), Type D2 (1.7%), Type E1 (1.7%) Type E2 (8.3%), and Type F (1.7%). Regarding the average dimensions of bile ducts outside the liver, the following average lengths and diameters were found: right hepatic duct, 10.64mm and 3.62mm; left hepatic duct, 10.74 mm and 3.66 mm; common hepatic duct, 25.59 mm and 4.97 mm, and common bile duct, 39.58 mm and 4.90 mm. In general, the anatomical features observed in most of the sample were similar to those reported in the literature.
Conclusions: Usual anatomical features were present in 78.3% of the cases, while anatomical variations were observed in 21.7%. The length and diameter of the bile ducts studied here is within the average range reported in the literature.
Keywords: Anatomy; Liver; Bile; Population (MeSH).

Quijano Y. Anatomical features of bile ducts in a sample of Colombian corpses. Rev. Fac. Med. 2020;68(1):66-72. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.70880.

Resumen

Introducción. En comparación con otros países, los estudios sobre características anatómicas de vías biliares en población colombiana son escasos.
Objetivo. Analizar las características anatómicas de las vías biliares en una muestra de 60 tractos gastrointestinales de población colombiana.
Materiales y métodos. Se realizó un estudio descriptivo analítico transversal donde se emplearon y disecaron las vías biliares de 60 tractos gastrointestinales humanos.
Resultados. Según la clasificación de Blumgart de las variaciones anatómicas del tracto biliar, se encontraron las siguientes variaciones: Tipo A (78.3%), Tipo B (5%), Tipo C2 (3.3%), Tipo D2 (1.7%), Tipo E1 (1.7%), Tipo E2 (8.3%) y Tipo F (1.7%). En cuanto a las dimensiones promedio de las vías biliares extrahepáticas, se encontraron los siguientes diámetros y longitudes: conducto hepático derecho, 3.62mm y 10.64mm; conducto hepático izquierdo, 3.66mm y 10.74mm; conducto hepático común, 4.97mm y 25.59mm, y conducto colédoco, 4.90mm y 39.58mm. En general, las características anatómicas observadas en la mayoría de la muestra fueron similares a las reportadas en la literatura.
Conclusiones. En el 78.3% de los casos se observaron características anatómicas usuales, mientras que las variantes anatómicas estuvieron presentes en el 21.7%. La longitud y el diámetro de las vías biliares están dentro del promedio reportado en la literatura.
Palabras clave: Anatomía; Hígado; Bilis; Población (DeCS).

Quijano Y. [Características anatómicas de las vías biliares en una muestra de cadáveres de población colombiana]. Rev. Fac. Med. 2020;68(1):66-72. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.70880.

Introduction

Bile duct diseases are highly prevalent worldwide and may be asymptomatic or turn into neoplasms with poor prognosis. Some studies report that one of the most common disorders is cholelithiasis, which affects up to 20% of the world population[1] and 15% of the inhabitants of Europe and North America.[2] Symptoms may worsen by the presence of cholangitis or pancreatitis,[3] so a large number of people with these conditions require some surgical procedure, either for diagnostic or therapeutic purposes. The bile ducts can also be affected by injury or iatrogeny,[4] which can be simple or complex with destruction of the bile duct wall.[5]

The increase in the population's health coverage has made it possible to identify a greater amount of people with biliary diseases.[6] To achieve this, it has been necessary to explore the anatomical features of the bile duct by means of endoscopic sphincterotomy, endoscopic retrograde cholangiopancreatography (ERCP), intraoperative cholangiography, laparoscopic or open cholecystectomy, clinical assessment and liver function tests.[7]

Nowadays, bile duct surgeries, with their different modalities, are essential procedures to guarantee the adequate state of health of the people. In addition, echoendoscopy allows obtaining better gallbladder cancer diagnoses.[8,9] Although this type of surgical procedure has been perfected, complications during surgery remain a concern for surgeons. The most frequent causes of these adverse events are the lack of expertise of the surgeon and the failure to perform a careful procedure;[10,11] however, the presence of anatomical variations unbeknownst to professionals also plays an important role for their occurrence.

The most common setbacks in bile duct surgery are bleeding, infection and injury to the bile ducts, which occur because anatomical variations are unknown. In Colombia, Ramos-Pachón *et al.*[12] conducted a follow-up study of patients with biliopancreatic diseases, finding that surgical complications occurred in 7.43% of ERCPs, the most frequent being acute cholangitis (3.34%), with mortality of 1.86%. In Latin America, there is little reported research explaining the features and anatomical variations of the bile ducts and, particularly, in Colombia there are no published studies regarding these variations.

Therefore, the aim of this research was to carry out a study on the features and possible anatomical variations of the bile ducts in the Colombian population. This characterization will allow morphologists, surgeons, radiologists and other medical specialists to have a better understanding of the possible biliary variations and their classifications, to analyze their morphometry and to contribute to the decrease of surgical complications derived from the lack of knowledge. This characterization will also allow a better interpretation in cases where such variations are present.

Materials and methods

A descriptive analytical cross-sectional study was conducted on 60 human gastrointestinal tracts comprising the liver, extrahepatic bile ducts, pancreas, and small and large intestines. The tracts were taken from corpses available at the amphitheater of the Medical program offered by the Universidad de Ciencias Aplicadas y Ambientales - U.D.C.A.; specimens that did not have any disease or previous surgeries of the bile ducts were included.

The bile ducts were dissected from the cadavers as follows: the gender of each body was established by identifying the ovaries and uterus in women or the prostate and testicles in men; the bile ducts in the gastrointestinal tract were identified and the peritoneum and omentum were removed; then, the distal intrahepatic bile ducts were dissected, along with a fraction of the liver, as well as the extrahepatic ducts, which were measured to obtain their length and caliber; finally, the anatomical features were described and a photographic record was taken.

The information obtained was analyzed and recorded in the Microsoft Excel 2013 program, and the statistical data was processed in the SPSS program, version 21, using the classification proposed by Blumgart as a parameter[13] (Figure 1).

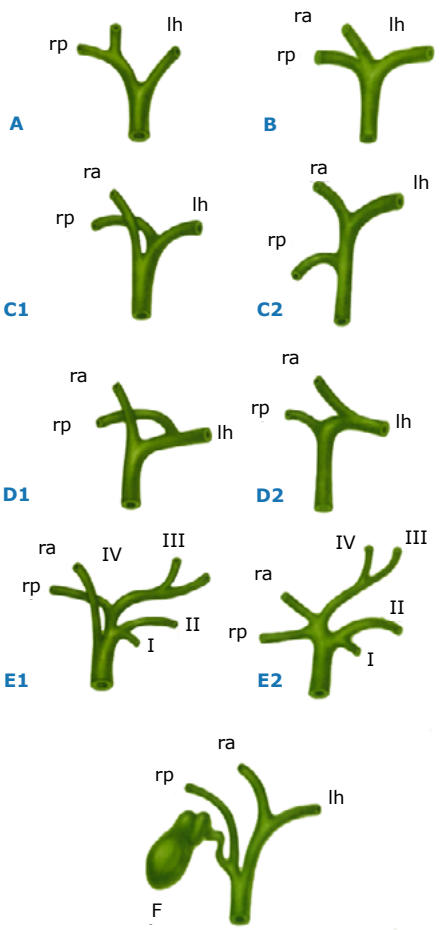

Figure 1. Main variations of the hepatic duct confluence according to Blumgart. A: usual confluence; B: triple confluence; C1: right anterior duct draining into RHD; C2: right posterior duct draining into the RHD; D1: right posterior duct draining into the LHD; D2: right anterior duct draining into the LHD; E1 and E2: absence of hepatic duct confluence; F: drainage of the right posterior duct into the cystic duct and absence of RHD. lh: left hepatic; ra: right anterior; rp: right posterior, RHD: right hepatic duct; LHD: left hepatic duct; CHD: common hepatic duct; I, II, III and IV: segmental ducts.
Source: Own elaboration based on Hahn & Blumgart.[13]

For the present study, the information was obtained based on the regulations for performing a medico-legal necropsy contained in Decree 786 of 1990 of the Colombian Ministry of Public Health.[14] Likewise, the principles contained in the Declaration of Helsinki[15] for treating the information derived from cadavers were followed, guaranteeing the confidentiality of the data of the deceased patient, his or her dignity and integrity. The regulations of Resolution 8430 of 1993 of the Colombian Ministry of Social Protection and Health were applied.[16] Similarly, this research was submitted for approval by the Ethics Committee of the Faculty of Health Sciences of the U.D.C.A., through unnumbered minutes of November 28, 2017.

Results

60 gastrointestinal tracts were analyzed, of which 4 corresponded to women and 56 to men. They were classified according to Blumgart[13] (Table 1 and Figures 2, 3 y 4).

Table 1. Frequency of bile duct variations according to Blumgart in a sample of cadaveric specimens in Colombia.

Type	A	B	C1	C2	D1	D2	E1	E2	F
Cases	44M+3F=47	3M	0	2M	0	1M	1M	4M+1F=5	1M
%	78.3	5	0	3.3	0	1.7	1.7	8.3	1.7

A: usual confluence; B: triple confluence; C1: right anterior duct draining into RHD; C2: right posterior duct draining into the RHD; D1: right posterior duct draining into the LHD; D2: right anterior duct draining into the LHD; E1 and E2: absence of hepatic duct confluence;F: drainage of the right posterior duct into the cystic duct and absence of RHD; M: Male, F: Female; CHC: common hepatic duct; LHD: left hepatic duct; RHD: right hepatic duct.
Source: Own elaboration.

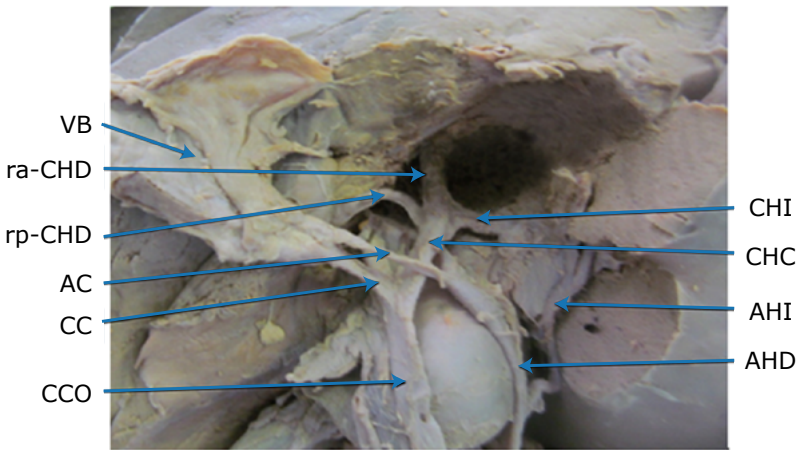

Figure 2. Hepatic duct type C2.
GB: gallbladder; ra-RHD: right anterior branch of the right hepatic duct; rp-RHD: right posterior branch of the right hepatic duct; CA: cystic artery; CD: cystic duct; BD: bile duct; LHD: left hepatic duct; CHC: common hepatic duct; LHA: left hepatic artery; RHA: right hepatic artery
Source: Document obtained during the study.

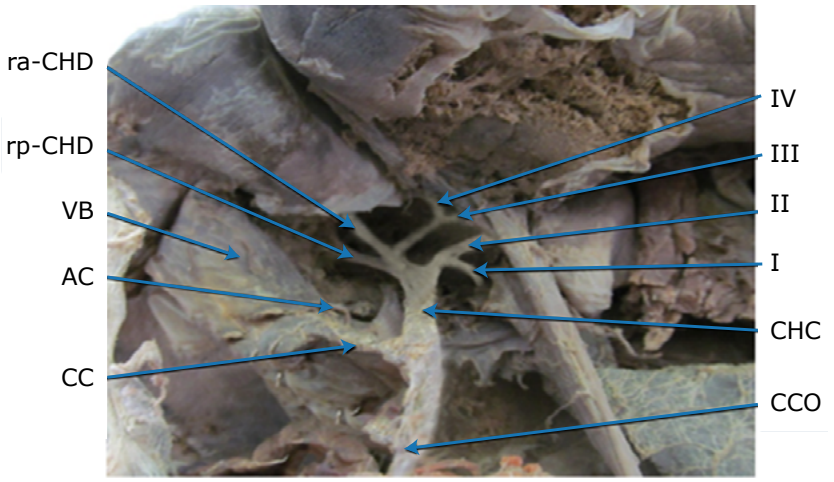

Figure 3. Hepatic duct type E2.
ra-RHD: right anterior branch of the right hepatic duct; rp-RHD: right posterior branch of the right hepatic duct; GB: gallbladder; CA: cystic artery; CD: cystic duct; I, II, III and IV: segmental ducts; CHC: common hepatic duct; BD: bile duct.
Source: Document obtained during the study.

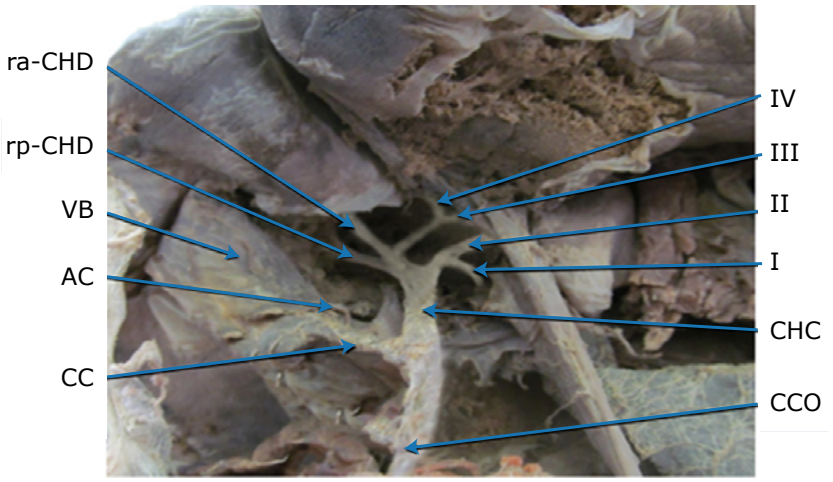

Figure 4. Hepatic duct type F.
GB: gallbladder; ACC: anterior cystic duct; PCC: posterior cystic duct; CC: cystic conduct; rp-RHD: right posterior branch of the right hepatic duct; ra-RHD: right anterior branch of the right hepatic duct; LHD: left hepatic duct; BD: bile duct.
Source: Document obtained during the study.

With regard to the path of the bile ducts, four portions were found in all gastrointestinal tracts:

1. A supraduodenal portion extending from the formation of the common hepatic duct to the crossing behind the first portion of the duodenum.
2. A retroduodenal portion extending behind the first portion of the duodenum and separating from the portal vein, which was pulled to the left of the bile ducts after being divided. This portion had two anatomical relationships: one through its back side with the inferior cava vein, from which it was separated by the retroduodenal fascia, and another through the left side with the retroduodenal artery.
3. A retropancreatic portion crossing the lower border of the duodenum was located behind the head of the pancreas; it then followed a downward path to the right, and ended up on the anterior/internal part of the second portion of the duodenum, in conjunction with the main pancreatic duct.
4. An intramural portion leading to the major duodenal ampulla.

It is worth noting that the three first portions had an anatomical relationship, through their back side, with the inferior cava vein.

The features of each duct analyzed are described below (Table 2).

The *right hepatic duct* was measured in only 47 gastrointestinal tracts since it did not form in the remaining tracts due to their anatomy. The length varied between 3.1mm and 18.5mm, with an average of 10.64mm; it was ≤9.05mm in 25% of the samples. The diameter varied between 2.1mm and 5.9mm with an average of 3.62mm, and ≤3.2mm in 25% of the samples.

The *left hepatic duct* was measured in 54 gastrointestinal tracts, since it did not form in the remaining tracts due to their anatomy. The length varied between 3.2mm and 35.1mm, with an average of 10.74mm, being ≤8.85mm in 25% of the samples. As for the diameter, it varied between 2.4mm and 5.5mm, with an average of 3.66mm, being ≤3.2 in 25% of the samples.

The length of the *common hepatic duct* varied between 5mm and 58.5mm, with an average of 25.59mm, being ≤16mm in 25% of the samples. Its diameter varied between 3.7mm and 7.9mm, with an average of 4.9mm, being ≤4.3mm in 25% of the samples.

The length of the *bile duct* varied between 11.9mm and 81mm, with an average of 38.58mm, being ≤32.25mm in 25% of the samples. Regarding the diameter, it varied between 3.5mm and 6.0mm, with an average of 4.79, being 4.3mm in 25% of the sample.

Table 2. Length and diameter of bile ducts in millimeters.

Conduct	Measurement	n	Minimum	Maximum	Average	Median	Percentile 25%
Right hepatic duct	Length	47	3.1	18.5	10.64	10.85mm	9.05mm
	Diameter	47	2.5	5.9	3.62	3.4mm	3.2mm
Left hepatic duct	Length	54	3.2	35.1	10.74	11.15mm	8.85mm
	Diameter	54	2.4	5.5	3.636	3.66mm	3.2mm
Common hepatic duct	Length	60	5.0	58.5	25.595	24.5mm	16mm
	Diameter	60	3.7	7.9	4.975	4.8mm	4.3mm
Bile duct	Length	60	11.9	81.0	39.585	39.6mm	32.25mm
	Diameter	60	3.5	6.0	4.790	4.9mm	4.3mm

Source: Own elaboration.

Discussion

According to Blumgart's classification, type A duct was the most common (78.3%) in the present study, which coincides with the findings by Hribernik *et al.*[17] (82%) and Cova & Louis[18] (78.7%); in contrast, type A was less frequent in the study by Tolino *et al.*[19] (41%). The second most common variation in this study was duct type E2, which differs from what was reported by Cova & Louis,[18] where type B was the second most common. Furthermore, the prevalence of type A found here is higher than that described by Al-Jiffry[20] (57%) and Brunicardi *et al.*[21] (59%), with type C1 duct being the second most frequent in these two studies.

On the other hand, Chaib *et al.*,[22] who used a different classification (type A1, A2, A3 and A4 for right hepatic ducts and B1, B2, B3, B4 and B5 for left hepatic ducts) reported a frequency of 61.3% and 76.2% for types A1 and B1, respectively (which would correspond to Blumgart's type A), and 14.5% and 15% for A2 and B2, respectively (which would correspond to Blumgart's type B). This means that the prevalence of type A is >60% and coincides with the results of the present study and most of the literature on the subject (Table 3).

The F-type variation, one of the less frequent in this study and in the existing literature, has a higher risk of being injured during cholecystectomy due to the proximity to the cystic duct outlet.

No studies on the length and diameters of the bile ducts are reported in Colombia, but similar averages are reported worldwide and are consistent with the bile duct paths of most of the data recorded in anatomy and surgical texts. However, some books do not measure or describe the dimensions of all ducts[23-34] (Table 4).

Table 3. Reported bile duct variations.

Study	Cases	Type A	Type B	Type C1	Type C2	Type D1	Type D2	Type E1	Type E2	Type F	Country
Cova & Louis18 2015	232 ERCP	78.9 %	10.77%	7.75%	0.862%	0.862%	0	0	0.43%	0	Venezuela
Tolino *et al.*19 2010	690 ERCP	41.16%	25.8%	15.94%	5.51%	1.16%	3.33%	2.6%	3.9%	0.58%	Argentina
Al-Jiffry20 2015	117 ERCP	59%	10.70%	11.3%	6.7%	4%	2.2%	2.7%	0	1.1%	Saudi Arabia
Brucardi *et al.*21 2015	No reported number	57%	12%	16%	4%	5%	1%	2%	1%	2%	United States
Quijano (present study) 2019	60 gastrointestinal tracts	78.3%	5%	0	3.3%	0	1.7%	1.7%	8.3%	1.7%	Colombia

ERCP: endoscopic retrograde cholangiopancreatography.
Source: Own elaboration.

Table 4. Length and diameter of extrahepatic bile ducts.

Study	Measurement	RHD	LHD	CHD	BD	Country (Editorial, if published in a book)
Brucardi *et al.*[21] 2015	Length	-	-	10-40mm	70-110mm	United States (McGraw Hill)
	Diameter	-	-	4mm	5-10mm	
Cachoeira *et al.*[23] 2012	Length	-	-	4.1-50mm	-	Brazil (Journal article)
	Diameter	-	-	-	-	
Moore *et al.*[24] 2013	Length	-	-	-	50-150mm	Spain (Wolters Kluver)
	Diameter	-	-	-	-	
Rouvier & Delmas[25] 2005	Length	-	-	30-40mm	50 mm	Spain (Mason)
	Diameter	-	-	5mm	6mm	
Latarjet & Ruiz[26] 2005	Length	-	-	40mm	80mm	Argentina (Panamericana)
	Diameter	-	-	6mm	6mm	
Snell[27] 2001	Length	-	-	40mm	80mm	Mexico (McGraw Hill)
Testud & Latarjet[28] 1993	Length	-	-	30mm	60-80mm	Spain (Salvat)
	Diameter	-	-	4-5mm	13mm	

Table 4. Length and diameter of extrahepatic bile ducts. (Continued)

Study	Measurement	RHD	LHD	CHD	BD	Country (Editorial, if published in a book)
Bouchet & Cuilleret[29] 19997	Length	-	-	-	80mm	Argentina (Panamericana)
Williams[30] 1998	Length	-	-	-	75mm	Spain (Hancourt)
	Diameter	-	-	-	6mm	
Lippert[31] 2013	Length	-	-	40-60mm	40-80mm	Spain (Marbán)
	Diameter	-	-	-	5mm	
Gardner[32] 2002	Length	-	-	-	40-80mm	Mexico (McGraw Hill)
Linder[33] 1990	Length	5-15mm	5-15mm	20-65mm	75-110mm	Mexico (Manual Moderno)
Cadena[34] 1992	Length	-	-	30mm	60-80mm	Colombia (Celsus)
	Diameter	-	-	4mm	-	
	Diameter	-	-	-	-	
Quijano (present study) 2019	Length	3.1-18mm	3.2-35.1mm	5-50mm	11.9-81mm	Colombia (Journal article)
	Diameter	2.5-5.9mm	2.4-5.5mm	3.7-7.9	3.5-6mm	

RHD: right hepatic duct; LHD: left hepatic duct; CHD: common hepatic duct; BD: bile duct.
Source: Own elaboration.

Conclusions

The usual anatomy of the bile ducts was observed in 78.3% of the cases; anatomical variations were frequent (21.7%). This prevalence should encourage morphologists, forensic scientists and surgeons to consider the variants during the study and management of biliary diseases in order to prevent complications and injuries.

The length, diameter, features and path of the extrahepatic bile ducts analyzed were within the average reported in the existing literature.

Conflicts of interest

None stated by the author.

Funding

This study was funded by the Universidad de Ciencias Aplicadas y Ambientales - U.D.C.A. through an internal call research program.

Acknowledgements

To the Universidad de Ciencia Aplicadas y Ambientales - U.D.C.A. and to the Instituto Nacional de Medicina Legal y Ciencias Forenses in Bogotá for providing the material under the teaching and research agreement; to Dr. Victor Rizo Tello for his support, and to the Medical Program of the Universidad de Ciencia Aplicadas y Ambientales - U.D.C.A. for approving this research.

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rfm
Revista *de la* Facultad *de* Medicina

ORIGINAL RESEARCH
DOI: http://dx.doi.org/10.15446/revfacmed.v68n1.72843
Received: 13/06/2018 **Accepted:** 13/08/2018

Use of medical eponyms and obsolete anatomical terms during the 13th Colombian Congress of Morphology 2017

Uso de epónimos médicos y términos anatómicos obsoletos durante el XIII Congreso Colombiano de Morfología de 2017

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Abstract

Introduction: Medical eponyms are names given to different body structures after the people who discovered them. They have been used for centuries and have deep cultural roots, mainly in the medical sciences field, but they do not provide relevant information on the anatomical structure they denote.
Objective: To identify the medical eponyms and obsolete anatomical terms used during the 13th Colombian Congress of Morphology.
Materials and methods: The 52 oral presentations given during the 13th Colombian Congress of Morphology, held in October 2017 at Universidad del Norte, Barranquilla, Colombia, were analyzed to quantify, in terms of percentage, the use of medical eponyms and obsolete anatomical terms.
Results: Medical eponyms were used in 53.84% oral presentations, while obsolete anatomical terms were identified in 21 presentations.
Conclusion: It was confirmed that, in general, professors, researchers and other health professionals who participated in the congress do not use Terminologia Anatomica as a reference source to name different body structures, which produces both communication and knowledge transfer problems.
Keywords: Eponyms; Anatomy; Terminology (MeSH).

Duque-Parra JE, Barco-Ríos J, Morales-Parra G. Use of medical eponyms and obsolete anatomical terms during the 13th Colombian Congress of Morphology 2017. Rev. Fac. Med. 2020;68(1):73-6. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.72843.

Resumen

Introducción. Los epónimos médicos son nombres que se adjudican a ciertas estructuras corporales en honor a los personajes que las descubrieron. Estos se han usado en el lenguaje morfológico por muchos siglos y han generado un enorme arraigo cultural, principalmente en las ciencias médicas, sin embargo, no brindan información relevante sobre la estructura anatómica en sí.
Objetivo. Identificar los epónimos y términos anatómicos obsoletos usados durante el XIII Congreso Colombiano de Morfología.
Materiales y métodos. Se analizaron los 52 trabajos que se presentaron durante el XIII Congreso Colombiano de Morfología, celebrado en la Universidad del Norte de Barranquilla (Colombia) en octubre de 2017, con el fin de cuantificar porcentualmente el uso de epónimos y términos anatómicos obsoletos.
Resultados. Los epónimos estuvieron presentes en 28 ponencias y los términos anatómicos obsoletos se usaron en 21.
Conclusión. Se comprobó que, en general, los profesores, investigadores y demás profesionales de la salud que participaron en el congreso no usan la Terminología Anatómica como referente para nombrar las distintas estructuras corporales, lo que genera problemas de comunicación y transmisión del conocimiento.
Palabras clave: Epónimos; Anatomía; Terminología (DeCS).

Duque-Parra JE, Barco-Ríos J, Morales-Parra G. [Uso de epónimos médicos y términos anatómicos obsoletos durante el XIII Congreso Colombiano de Morfología de 2017]. Rev. Fac. Med. 2020;68(1):73-6. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.72843.

Introduction

The purpose of international standards on human anatomical terminology is to unify the language related to morphology used in medical sciences and to facilitate the teaching-learning process. Therefore, it does not pursue aesthetic or recreational purposes, as literary language does.[1]

Medical terms used in morphology date back to 25 centuries ago, and it is estimated that until the end of the 19th century, there were about 50 000 anatomical terms to name just over 5 000 body structures.[2] This proliferation of terms included medical eponyms —names given to certain body structures in honor of their discoverers—, which generated confusion and made communication difficult between anatomists,[3] histologists[4,5] and embryologists.[4]

With the creation of the Basle Nomina Anatomica in 1895 and the subsequent codes of terminology, the multiplicity of terms used to name the same structure began to be refined, allowing morphologists and other health professionals to begin to speak the same language; however, the use of eponyms has persisted. These terms do not provide any relevant information[6] about the structure under study, and its use is inconsistent, arbitrary and often influenced by the geography and local culture of the time.[7] In this sense, it could be said that the allocation of these names has some degree of randomness[8] and injustice, constituting a blunder for the logic of current thinking.[9] Although the declaration of the International Committee on Anatomical Terminology in 1933[10] proposed the elimination of these terms, their use remains a controversial issue.[11]

During the 13th Federative International Congress of Anatomy in 1989, the International Federation of Association of Anatomists (IFAA) created a new Federative International Committee on Anatomical Terminology (FICAT),[12] which has the task of reviewing, correcting and updating international anatomical terminology to facilitate the learning of this scientific discipline and make communication among medical science professionals clear and fluid, thus minimizing the possibility of errors and misunderstandings.[5] Thus, in 1998, FICAT published the book Terminologia Anatomica, which compiles all the necessary terms to name the different anatomical structures; there, each name provides information that allows associating the morphological characteristics of a structure with its function.[13]

On the other hand, in 2009 the Pan American Association of Anatomy (PAA) created the Ibero-Latin American Symposium on Anatomical, Histological and Embryological Terminology (SILAT), which is an open group of experts in morphology from most Latin American countries that study, analyze, translate, disseminate and promote international morphological terminology,[2] always respecting the parameters established by FICAT in Terminologia Anatomica. Furthermore, this association ensures that all sources of scientific dissemination, whether oral or written, use appropriately the official language. However, despite its worldwide dissemination, most professionals of the health sciences are unaware of or unfamiliar with the correct use of this work,[14] so the use of obsolete terms and eponyms is common among them, mostly in the clinical and surgical areas. Bearing in mind that eponyms are not official terms, they should not be used for anatomical description, since they make communication difficult and hinder the teaching-learning process; in this sense, they can only be of historical interest.[15,16]

Based on the above-mentioned concerns, the objective of the present study was to identify the obsolete eponyms and anatomical terms used during the 13th Colombian Congress of Morphology.

Materials and methods

The 52 papers exposed during oral presentations at the 13th Colombian Congress of Morphology, an event held at the facilities of the Universidad del Norte in Barranquilla (Colombia) in October 2017, were analyzed. The eponyms and obsolete anatomical terms used during each of the presentations were identified and quantified, and the percentage of papers that did not use correctly the terms included in Terminologia Anatomica was established. Data were taken in person by the authors after attending each and every one of the presentations.

Works that analyzed eponyms from a historical point of view and those that included chemical names of colors, pathological entities and biological rules, as well as medical doctrines and study parameters, were excluded from the study.

Results

Of the total number of oral presentations, 28 (53. 84%) used and named the following eponyms repeatedly: Golgi apparatus, Gantzer muscle, circle of Willis, Langerhans cells, Merkel cells, Meissner corpuscles, Kupffer cells, Graafian follicle, Meckel's diverticulum, space of Disse, Hesselbach's triangle, Ito cells, Fallopian tube, Pitwise cells, Gerdy's tubercle, canals of Hering, Achilles tendon, Kiernan's lobule and Glisson's capsule. Moreover, the following obsolete anatomical terms were used repeatedly in 21 presentations (40.38%): *músculo pellejero* (platysma muscle), *hueco supra esternal* (suprasternal notch), *epiplón* (omentum), *válvulas conniventes* (circular folds), *líquido cefalorraquídeo* (cerebrospinal fluid), and *cuero cabelludo* (scalp).

Discussion

This study shows that many professors, researchers and other health professionals use a morphological language that does not match the international anatomical terminology. This suggests that the official FICAT book is not being used as a reference for naming the different body structures, perhaps because they do not know it or because they are reluctant to change their traditional language, factors that were not evaluated in this paper.

This is evidenced by the abundant use of eponyms and obsolete anatomical terms in the papers presented during the 13th Colombian Congress of Morphology. It is inconvenient that such works have been accepted and presented in the most important event that brings together professionals and students involved in the field of morphological sciences in Colombia. Thus, the members of the scientific committee appointed for this Congress should have emphasized the correct use of international anatomical terminology.

Certain knowledge is incorporated during the learning process, but there are emotional bonds with the

language used by the professors during the training. In this sense, if the terminology used in the teaching of the medical sciences is not appropriate, the students end up incorporating eponyms and obsolete anatomical terms into their vocabulary that will eventually make learning and communication difficult.

Eponyms, in general, do not describe the findings associated with a disease or with the structure to which they are associated;[17] therefore, they do not provide any relevant information that would allow establishing or knowing what the structure is.[6] However, the defenders of their use argue that scientific names are more difficult to remember and communicate.[17]

The names in Terminologia Anatomica were designed using an analytical method and morphofunctional reasoning that allowed constructing a well-structured morphological language,[5] in which the terms intrinsically contain anatomical and functional information that clearly describes each structure. In contrast, naming a structure by its eponym only recalls the name of the historical figure that first discovered or described it, but does not provide any information on the structure itself. Therefore, all types of academic dialogue and all scientific work that is published —whether oral or written—, and that involve morphological sciences, should advocate for the correct use of international anatomical terminology, regardless of the language. In this way, it is possible to guarantee that the information that is being transmitted will be received in a clear and precise manner.

Terminology is a specialized linguistic tool that every science uses to transmit knowledge accurately and unambiguously; it is the tool that allows for the universal understanding of scientific and technical communication.[18] However, if professors, experts, and researchers in the field of morphological sciences do not comply with the precepts established by FICAT regarding the correct use of terminology, and instead persist in the use of an unofficial language with a predominance of eponyms and obsolete anatomical terms, they will be leading to a terminological chaos that affects understanding.[6] This is precisely what has happened in important events such as the 13th Colombian Congress of Morphology in 2017, the 18th Congress of International Federation of Associations of Anatomists, held in Beijing (China) in 2014,[9] and the 2nd Peruvian Congress of Morphological Sciences, held in March 2018 in Lima (Peru).

This lack of clarity in communication due to the misuse of terminological language is worrisome, since the transmission of morphological knowledge is hindered by not being captured or learned as it should be, and this is reflected in learning problems and school failure.[19,20] This creates an urgent need to reinforce the appropriate use of international anatomical terminology among the new generations of students and health professionals, which will prevent the continued use of obsolete eponyms and terms in and out of the classroom in the near future.[21] Thus, professors have the responsibility to eliminate eponyms from their vocabulary and prevent them from further use within the descriptive language of morphology. In general, eponyms should be relegated to the field of medical history, in order to preserve the historical memory of the people who made great contributions to morphological knowledge; they can also be used in regionalism dictionaries.[22]

Conclusion

The findings of the present study allow concluding that, at least in the 13th Colombian Morphology Congress, a high percentage of professors, researchers, and other health professionals did not use Terminologia Anatomica as a reference to name body structures, maybe because they did not know that it existed, or because they are used to traditional morphological language, in which eponyms and other obsolete terms predominate. This shortcoming can be attributed to the organization of this congress since the appropriate filters were not established during the selection of papers, nor were the authors informed beforehand that morphological language had to conform to international anatomical terminology.

Conflicts of interest

None stated by the authors.

Funding

None stated by the authors.

Acknowledgements

None stated by the authors.

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Rev. Fac. Med. 2020 Vol. 68 No. 1: 77-83

rfm
Revista *de la* Facultad *de* Medicina

ORIGINAL RESEARCH
DOI: http://dx.doi.org/10.15446/revfacmed.v68n1.70515
Received: 17/02/2018 **Accepted:** 05/07/2018

Quality of clinical practice guidelines approved in Peru between 2015 and 2017

Calidad de las guías de práctica clínica aprobadas en Perú entre 2015 y 2017

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Abstract

Introduction: The diagnosis and management of patients with the same medical condition may vary significantly depending on the treating physician. Clinical practice guidelines (CPG) are used to reduce this variation and to promote evidence-based management in clinical practice.
Objectives: To describe the characteristics of the CPGs adopted by public health institutions in Peru from July 2015 to September 2017.
Materials and methods: Cross-sectional, descriptive study. The following quality criteria were assessed in each CPG: the panel of experts responsible for the development of the CPG; protocols regarding the evidence identification, collection and assessment systems; and the level of evidence supporting each recommendation.
Results: 558 CPGs were included, of which 65.8% did not provide information on having an explicit author or only listed one author. In addition, 81.5% did not have citations, nor a reference list, and 97.7% did not clearly provide supporting evidence on how the recommendations were reached.
Conclusions: Most of the CPGs did not meet the quality criteria assessed in the present study, thus it is necessary to improve the skills of Peruvian health professionals to develop quality CPGs that adjust to their local context.
Keywords: Practice Guideline; Evidence-Based Practice; Practice Guidelines as Topic (MeSH).

Huapaya-Huertas OS, Zafra-Tanaka JH, Viru-Bazan CR, Gil-Loayza KA, Cruzado-Zafra IM, Taype-Rondan A. Quality of clinical practice guidelines approved in Peru between 2015 and 2017. Rev. Fac. Med. 2020;68(1):77-83. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.70515.

Resumen

Introducción. El diagnóstico y el manejo de pacientes con la misma condición médica pueden variar de manera significativa de profesional a profesional. Una manera de controlar esta variación y promover un manejo basado en evidencias es mediante el uso de guías de práctica clínica (GPC).
Objetivos. Describir las características de las GPC aprobadas por entidades públicas de salud de Perú entre julio de 2015 y setiembre de 2017.
Materiales y métodos. Se realizó un estudio transversal descriptivo donde se evaluaron los siguientes criterios de calidad de las GPC: panel de expertos que elaboró la guía; protocolos respecto a los sistemas de identificación, recogida y evaluación de la evidencia, y nivel de evidencia que sustenta cada recomendación.
Resultados. Se incluyeron 558 GPC, de las cuales 65.8% no contaba con autor explícito o solo describía un autor y no una lista, 81.5% no contaba con citas ni referencias bibliográficas y 97.7% no sustentaba de forma clara la elaboración de sus recomendaciones.
Conclusiones. La mayoría de las GPC no cumplieron los criterios de calidad evaluados en el presente estudio, por tanto es necesario mejorar las habilidades de los profesionales de la salud en Perú para elaborar GPC de calidad.
Palabras clave: Guía de práctica clínica; Práctica clínica basada en la evidencia; Guías para la Práctica Médica (DeCS).

Huapaya-Huertas OS, Zafra-Tanaka JH, Viru-Bazan CR, Gil-Loayza KA, Cruzado-Zafra IM, Taype-Rondan A. [Calidad de las guías de práctica clínica aprobadas en Perú entre 2015 y 2017]. Rev. Fac. Med. 2020;68(1):77-83. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.70515.

Introduction

The diagnosis and management of patients with the same medical condition and similar characteristics can vary significantly from one professional to another, making it challenging to ensure the quality of the services provided by health institutions.[1] One way to reduce this variation and promote evidence-based management is through the use of clinical practice guidelines (CPGs), which Lohr *et al.* define as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances".[2] Currently, CPGs play a key role in strategies to improve decision-making in health systems.[3,4]

To ensure the quality of the recommendations, CPGs should be elaborated following specific rigorous methodological standards that include the formulation of PICO questions (population, intervention, comparison, and outcome), the systematic search for studies to answer each question, and the assessment of the methodological quality of those studies by the experts who elaborated the guidelines.[5] However, a substantial number of guidelines do not meet these quality criteria, as has been reported in studies that evaluate the guidelines published in MEDLINE[6] and produced in different countries such as Argentina,[7] Canada, USA,[8] and Spain.[9]

In Peru, 3 studies have assessed the quality of CPGs using the Advancing guideline development, reporting and evaluation in health care (AGREE II) instrument, which allows for an assessment of the methodological rigor with which the guidelines were prepared and the transparency of the development process.[10] According to this instrument, a CPG has poor quality when it has a score of <60%.[11] The first of these studies evaluated the CPGs that address the diagnosis and management of hypertension and diabetes published by the Ministry of Health (MINSA) in 2015.[12] The second evaluated the quality of CPGs regarding various health issues such as obstetric pathologies, infectious diseases and non-communicable diseases —available on the website of MINSA's executive quality directorate for the period 2009-2014.[13] The third evaluated 12 CPGs of gynecological-obstetric diseases from a hospital in Peru.[14] In all 3 studies, the researchers found that the mean score for the AGREE-II instrument domains was <60%.

These studies[12-14] suggest that the methods used to elaborate CPGs have shortcomings that could affect the validity of the recommendations. However, all of them assess the guidelines issued before 2015, when the *Norma Técnica de Salud para la Elaboración y Uso de Guías de Práctica Clínica del Ministerio de Salud* (Technical Standards for the Development and Implementation of Clinical Practice Guidelines of the Ministry of Health)[15] and the technical document *Metodología para la Elaboración de Guías de Práctica Clínica del Ministerio de Salud* (Methodology for the Development of Clinical Practice Guidelines of the Ministry of Health) were published.[16] These documents establish the methodology for developing CPGs based on the Grading of Recommendations Assessment, Development, and Evaluations system to standardize and homogenize the preparation of the guidelines by providing a clear methodology. It is therefore expected that, by using these tools, the methodological quality of the CPGs developed from that date onwards is better than those developed before their publication.

In this context, it is essential to study the CPGs developed in Peru after the issuance of these regulations, which would allow evaluating the compliance with the regulations and proposing strategies to improve the quality of CPGs. Therefore, the objective of this study is to describe the characteristics of the CPGs approved by public health entities in Peru between July 2015 and September 2017.

Materials and methods

Study design and population

Descriptive cross-sectional study that analyzed the CPGs approved by public health entities in Peru. The guidelines collected by the General Directorate of Insurance and Benefit Exchange (DGAIN) of MINSA between July 2015 and September 2017 that met the following criteria were included: 1) being approved through a resolution issued by the directorate; 2) having consistent information, that is, including the name of the CPG and the number of the approval resolution; 3) being approved as of July 2015, and 4) being submitted to DGAIN in physical or digital media.

Procedures

In July 2017, to evaluate the approved CPGs in Peru, MINSA's DGAIN requested the submission of the CPGs regardless of their date of approval. The request was made to all secondary and tertiary health service provider institutions (IPRESS) —centers that develop and approve local CPGs in Peru[15] and belong to the Regional Government (GORE)—, the comprehensive health network directorates (DIRIS), social security (EsSalud), the Peruvian Armed Forces and National Police health departments, and MINSA's General Directorate of Strategic Interventions in Public Health (DIGIESP) (the body responsible for the production of national CPGs).[17] One month later, a reminder phone call was made to the institutions that had not responded to the request.

For this study, the CPGs were selected according to the criteria mentioned above. The variables of interest were extracted by a reviewer trained to evaluate this type of guideline. The information was digitized in an *ad hoc* database.

Variables

Quality criteria

A tool developed by the Analysis and Evidence Generation Unit of the National Health Institute of Peru was used to describe the quality of the CPGs. This instrument took into account three quality criteria suggested by Carrasquilla-Guitiérrez *et al.*,[18] which were proposed because they pose fundamental differences between evidence-based guidelines and guidelines based on expert opinion or consensus.[19] Each criterion was a variable with three possible categories:

Criterion 1. Persons in the panel of experts making the CPG: 1) only one author is mentioned or none is mentioned, 2) the list with the names of the people that developed the guidelines is available, and 3) the list with the names of the people that elaborated the guidelines

is available and specifies who were clinicians and who were in charge of the methodology.

Criterion 2. The protocols implemented in the systems of identification, collection, and evaluation of evidence are presented: 1) CPGs do not include bibliographic references, 2) CPGs have bibliographic references, and 3) CPGs include bibliographic references and assess their level of evidence.

Criterion 3. The level of evidence that supports each recommendation is clear: 1) CPGs do not present the level of evidence or it is not clear, 2) CPGs referrer manual or non-systematic search methods, and 3) CPGs refer systematic search methods.

Other variables

The following information was collected for each CPG: region where it was elaborated, year of approval, institution that elaborated it (MINSA- regional governments or comprehensive health network directorates, EsSalud or Armed Forces), level of the healthcare facility (secondary level: II-1, II-2 or II-E and tertiary level: III-1, III-2 or III-E), and clinical condition addressed in the guideline (using its ICD-10 code).

It should be noted that, according to the organization of the Peruvian health system, the secondary level consists of healthcare facilities that provide intermediate care and that meet 12-22% of the demand for health care. The tertiary level, in turn, consists of healthcare facilities that provide highly complex services, i.e., highly specialized, and meet 5-10% of the care demand.[20]

Statistical analysis

Frequencies and percentages were used for the descriptive analysis. Moreover, a chi-square test or an exact Fisher test, as appropriate, was performed to evaluate the association between CPG characteristics and quality criteria. Stata v14.0 was used for the analyses.

Results

A total of 6 147 CPGs approved in the period 2002-2017 were collected, of which 5 140 were approved using a resolution, and 5 107 had consistent information. Of the latter, 1 376 were approved through a resolution from July 2015, with the most recent CPG being approved in September 2017. However, of these 1 376 guidelines only 558 were received by the DGAIN and were, therefore, included in the study (Figure 1).

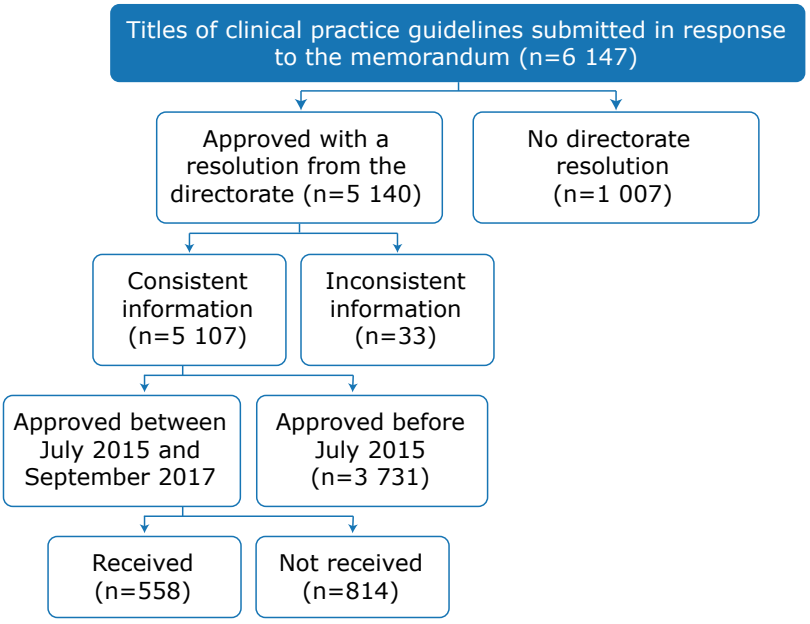

Figure 1. Clinical practice guidelines included in the study.
Source: Own elaboration.

Of the 558 CPGs included, 316 were elaborated by institutions in the department of Lima and 254 were approved between July and December 2015. DIRIS produced most of these documents (n=276), followed by regional governments (n=235). Regarding healthcare facilities, most of the CPGs were prepared by level III-1 (n=359).

Table 1 shows the characteristics of the CPGs included in the study. It is worth mentioning that only 553 CPGs were considered in the analysis of the variable "institution level", since 5 guidelines of the General Directorate of Strategic Interventions in Public Health did not have a level assigned.

The 558 guidelines were evaluated using the 3 quality criteria. Regarding *Criterion* 1, 65.8% did not specify explicitly an author or described only one author, and none listed the elaboration group separating clinicians from methodologists. As for *Criterion* 2, 81.5% had no citations or bibliographic references. Finally, about *Criterion 3*, 97.7% did not describe any evidence search method that supported their recommendations. Table 2 shows the evaluation of CPGs.

Table 1. Characteristics of the clinical practice guidelines included in the study (n=558).

Variables			n (%)
Department		Lima	316 (56.6)
		Loreto	170 (30.5)
		Tumbes	30 (5.4)
		La Libertad	29 (5.2)
		Huancavelica	13 (2.3)
Year of approval		July to December 2015	254 (45.5)
		2016	223 (40.0)
		2017	81 (14.5)
Institution	Regional governments (n=235, 42.1%)	Hospital 1 (outside the city of Lima)	95 (17.0)
		Hospital 2 (outside the city of Lima)	51 (9.1)
		Hospital 3 (outside the city of Lima)	30 (5.4)
		Hospital 4 (outside the city of Lima)	29 (5.2)
		Hospital 5 (outside the city of Lima)	17 (3.0)
		Hospital 6 (outside the city of Lima)	13 (2.3)
	Comprehensive Health Network Directorates (n=276, 49.5%)	Hospital 1 (city of Lima)	111 (19.9)
		Hospital 2 (city of Lima)	88 (15.8)
		Hospital 3 (city of Lima)	36 (6.5)
		Hospital 4 (city of Lima)	25 (4.5)
		Hospital 5 (city of Lima)	7 (1.3)
		Hospital 6 (city of Lima)	4 (0.7)
		Hospital 7 (city of Lima)	3 (0.5)
		Hospital 8 (city of Lima)	2 (0.4)
	Essalud	Hospital 1 (outside the city of Lima)	24 (4.3)
	Armed Forces	Hospital 1 (city of Lima)	18 (3.2)
	General Directorate of Strategic Interventions in Public Health - Ministry of Health		5 (0.9)
Institution level (for hospital guidelines) (n=553)	II-1		155 (28.0)
	III-1		359 (64.9)
	III-E		39 (7.1)
ICD-10	No ICD-10		28 (5.0)
	ICD-10 code (n=530, 95%)	A41.9	9 (1.6)
		O60.X	7 (1.3)
		J18.8	6 (1.1)
		K85.X	6 (1.1)
		N39.0	6 (1.1)
		O00.9	6 (1.1)
		O06.X	6 (1.1)
		Other ICD-10 codes	484 (91.3)

Source: Own elaboration.

Table 2. Evaluation of the quality of clinical practice guidelines (n=558).

Criterion		n (%)
Level of participation	A. Individual or without explicit author	367 (65.8)
	B. List of the members in the elaboration group	191 (34.2)
	C. List of the members in the elaboration group: clinicians and methodologists	0 (0.0)
Support of the recommendations	A. No citations and/or bibliographic references	455 (81.5)
	B. With bibliographic references	54 (9.7)
	C. With bibliographic references and evidence level assessment	49 (8.8)
Method for finding evidence that supported the recommendations	A. Not described/not clear	545 (97.7)
	B. Manual / non-systematic	2 (0.4)
	C. Systematic search	11 (2.0)

Source: Own elaboration.

After conducting the bivariate analysis, it was found that the frequency of "supporting the recommendations with bibliographic references" and "reporting and conducting a systematic search for the evidence" were higher in the Lima CPGs published in 2017 and by MINSA ($p<0.05$). Table 3 shows the association between the characteristics of CPGs and their indicators.

Table 3. Association between the characteristics of the clinical practice guidelines and their quality indicators.

Variable		Description of elaboration group		Description of the support of the recommendations with bibliographic references (with or without evaluation of the level of evidence)		Description of a systematic search for evidence	
		Reported n (%)	p-value	Reported n (%)	p-value	Reported n (%)	p-value
Department	Lima	62 (19.6)	<0.001	85 (26.9)	<0.001	10 (3.2)	0.028
	Other departments	129 (53.3)		18 (7.4)		1 (0.4)	
Year of approval	2015	86 (33.9)	<0.001	13 (5.1)	<0.001	1 (0.4)	<0.001
	2016	100 (44.8)		45 (20.2)		0 (0.0)	
	2017	5 (6.2)		45 (55.6)		10 (12.3)	
Institution	Regional Government	116 (49.4)	<0.001	18 (7.7)	<0.001	1 (0.4)	<0.001
	Comprehensive Health Network Directorates	62 (22.5)		82 (29.7)		10 (3.6)	
	EsSalud	13 (54.2)		0 (0.0)		0 (0.0)	
	Peruvian Armed Forces and National Police health departments	0 (0.0)		0 (0.0)		0 (0.0)	
	General Directorate of Strategic Interventions in Public Health.	0(0.0)		3 (60.0)		0 (0.0)	
Level of center (n=553)	II-1	87 (56.1)	<0.001	6 (3.9)	<0.001	1 (0.6)	0.328
	III-1	68 (18.9)		78 (21.7)		10 (2.8)	
	III-E	36 (92.3)		16 (41.0)		0 (0.0)	

Source: Own elaboration.

Discussion

A total of 558 CPGs were studied nationwide. Concerning the minimum criteria evaluated, more than half of the guidelines had no explicit author or described only one author and had no citations or bibliographic references. Also, few referred to or made clear the method of searching for evidence to support their recommendations.

Quality criteria

Most of the guidelines evaluated, which were approved as of July 2015, did not meet the minimum criteria for level of participation, support of their recommendations, or method of searching for evidence. This is consistent with previous studies on CPGs in Peru,[12,13] which have reported scores <60% in all domains of the AGREE-II instrument.

These results reflect the poor methodological quality of the guidelines, which may lead to inadequate recommendations. Thus, health staff must take into account that currently approved CPGs do not meet certain minimum quality criteria and, therefore, must carefully assess the CPGs before applying them to the clinical practice.

The shortcomings of CPGs may be explained by the lack of human or material resources for a rigorous methodological elaboration, as well as insufficient monitoring of their methodological quality.

It is worth mentioning that the *Norma Técnica de Salud para la Elaboración y Uso de Guías de Práctica Clínica del Ministerio de Salud*[15] and the technical document *Metodología para la Elaboración de Guías de Práctica Clínica*[16] detail the methodology for preparing CPGs, including the 3 criteria evaluated. However, the model for the presentation of the CPGs exposed in Annex 01 of the *Norma Técnica* does not require explicitly reporting these criteria, which seems contradictory since evaluating the methodological quality of the CPG without proper support of how it was elaborated is difficult.

Moreover, "reporting the development of a systematic search for evidence" was found to be more common in CPGs approved in 2017 than in those approved in 2015 and 2016. This may indicate that the methodology or the report of the Peruvian CPGs is improving, and it may be due to better knowledge of the technical standard for its elaboration. However, just over 10% of the CPGs approved in 2017 report conducting a systematic search for evidence.

Number of guidelines

A list of more than 5 000 CPGs was compiled with consistent information and resolution number; 1 376 of them were approved between July 2015 and September 2017. Since only the guidelines submitted voluntarily by the institutions that approve them were collected, this figure may be below the actual records, so the number of guidelines approved in the period evaluated could be higher.

This high number of recently approved CPGs is perhaps explained by the fact that, since 2006, the Health and Medical Support Facilities Regulations[21] require IPRESS to have technical policy documents and CPGs to start operations. Also, since 2017, the accreditation of healthcare centers and medical support services establishes as one of its criteria the existence of CPGs for the 10 most frequent pathologies in each service.[22] For this reason, an increase in the number of guidelines developed in Peru is expected, especially in institutions whose IPRESS can be developed without the need for approval by an evaluation committee.

In this context, EsSalud established in 2016 that the elaboration of CPGs in this institution must be supervised and approved by its Institute for Health Technology Assessment and Research (IETSI).[23] This could be a useful strategy to guarantee the necessary methodological rigor and adequate reporting of the guidelines, although it needs to be complemented by adequately prioritizing the documents to be elaborated, as well as providing appropriate training to clinicians and methodologists for their development and evaluation.[24]

Limitations and strengths

One of the limitations of this study is that an instrument developed ad hoc and not one used internationally, such as AGREE-II, was employed to describe the quality of CPGs. This could have happened because it was not feasible to apply AGREE-II in all the guidelines evaluated, and the minimum criteria that all should meet were used instead. Likewise, the CPGs evaluated are likely to be the short versions approved by the resolution, which makes it difficult to conduct proper evaluations given that, many times, they do not have complete methodological information.

Another limitation is that, although all relevant institutions were asked to submit the guidelines, participation was voluntary, which may have generated a participation bias considering that those with lower quality CPGs may have chosen not to submit them. Therefore, the results could overestimate compliance with the quality criteria assessed.

Despite the abovementioned limitations, the present study is the first to evaluate some quality criteria in a broad sample of Peruvian CPGs, including the main health subsystems that produce them in the country.

Conclusion

Most CPGs did not meet the quality criteria assessed in this study, so there is a need to improve the skills of health professionals in Peru to produce quality CPGs.

Conflicts of interest

OSHH, CRVB, KAGL and IMCZ work in the General Directorate of Insurance and Benefit Exchange of the Peruvian Ministry of Health; JHZT and ATR worked for the Institute for Health Technology Assessment and Social Security Research of Peru (EsSalud). Both institutions are involved in the elaboration, monitoring and regulation of clinical practice guidelines.

Funding

OSHH, CRVB, KAGL and IMCZ received financial support from the Ministry of Health.

Acknowledgements

None stated by the authors.

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rfm
Revista *de la* Facultad *de* Medicina

ORIGINAL RESEARCH
DOI: http://dx.doi.org/10.15446/revfacmed.v68n1.71690
Received: 13/04/2018 **Accepted:** 03/09/2018

Gait parameters in a sample of healthy Colombian adults aged between 18 and 25 years: a cross-sectional study

Parámetros de la marcha en una muestra de adultos sanos colombianos entre 18 y 25 años, un estudio transversal

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Abstract

Introduction: Gait analysis is fundamental for assessing the functional capacity and motor skills of any individual. Therefore, a reliable and specific analysis method is necessary to study gait in different populations. However, the reference values of gait parameters currently used in Colombia come from studies conducted on population groups from other countries or regions.
Objective: To identify the reference values of gait kinematic parameters in healthy Colombian young adults.
Materials and methods: A quantitative, descriptive, and cross-sectional study was conducted. The sample consisted of 155 Colombian young adults (aged 18 to 25). Temporal-spatial parameters and kinematics data of each participant were measured through 3D motion capture, which was performed using 8 infrared cameras (Bonita 10) and the VICON NEXUS 1.8.5. software. POLYGON 4.1. software was used for data analysis, and statistical analysis was performed using the STATA 12.1. software package.
Results: Average age, height and BMI were 20.3 years, 1.66m and 21.91T kg/m^2, respectively. 41.29% of participants were male. The average values obtained for the cadence, stride time, speed and initial swing temporal-spatial parameters were as follows: 103 steps/min, 1.16 seconds, 1.01 m/s, and 59.62% of the gait cycle (both sides), respectively.
Conclusion: Normal gait kinematic and temporal-spatial parameters of a group of healthy Colombian young adults were obtained, which will allow establishing the characteristics of normal gait in this population, improving intervention strategies, and designing and implementing technical aids aimed at improving locomotion in Colombian individuals.
Keywords: Gait; Gait Analysis; Spatio-Temporal Analysis; Kinematics; Reference Values (MeSH).

Duque-Ramírez JR, Vélez-Uribe JD, Gómez-Suárez NE, Manrique-Hernández RD. Gait parameters in a sample of healthy Colombian adults aged between 18 and 25 years: a cross-sectional study. Rev. Fac. Med. 2020;68(1):84-91. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.71690.

Resumen

Introducción. El análisis de la marcha es un componente fundamental para evaluar la capacidad motora y funcional de un individuo, por lo que su estudio en diferentes poblaciones requiere un método de análisis confiable y específico. Sin embargo, los parámetros de referencia usados en Colombia provienen de poblaciones de otros países o regiones.
Objetivo. Identificar los parámetros cinemáticos de referencia de la marcha en adultos sanos colombianos con edades entre 18 y 25 años.
Materiales y métodos. Estudio cuantitativo, descriptivo y de corte transversal realizado en 155 colombianos sanos entre 18 y 25 años. Los parámetros temporo-espaciales y los datos cinemáticos de cada participante fueron medidos mediante captura de movimiento 3D, la cual fue realizada con 8 cámaras infrarrojas (Bonita 10) y el software VICON NEXUS 1.8.5. Los datos fueron analizados con el programa POLYGON 4.1; para el análisis estadístico se utilizó el software STATA 12.1.
Resultados. Los promedios de edad, altura e IMC de la muestra fueron 20.3 años, 1.66m y 21.91 kg/m2, respectivamente; además, el 41.29% de los participantes eran hombres. Los promedios obtenidos para los parámetros temporo-espaciales cadencia del paso, duración de la zancada, velocidad e inicio del balanceo fueron: 103 pasos/min, 1.16 segundos, 1.01 m/s y 59.62% del ciclo (ambos lados), respectivamente.
Conclusión. Se obtuvieron los parámetros cinemáticos y temporo-espaciales de la marcha normal de un grupo de jóvenes sanos colombianos, lo cual permitirá establecer las características de la marcha patológica en los adultos jóvenes del país, perfeccionar estrategias de intervención y diseñar e implementar ayudas técnicas que busquen mejorar la locomoción en población colombiana.
Palabras clave: Marcha; Cinemática; Valores de referencia; Análisis de la marcha; Análisis Espacio-Temporal (DeCS).

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Introduction

Gait is a rhythmic and cyclical activity that engages the entire body, especially the lower limbs, to generate the characteristic bipedal locomotion of humans.[1] Exploring and analyzing gait in the context of the clinical and functional evaluation of human body locomotion constitutes a fundamental tool to uncover possibilities of movement, the capacity to fulfill different daily activities, and the level of social interaction of each individual.[1] For this reason, the aims of computerized gait analysis include establishing a differential diagnosis of related illnesses; assessing the severity, extension and nature of injuries; monitoring changes in the presence and absence of intervention or treatment; and predicting the outcomes of these interventions.[2]

In this regard, there are observational methods[1] available in clinical practice that have been used in combination with quantitative parameters to achieve accurate gait analyses. Nevertheless, since some intra- and inter-subject inconsistencies have been found in observational studies with respect to clinical gait assessment, it is necessary to resort to the expertise of the observers to avoid errors and biases that could lead to the inability to perform comparable follow-ups.

The quantitative data that is measured and used in therapeutic and diagnostic decision-making includes kinematic articulation in the three planes of motion (sagittal, frontal, and transverse), walking speed, swing period, support period and the subphases of the gait cycle. All these aspects allow accurately interpreting the outcomes.[3-5]

To provide a solution for the measurement issues mentioned above and to perform a more objective evaluation, high-quality systems such as gait analysis laboratories have been designed. These laboratories are considered as one of the most comprehensive and sophisticated evaluation methods since they provide an objective and quantitative assessment of the different parameters of human gait,[2] which are essential and necessary for the proper evaluation and diagnosis of gait alterations, and, also, for therapeutic follow-up and making clinical decisions (surgeries, orthoses, prosthesis).[1] Previous studies have been performed in other countries to determine the parameters of normal gait in their populations;[6-10] however, studies reporting gait reference parameters in Colombian adults are yet to be conducted.

Consequently, a precise, accurate, and reliable qualitative and quantitative method of analysis is required to standardize gait parameters in a specific population group. Therefore, the objective of this cross-sectional study is to describes gait parameters in healthy Colombian young adults (aged 18 to 25 years), living in the department of Antioquia, Colombia.

Materials and methods

Study design and participants

This was a cross-sectional quantitative study. Participants were selected by non-probability convenience sampling. A total of 155 participants were recruited. Gait kinematics and temporal-spatial gait parameters were evaluated. Participants selected to join the study met the following inclusion criteria: being Colombian, male or female, aged 18 to 25 years, and willing to participate in the study and provide signed informed consent. Exclusion criteria included individuals with a history of neurological or musculoskeletal disease; patients with soft tissue injuries, surgeries affecting the center of gravity or core muscles; individuals requiring walking aids, orthosis and/or prosthesis; being pregnant; individuals showing any gait alteration; being overweight (body mass index (BMI) >24.9 kg/m^2); being underweight (BMI<18 kg/m^2); high-performance athletes; having undergone lower limb surgeries, and having pain during evaluation or in the week before the assessment.

Pre-capture measurements

Prior to gait capture, height and BMI were calculated. Data from each participant was collected by means of a survey administered by a member of the research team. Anthropometric measurements were made following Plug-in Gait full body modeling references in the VICON NEXUS 1.8.5 motion capture software, which includes 35 markers.[11]

Capture

The system was previously calibrated and fed with the anthropometric measurements of each participant. Participants walked on a 6-meter straight track, at their own speed, and barefoot. At first, movement was not recorded so that participants could adapt to the laboratory environment and the markers. Subsequently, a 3D capture system with following characteristics was used: eight 1.0 megapixel infrared cameras (Bonita 10) with a speed of 250 frames per second.[12] The VICON NEXUS 1.8.5 software was used to assess gait kinematics. A minimum of 7 captures were taken, 3 strides per capture. The acquired data were processed using the POLYGON 4.1 software.[13]

Statistical analysis

Values from an algorithm implemented in the Octave software were used to obtain the normal values for gait kinematics (movement of the arc in the sagittal, coronal and transverse planes of the main joints of the lower limbs) and temporal-spatial gait parameters (cadence, stride time, opposite foot-off, opposite foot contact, step time, single support, double support, foot-off, stride and step length, and walking speed). The obtained data followed a normal distribution, so mean and standard deviation measures were calculated. With that in mind, the standard error was calculated with a 95% confidence interval (CI); the resulting value was added and subtracted from the mean to obtain the upper and lower limits of the CI for each of the variables. Subsequently, variables X and Y were plotted: X was defined as the percentage of the gait cycle, and Y as the kinematic variable of interest; in this way, it was possible to determine an area with the upper and lower interval limits of a 95%CI. Data were processed using the STATA v. 12.1 software.

Ethical considerations

This work was carried out in accordance with the Declaration of Helsinki[14] and Resolution 8430 of 1993 of the

Colombian Ministry of Health.[15] The Ethics Committee of Universidad CES approved and endorsed this study through Minutes 77 of February 16, 2015. All participants in this study were provided with and signed an informed consent.

Results

A total of 155 participants were included. The study population consisted of 41.29% (n=64) males, with an average age of 20.3 years, average height of 166 cm, and average BMI of 21.91. The following temporal-spatial gait parameters were measured in all participants: cadence, stride period, opposite foot-off, step time, single support, double support, foot-off, stride length, step length, and walking speed.

Table 1 shows the mean and standard deviation of each of the analyzed parameters. Figures 1 and 2 depict the peak joint angles in the different planes assessed during the gait cycle of both lower limbs, as well as the left and right lower limb kinematic parameters (95%CI), respectively.

Table 1. Temporal-spatial gait parameters.

	Left		Right	
	Mean	SD	Mean	SD
Cadence (steps/min)	103.74	6.94	103.95	7.00
Stride Time (seconds)	1.16	0.08	1.16	0.08
Opposite Foot-Off (percent)	9.32	1.62	9.40	1.57
Opposite Foot Contact (percent)	49.85	1.28	50.12	1.37
Step Time (seconds)	0.58	0.04	0.58	0.05
Single Support (percent)	40.53	1.73	40.71	1.70
Double Support (percent)	19.09	2.79	18.90	2.84
Foot-Off (percent)	59.62	1.65	59.62	1.77
Stride Length (meters)	1.17	0.09	1.17	0.09
Step Length (meters)	0.58	0.05	0.58	0.05
Walking Speed (meters per second)	1.01	0.11	1.01	0.11

Source: Own elaboration.

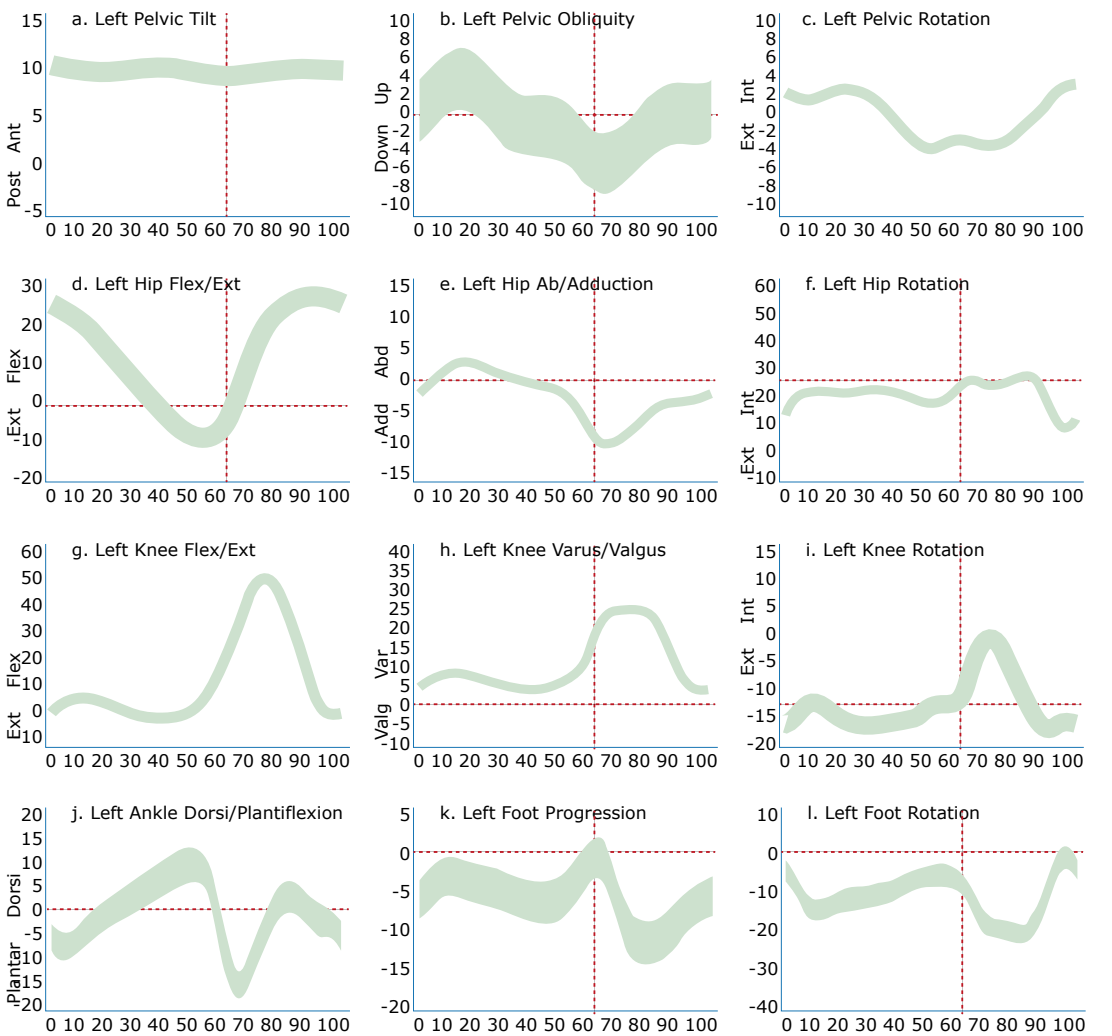

Figure 1. Left lower limb kinematics. The horizontal axis shows the percentage of gait cycle. Pelvic mobility: a) lateral plane (posterior and anterior pelvic obliquity), b) frontal plane, upper and lower pelvic obliquity; and c) transverse plane (external and internal pelvic rotation). Hip mobility: d) lateral plane (extension and flexion), e) frontal plane (abduction and adduction), f) transverse plane (external and internal hip rotation). Knee mobility: g) lateral plane (extension and flexion), h) frontal plane (valgus/varus), i) transverse plane (external and internal knee rotation). Ankle mobility: j) lateral plane (dorsiflexion and plantar flexion), k) frontal plane (foot progression angle), l) transverse plane (external and internal ankle rotation). Source: Own elaboration.

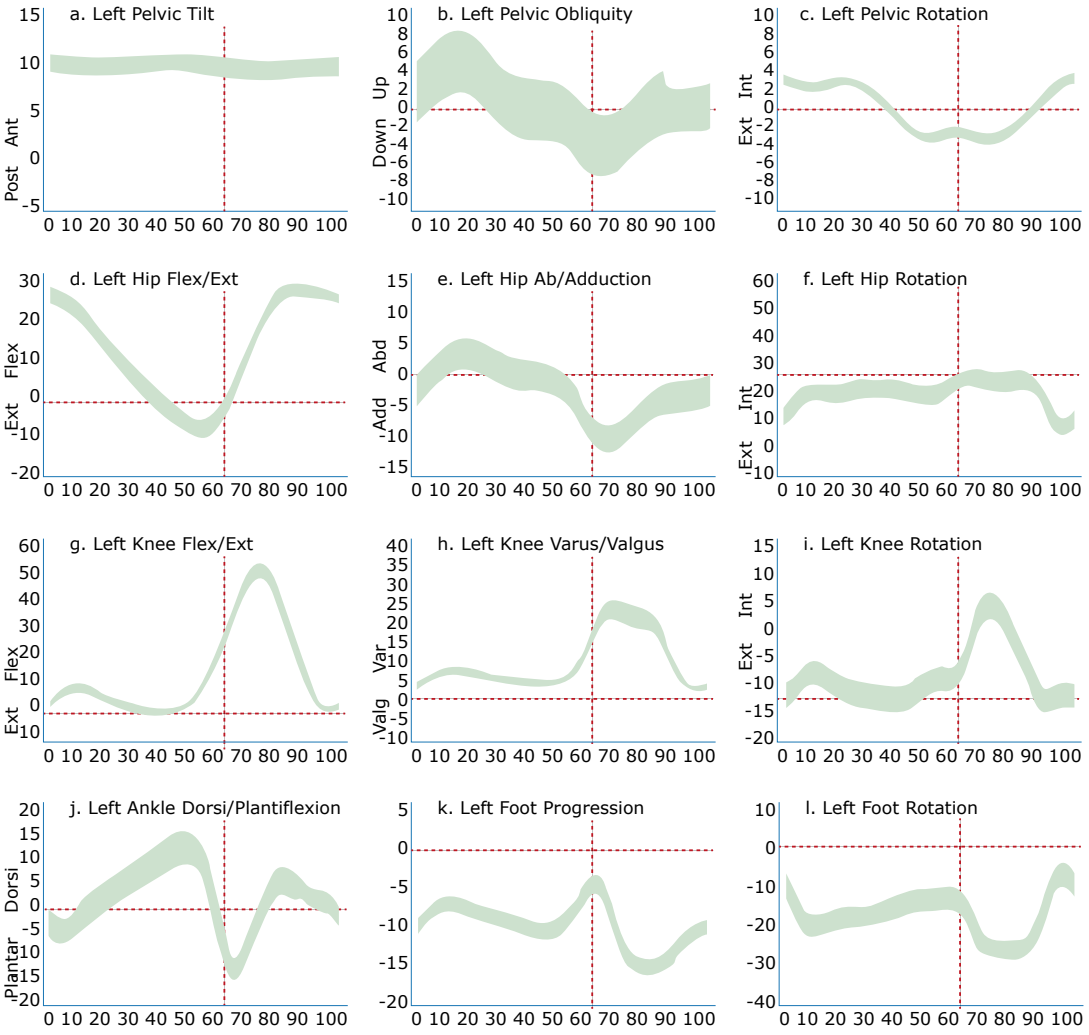

Figure 2. Right lower limb kinematics. The horizontal axis shows the percentage of gait cycle. Pelvic mobility: a) lateral plane (posterior and anterior pelvic obliquity), b) frontal plane, upper and lower pelvic obliquity, and c) transverse plane (external and internal pelvic rotation). Hip mobility: d) lateral plane (extension and flexion), e) frontal plane (abduction and adduction), f) transverse plane (external and internal hip rotation). Knee mobility: g) lateral plane (extension and flexion), h) frontal plane (valgus/varus), i) transverse plane (external and internal knee rotation). Ankle mobility: j) lateral plane (dorsiflexion and plantar flexion), k) frontal plane (foot progression angle), l) transverse plane (external and internal ankle rotation). Source: Own elaboration.

Regarding gait kinematics, the following parameters were analyzed in the sagittal, coronal, and transversal planes: pelvic tilt, obliquity, and rotation; hip flexion-extension, abduction/adduction, and rotation; knee flexion-extension, valgus/varus, and rotation; foot dorsi-flexion, progression, and rotation (Annex 1). The average values of the angles of each of the evaluated kinematic parameters are shown in Figures 1, 2 and Annex 1.

Discussion

Motion capture software was used in this study to describe gait parameters in healthy Colombian young adults. Compared to descriptive observational studies, gait assessment and analysis in motion labs provide more accurate data; for this reason, they have become the leading method to evaluate the movements of the human body. Furthermore, data obtained in said labs offer the necessary information for proper patient care, treatment decision-making, and diagnosis of alterations in gait. Also, it is a useful tool for the research and design of intervention strategies.[16]

By performing a cross-sectional study, this paper describes reference gait parameters in healthy Colombian adults aged 18 to 25 years old. In this regard, reference values for gait parameters are needed to identify deviations from the normal pattern.[16,17] Previous studies have established reference temporal-spatial gait parameters in healthy populations and have even reported sex differences.[17-21]

According to Al-Obaidi *et al.*,[5] the average walking speed can be calculated and classified as slow (average speed of 0.82 m/s), medium (average speed of 1.191 m/s) or fast (average speed of 1.675 m/s); the average speed of the participants in the present study was of 1.00±0.1 m/s. Based on previous works, this speed could be classified as slow gait, and it is lower than that reported by other authors in similar populations,[5,17,22] with a walking speed between 1.2238 m/s and 1.38 m/s. The differences in these values are likely explained by differences

in stride and height since the average step length in the present study was 0.58±0.05m, compared to 0.66m and 0.61m for Swedish men and 0.59m for Swedish women as reported by Al-Obaidi *et al.*[5]

Speed has been associated with variables such as step length, limbs length, height and cadence.[3] In this study, the step length was 0.58m and the average height was 166 cm, which are similar to those reported in studies conducted in similar age groups, with step lengths between 0.59m and 0.70m and heights that oscillate between 164cm and 180cm.[5,17,22] To make the data comparable between populations of different heights, several standardizations that include height, step length or limb length are frequently used.[23,24] Thus, after normalizing the walking speed with respect to height, the present study found an average walking speed of 0.6 height/sec, which is lower than the values reported by Al-Obaidi *et al.*[5] (0.66-0.70). It should be noted that the environment, the surroundings and the individual's mood can modify gait;[2,16,18] consequently, participants analyzed here were asked to walk as they usually do, and were given around 3 minutes to adapt to the markers and the lab setting.

Moreover, gait kinematics results obtained here are comparable to those reported by similar studies; however, asymmetries between sides in reference curves are rarely mentioned,[4,25,26] in spite of their relevance since they are usually related to cerebrovascular disease, amputations, osteoarthritis, and ankle sprains in the clinical setting.[27] Recent studies, such as the Global Gait Asymmetry (GGA) index, have attempted to identify the normalcy range of gait asymmetry,[28] and even though this study was not intended to quantify asymmetries, or use such indexes, it allowed establishing gait kinematic reference parameters for the right and left side in the study population.

The kinematic findings of the present study are consistent with those reported in similar studies that illustrate joint movement during walking.[26,29,30] However, this study describes joint movement with ranges of normality that are narrower than those reported by said studies,[22,29,31] which implies lower amplitude graphs. For example, Fryzowicz *et al.*[22] show an articular arc in the sagittal plane of the pelvis close to 6 degrees, while Bruening *et al.*[32] report 4.5 degrees of anteversion in men, which is significantly lower than the 9.5 degrees reported in the present study, thus denoting greater pelvic anteversion in our study population.

The availability and use of these data may allow for a better physical therapy and orthopedic approach, as well as specific occupational interventions for the Colombian population. Moreover, it provides a starting point for further research of different pathologies and for establishing novel methods to treat and predict musculoskeletal alterations.[33,34] Further gait analysis requires the inclusion of kinetic results that consider the forces generated in the joints.[26,28,35]

Conclusions

The findings reported here show the behavior of joint kinematics in a sample of Colombian young adults. This is the first study of its kind in Colombia conducted in a healthy population group, and it describes differences in kinematic and temporal-spatial variables when compared to data reported by similar studies conducted in populations of other countries. Findings differ in terms of normalcy ranges, which lead us to think that the ranges used to compare patients in Colombia are not adequate, making it necessary to conduct more studies to establish comparison parameters.

In conclusion, the data obtained here will allow establishing the characteristics of normal gait in Colombian young adults, improving intervention strategies, and leading to design and implement technical aids aimed at improving locomotion in Colombian individuals.

Conflicts of interest

None stated by the authors.

Funding

None stated by the authors.

Acknowledgments

To students Isabela Tamayo, Alexandra Gallego and Natalia Bustamante.

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Annex 1. Kinematic parameters by plane, articulation, and gait phase.

		Sagittal				Coronal				Transversal			
		Pelvic tilt				Pelvic obliquity				Pelvic Rotation			
GC		L (°)	± CI	R (°)	± CI	L (°)	± CI	R (°)	± IC	L (°)	± CI	R (°)	± CI
IC	Start	10.1	1	9.89	0.08	0.57	3.2	1.87	0.26	2.4	0.54	3.12	0.04
0-2 %	End	10.02	1	9.81	0.08	1.06	3.2	2.38	0.26	2.33	0.55	3.01	0.04
LR	Start	10.1	1	9.89	0.08	0.57	3.2	1.87	0.26	2.4	0.54	3.12	0.04
0-10 %	End	9.58	1	9.52	0.08	3.38	3.24	4.72	0.26	1.79	0.55	2.33	0.04
MSt	Start	9.58	1	9.52	0.08	3.38	3.24	4.72	0.26	1.79	0.55	2.33	0.04
11-30 %	End	9.59	1	9.75	0.08	-0.03	3.24	1.15	0.26	1.55	0.53	1.86	0.04
TS	Start	9.59	1	9.75	0.08	-0.03	3.24	1.15	0.26	1.55	0.53	1.86	0.04
31-50 %	End	9.63	0.98	9.83	0.08	-1.85	3.24	-0.6	0.26	-3.39	0.56	-2.96	0.04
Pre-S	Start	9.63	0.98	9.83	0.08	-1.85	3.24	-0.6	0.26	-3.39	0.56	-2.96	0.04
51-60 %	End	9.26	1	9.33	0.08	-4.71	3.22	-3.45	0.26	-2.48	0.55	-2.24	0.04
IS	Start	9.26	1	9.33	0.08	-4.71	3.22	-3.45	0.26	-2.48	0.55	-2.24	0.04
61-73 %	End	9.25	1.01	9.17	0.08	-3.43	3.22	-2.4	0.26	-3.09	0.48	-3.02	0.04
MSw	Start	9.28	1.01	9.21	0.08	-2.79	3.22	-1.77	0.26	-2.88	0.48	-2.84	0.04
74-87 %	End	9.51	1	9.53	0.08	0.03	3.21	-0.08	0.26	-0.02	0.49	-0.05	0.04
TSw	Start	9.55	0.99	9.57	0.08	0.11	3.21	0.03	0.26	0.64	0.5	0.61	0.04
88-100 %	End	9.48	0.97	9.65	0.08	0.77	3.2	0.64	0.26	3.21	0.51	3.19	0.04
		Hip flexion-extension				Hip Adduction-abduction				Hip rotation			
IC	Start	29.12	3.68	30.67	0.3	-2.08	0.63	-2.07	0.05	12.69	2.65	9.5	0.21
0-2 %	End	28.43	3.68	30.1	0.3	-1.38	0.64	-1.3	0.05	15.52	2.61	12.43	0.21
LR	Start	29.12	3.68	30.67	0.3	-2.08	0.63	-2.07	0.05	12.69	2.65	9.5	0.21
0-10 %	End	23.68	3.64	25.67	0.29	2.16	0.69	2.43	0.06	21.39	2.4	18.28	0.19
MSt	Start	23.68	3.64	25.67	0.29	2.16	0.69	2.43	0.06	21.39	2.4	18.28	0.19
11-30 %	End	4.95	3.46	6.82	0.28	0.57	0.61	1.06	0.05	21.01	2.51	19.85	0.2
TS	Start	4.95	3.46	6.82	0.28	0.57	0.61	1.06	0.05	21.01	2.51	19.85	0.2
31-50 %	End	-8.77	3.41	-7.11	0.27	-2.48	0.58	-1.72	0.05	17.75	2.63	18.1	0.21
Pre-S	Start	-8.77	3.41	-7.11	0.27	-2.48	0.58	-1.72	0.05	17.75	2.63	18.1	0.21
51-60 %	End	-3.19	3.4	-1.38	0.27	-8.76	0.58	-8.28	0.05	23.28	2.75	22.64	0.22
IS	Start	-3.19	3.4	-1.38	0.27	-8.76	0.58	-8.28	0.05	23.28	2.75	22.64	0.22
61-73 %	End	19.51	3.53	21.21	0.28	-8.08	0.61	-7.93	0.05	24.43	2.74	22.49	0.22
MSw	Start	22.67	3.56	24.37	0.29	-7.19	0.62	-7.05	0.05	24.58	2.74	22.38	0.22
74-87 %	End	30.62	3.62	31.77	0.29	-3.61	0.64	-3.48	0.05	24.55	2.48	21.17	0.2
TSw	Start	30.5	3.61	31.69	0.29	-3.38	0.63	-3.26	0.05	21.15	2.51	17.91	0.2
88-100 %	End	28.32	3.65	29.79	0.29	-1.85	0.64	-1.99	0.05	12.21	2.65	9.22	0.21
		Knee flexion - extension				Knee varus/valgus				Knee rotation			
IC	Start	1.48	1.04	2.94	0.08	4.43	0.57	3.91	0.05	-16.32	2.29	-12.17	0.18
0-2 %	End	2.89	1.1	4.6	0.09	5.27	0.62	4.7	0.05	-16.18	2.31	-11.81	0.19
LR	Start	1.48	1.04	2.94	0.08	4.43	0.57	3.91	0.05	-16.32	2.29	-12.17	0.18
0-10 %	End	6.78	1.37	8.95	0.11	8.19	0.77	7.51	0.06	-12.61	2.33	-8.04	0.19
MSt	Start	6.78	1.37	8.95	0.11	8.19	0.77	7.51	0.06	-12.61	2.33	-8.04	0.19
11-30 %	End	0.13	1.12	1.65	0.09	5.26	0.58	5.13	0.05	-16.58	2.46	-12.4	0.2
TS	Start	0.13	1.12	1.65	0.09	5.26	0.58	5.13	0.05	-16.58	2.46	-12.4	0.2
31-50 %	End	4.1	1.12	5.42	0.09	5.91	0.6	5.71	0.05	-13.12	2.35	-9.63	0.19
Pre-S	Start	4.1	1.12	5.42	0.09	5.91	0.6	5.71	0.05	-13.12	2.35	-9.63	0.19
51-60 %	End	23.37	1.98	25.11	0.16	17.05	1.45	16.97	0.12	-11.74	2.39	-8.1	0.19

Annex 1. Kinematic parameters by plane, articulation, and gait phase. (Continued)

IS	Start	23.37	1.98	25.11	0.16	17.05	1.45	16.97	0.12	-11.74	2.39	-8.1	0.19
61-73 %	End	50.54	2.85	52.03	0.23	24.1	2.59	22.66	0.21	-1.4	2.66	3.59	0.21
MSw	Start	49.82	2.85	51.18	0.23	23.97	2.59	22.21	0.21	-2.33	2.64	2.41	0.21
74-87 %	End	17.96	1.8	20.29	0.14	14.71	1.24	13.21	0.1	-15.56	2.34	-10.87	0.19
TSw	Start	11.98	1.5	14.14	0.12	10.67	0.98	9.56	0.08	-16.95	2.35	-12.47	0.19
88-100 %	End	1.42	1.04	2.98	0.08	4.47	0.6	4.04	0.05	-16.41	2.31	-12.29	0.19
		Plantar and dorsi flexion				Foot progression				Foot rotation			
IC	Start	-5.52	2.87	-2.78	0.23	3.57	2.25	3.92	0.18	-4.96	2.9	-8.97	0.23
0-2 %	End	-7.25	2.79	-4.52	0.22	3.1	2.3	3.44	0.19	-7.67	2.91	-11.84	0.23
LR	Start	-5.52	2.87	-2.78	0.23	3.57	2.25	3.92	0.18	-4.96	2.9	-8.97	0.23
0-10 %	End	-5.32	3	-2.23	0.24	1.96	2.32	2.73	0.19	-15.56	2.73	-19.74	0.22
MSt	Start	-5.32	3	-2.23	0.24	1.96	2.32	2.73	0.19	-15.56	2.73	-19.74	0.22
11-30 %	End	3.52	3.39	7.07	0.27	5.49	2.2	6.39	0.18	-11.27	2.67	-16.45	0.21
TS	Start	3.52	3.39	7.07	0.27	5.49	2.2	6.39	0.18	-11.27	2.67	-16.45	0.21
31-50 %	End	9.05	3.65	12.29	0.29	5	2.21	6.14	0.18	-6.77	2.74	-12.67	0.22
Pre-S	Start	9.05	3.65	12.29	0.29	5	2.21	6.14	0.18	-6.77	2.74	-12.67	0.22
51-60 %	End	-10.92	3.04	-7.84	0.24	3.25	2.46	4.19	0.2	-8.5	2.79	-13.41	0.22
IS	Start	-10.92	3.04	-7.84	0.24	3.25	2.46	4.19	0.2	-8.5	2.79	-13.41	0.22
61-73 %	End	-4.89	3.05	-1.51	0.24	1.9	2.32	2.73	0.19	-20.3	2.48	-25.53	0.2
MSw	Start	-2.19	3.12	1.19	0.25	2.05	2.27	3.02	0.18	-20.54	2.49	-25.52	0.2
74-87 %	End	0.5	3.16	4.6	0.25	0.92	2.24	0.64	0.18	-17.33	2.73	-21.6	0.22
TSw	Start	-0.86	3.11	3.21	0.25	1.23	2.25	0.82	0.18	-13.42	2.78	-17.63	0.22
88-100 %	End	-6.02	2.92	-1.88	0.23	4	2.24	3.01	0.18	-4.82	2.87	-9.31	0.23

GC: gait cycle; IC: Initial contact phase; LR: loading response; MSt: Mid stance; TSt: terminal stance; Pre-S: pre-swing; IS: initial swing; MSw: mid-swing; TSw: terminal swing; L: Left laterality; R: Right laterality; CI: confidence interval.
Source: Own elaboration.

rfm
Revista *de la* Facultad *de* Medicina

ORIGINAL RESEARCH
DOI: http://dx.doi.org/10.15446/revfacmed.v68n1.69977
Received: 24/01/2018 **Accepted:** 06/06/2018

Analysis of physical fitness according to sex, age, body mass index and level of physical activity in Spanish elementary school students

Análisis de la condición física según sexo, edad, índice de masa corporal y nivel de actividad física en estudiantes de primaria en España

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Abstract

Introduction: Scientific evidence suggests that schoolchildren's quality of life is directly related to their physical fitness (PF).
Objective: To analyze the physical fitness of elementary school students according to age, sex, body mass index (BMI) and level of physical activity (PA).
Materials and methods: Cross-sectional and descriptive study conducted in 103 schoolchildren (aged 8-12 years) from Spain. PF and PA were measured using the ALPHA-fitness test battery and the Physician-based Assessment and Counseling for Exercise instrument, respectively. Participants were classified according to their level of PA (physically inactive vs. physically active) and their BMI (normal weight vs. overweight-obese). Parametric statistics were used for data analysis.
Results: Male participants had a better level of PF. In addition, it was found that PF slightly increases as age increases, regardless of the sex. Normal weight or physically active schoolchildren had better aerobic capacity and a healthier body composition.
Conclusion: Keeping optimal PF levels at any stage of life requires adopting a healthy lifestyle since childhood; therefore, it is necessary to encourage schoolchildren to do physical activity on their own.
Keywords: Health; Exercise, Physical; Obesity (MeSH).

Rosa-Guillamón A, Carrillo-López PJ, García-Cantó E. Analysis of physical fitness according to sex, age, body mass index and level of physical activity in Spanish elementary school students. Rev. Fac. Med. 2020;68(1):92- 9. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.69977.

Resumen

Introducción. La evidencia científica sugiere que la calidad de vida de los escolares se relaciona de forma directa con el estado de su condición física (CF).
Objetivo. Analizar la CF según edad, sexo, índice de masa corporal (IMC) y nivel de actividad física en estudiantes de primaria.
Materiales y métodos. Se realizó un estudio descriptivo transversal con 103 escolares entre 8 y 12 años de España. La CF se midió mediante la batería ALPHA-Fitness y la actividad física, con el cuestionario Physician-based Assessment and Counseling for Exercise. Los participantes se categorizaron según su nivel de actividad física (no activos versus activos) y su IMC (normo-peso versus sobrepeso-obesidad). Para el análisis se aplicó estadística paramétrica.
Resultados. Los varones tuvieron un mejor nivel de CF, pero en ambos sexos se observó un leve incremento de esta a medida que aumentaba la edad. Los escolares con normopeso o activos físicamente tuvieron una mejor capacidad aeróbica y una composición corporal más saludable.
Conclusión. Mantener niveles óptimos de CF a lo largo de la vida requiere de la adopción de un estilo de vida saludable desde la infancia, por tanto, es necesario promover la práctica autónoma de actividad física en los escolares.
Palabras clave: Salud; Ejercicio físico; Obesidad (DeCS).

Rosa-Guillamón A, Carrillo-López PJ, García-Cantó E. [Análisis de la condición física según sexo, edad, índice de masa corporal y nivel de actividad física en estudiantes de primaria en España]. Rev. Fac. Med. 2020;68(1):92-9. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.69977.

Introduction

Scientific evidence suggests that health status and quality of life in students are directly related to their physical fitness (PF).[1] PF is understood as a set of capacities and functions that allows people to perform physical and sport-based exercises and physical activities with vigour[2] and efficiency[3] in their daily life.

Recent studies suggest an association between having low PF levels in life stages such as childhood and adolescence and having a higher risk of developing physiological events (abnormal levels in parameters such as systolic blood pressure, lipoprotein cholesterol and plasma glucose; insulin resistance; deterioration of bone tissue; among others) and psychosocial disorders (stress, psychological distress, among others) in adulthood.[4,5] Given its importance for health, normative values have been established to analyze the evolution of the PF status in young people, finding that the optimal level has not been reached in some places of Europe,[6,7] Oceania[8], Asia[9], Africa[10] and America.[11,12]

Epidemiological studies have reported a progressive increase in PF levels as age increases.[11,13,14] In this context, men have shown better values in different components such as cardiovascular, musculoskeletal and motor capacity,[15] while women have better scores in morphological indicators such as anterior trunk flexibility.[8]

Another morphological indicator considered when analyzing PF is body composition. [16,17] A body mass index (BMI) indicative of overweight or obesity may favor the onset of concomitant cardiovascular and metabolic diseases and psychosocial disorders.[4,6,18] Moreover, body composition associates weight with height[19] and, although it does not distinguish whether overweight is caused by fat or lean mass, it is a valid indicator of body mass index,[20] which has been established in the scientific literature as the most accurate anthropometric predictor of PF status.[21]

Other valid and reliable anthropometric indicators are waist circumference (WC) and waist-to-hip ratio (WHR), which have been classified into percentiles in order to estimate metabolic risk,[22] total body fat and intra-abdominal and central fat in young individuals.[23] In this regard, Mazicioglu *et al.*[24] state that WHR values >0.85 in women and >0.94 in men are closely related to the development of high blood pressure in the future.

The relationship between the anthropometric indicators described and the risk of suffering from overweight or obesity is well established and has been well analyzed around the world.[6] This relationship includes both genetic[25] and lifestyle factors, including a deficit of physical activity (PA) and PF.[3]

According to the scientific literature, regular and adequate physical activity is one of the best (complementary) strategies to combat increasing rates of overweight and obesity in children and adolescents.[3,26] Therefore, physical exercise is understood as the practice of PA in a structured, planned, and systematic way with the objective of improving one or more components of PF.[25]

Although much of the variability of PF is determined by genes, environmental constraints, especially PA, can influence it,[25] perhaps in a two-way relationship.[3] However, whether this relationship is consistent has been questioned, considering that PA performance among young people is characterized by being unpredictable, unsystematic and of short duration and, consequently, may not change the status of PF, especially at the cardiovascular level.[27]

In summary, in young individuals, it has been described that being younger,[13,28] female,[17,29] overweight,[30-33] and having a PA deficit is associated with a worse PF status.[15,34] However, some studies suggest that, regardless of age and sex, a person can be overweight and have a healthy PF status if there is an optimal PA level, confirming the phenotype known as *fat but fit*. Said concept refers to overweight or obese people who have acceptable PF levels and who may have better health conditions than those who have the same level of overweight but worse PF status.[35-37] Based on this information, the objective of this work was to analyze the PF status of a sample of elementary students taking into account age, sex, BMI and PA level.

Materials and methods

Design and participants

Ex post facto descriptive and cross-sectional empirical study of 103 participants (63 females and 40 males) aged 8-12 years (9.94±1.40 years). A sample was obtained for convenience and the participants, who were enrolled in schools from the Region of Murcia (Spain), provided the informed consent signed by their parents or legal guardians. Schoolchildren with osteoarticular pathologies were excluded from the study.

Ethical considerations

This study followed the ethical principles established by the Declaration of Helsinki[38] for human research. This article derives from a doctoral thesis developed at the Department of Plastic, Musical and Dynamic Expression of the Universidad de Murcia (Murcia, Spain), and was approved by the doctoral committee of the Faculty of Education of that university; this body verifies compliance with the corresponding ethical considerations during the conduct of the study.

Instruments

PF was measured using the ALPHA-Fitness test battery, which was modified as follows: the skin folds were not measured and the 4x10m shuttle run test of the extended version was added.[2,16] The reliability and validity tests of this battery were verified with individuals from similar socio-cultural environments.[17]

Body weight was measured with an electronic scale (model 220, SECA, Hamburg-Germany) and height with a stadiometer (Holtain Ltd., Dyfed, UK). Based on these values, BMI was calculated using the formula: weight (kg)/height (m²). Considering the specific international standards for age and sex, schoolchildren were classified according to their BMI into *normal weight* (<25 kg/m²) and *overweight-obesity* (≥25 kg/m²).[19]

Waist circumference (WC) and hip circumference (HC) were measured using an anthropometric tape (Harpenden Anthropometric Tape, Holtain Ltd, Dyfed-UK) and WHR was estimated using the WC/HC ratio. Speed-agility was deduced through the 4x10m shuttle run test,[39] for which a professional stopwatch was used (HS-80TW-1EF,

Casio, Tokyo, Japan). To calculate the maximal handgrip strength, a hand-held dynamometer test[40] was performed using a digital dynamometer with adjustable grip (TKK 5041 Grip D, Takei, Tokyo, Japan), as well as a ruler to adapt the grip width. The explosive power of the lower body was established through a standing long jump test[41] using a PVC fiberglass measuring tape (74-Y100M, CST/Berger, Chicago, USA).

Aerobic capacity was estimated by means of the 20m shuttle run test, using a portable audio device (Behringer EPA40, Thomann, Burgebrach, Germany) and a USB flash drive (Hayabusa, Toshiba, Tokyo, Japan).[42] The record considered for the study was the last completed stage or half-stage.

In order to obtain the overall PF variable, known as zPF-ALPHA, maximal handgrip strength, explosive power of the lower body and aerobic capacity values were added, and the speed-agility value was subtracted.[17]

PA was measured with the Physician-based Assessment and Counseling for Exercise (PACE)[43] instrument, which consists of 2 items that estimate the weekly PA performed by an individual for at least 60 minutes (PACE 1, how many times in the last week; PACE 2, how many days in a typical week). Internal consistency, reliability and validity were verified in individuals of similar ages by Rosa-Guillamón *et al.*[3], and Cronbach's Alpha for the present study was 0.847.

Based on the results of the last questionnaire, and taking into account the criteria established by the Department of Health and Social Care of the United Kingdom,[44] the participants were classified into 2 groups according to their level of PA: *physically inactive* (X<5 hours) and *physically active* (X≥5 hours).[45] Likewise, a variable that combined BMI and PA level was created, which resulted in 4 groups: A: normal weight/physically inactive, B: normal weight/physically active, C: overweight-obesity/physically inactive, and D: overweight-obesity/physically active.

Procedure

This study was carried out during the 2016-2017 academic year, and the data were collected in October 2016. Before applying the tests, a warm-up based on joint mobility and dynamic stretching was performed for 8 minutes.

Only one trial was allowed for each test and the PACE questionnaire was administered in the presence of the interviewer, so that any doubts that could arise could be promptly solved.

Statistical analysis

Sex differences were analyzed using Mann-Whitney U-test for continuous variables and Pearson's chi-square test for categorical variables. The Mann-Whitney U test was also applied to study the relationship between weight status and PF. On the other hand, to analyze the combined association between PA and weight status with PF, the Kruskal-Wallis H test was applied using the SPSS program (v.23.0, Chicago, Illinois, USA), with a significance level of $p<0.05$.

Results

Table 1 shows that males had better physical performance in the 4x10m shuttle run test, hand-held dynamometry and 20m shuttle run test ($p<0.05$), as well as in the variable zPF-ALPHA ($p<0.01$). It also shows that there is a trend towards increasing PF levels as age increases in both sexes.

Table 1. Physical fitness by age and sex (males: 40 and females: 63).

Variable		8 years	9 years	10 years	11 years	12 years	Total
Weight (kg)	M	29.3±4.6	32.7±6.0	38.9±10.1	42.2±9.8	43.3±7.9	37.5±9.6
	F	27.0±6.0	31.4±5.9	40.0±6.7	41.4±19.1	43.4±12.2	36.3±11.8
Height (cm)	M	127.6±5.8	132.7±5.9	137.4±6.1	143.3±8.0	150.9±5.3	138.5±10.4
	F	125.5±5.8	130.5±6.3	135.7±7.4	144.6±11.1	149.0±7.7	136.2±11.2
BMI (kg/m2)	M	17.9±1.8	18.5±2.5	20.5±4.9	20.4±3.4	19.0±2.7	19.3±3.3
	F	17.0±2.5	18.4±3.0	21.8±3.8	19.2±5.6	19.3±4.0	19.2±4.0
WC (cm)	M	62.5±6.0	65.5±3.9	70.0±15.4	68.2±13.3	67.5±8.5	66.8±10.7
	F	61.8±7.1	64.8±9.0	71.5±8.5	69.4±16.8	65.5±11.5	66.7±10.9
HC (cm)	M	69.3±4.3	67.75±6.8	76.89±9.5	79.3±14.0	78.2±7.2	74.9±9.8
	F	6.2±6.8	70.33±5.7	80.67±6.8	79.9±14.1	80.4±9.3	75.5±10.1
WHR (cm)	M	0.90±0.044	0.97±0.04	0.90±0.10	0.86±0.11	0.86±0.08	0.89±0.09
	F	0.92±0.05	0.92±0.07	0.89±0.08	0.86±0.07	0.81±0.07	0.88±0.08
4x10m shuttle run (s)	M	14.1±1.5	14.2±0.8	13.2±0.6	13.3±0.9 *	12.4±0.7	13.4±1.1 †
	F	14.7±1.6	14.6±1.0	13.9±0.8	14.2±0.9	12.6±0.8	14.1±1.2
RHHD (kg)	M	13.2±3.0 *	13.5±5.2	15.3±3.7	16.1±3.2	20.6±4.2	15.8±4.4 *
	F	10.5±3.0	11.6±2.0	14.2±2.8	15.5±2.8	19.3±4.8	14.0±4.3 *
LHHD (kg)	M	11.8±2.3	13.5±5.7	14.5±4.0	16.6±4.1	19.9±5.5	15.3±4.9 *
	F	9.6±3.1	11.5±2.3	12.7±2.4	15.9±3.1	18.8±5.0	13.4±4.4

Table 1. Physical fitness by age and sex (males: 40 and females: 63). (Continued)

Variable		8 years	9 years	10 years	11 years	12 years	Total
RHHD +L (kg)	M	25.0±5.0 *	27.0±10.8	29.8±7.5	32.7±7.1	40.5±8.8	31.1±9.0
	F	20.1±5.8	23.1±3.9	26.9±4.7	31.4±5.5	38.1±9.1	27.4±8.4
SLJT (cm)	M	83.2±8.8	116.8±6.7 *	94.1±17.8	101.2±14.7	114.1±18.7	99.3±18.5
	F	82.8±11.2	92.7±21.3	92.7±19.3	99.4±10.0	105.5±20.3	94.1±18.5
20m shuttle run (stages)	M	2.4±1.5	2.4±1.4	2.8±1.2	3.5±1.4	3.7±1.7	3.0±1.5
	F	2.0±0.7	2.4±0.9	2.1±1.1	2.9±1.2	3.2±1.3	2.5±1.1
zPF-ALPHA	M	0.16±0.07	0.22±0.06	0.22±0.07	0.28±0.08	0.35±0.10	0.25±0.10 †
	F	0.11±0.07	0.16±0.07	0.17±0.08	0.23±0.08	0.31±0.09	0.19±0.10

M: male; F: female; BMI: body mass index; WC: waist circumference; HC: hip circumference; WHR: waist-to-hip ratio; RHHD: right hand-held dynamometry; LHHD: left hand-held dynamometry; RHHD +L: right hand-held dynamometry + left; SLJT: standing long jump test; zPF-ALPHA: physical fitness-ALPHA.
* p< 0.05.
† p< 0.01.
Source: Own elaboration.

Schoolchildren with normal weight had lower WC, HC (p<0.01) and WHR (p<0.05) values, as well as better physical performance in the 20m shuttle run (p<0.001). Overweight-obese children had higher values in the right hand-held dynamometry (RHHD), left hand-held dynamometry (LHHD) and right + left hand-held dynamometry (RHHD+L) tests (p<0.05) (Table 2). Physically active schoolchildren had lower BMI, WC and HC (p<0.05) and better performance in the 20m shuttle run test (p<0.01) (Table 3).

Table 2. Relationship between body mass index and physical fitness.

Variable	Normal weight (n=65)	Overweight-obesity (n=38)	Z
WC (cm)	61.4±6.7	75.9±10.3	-6.802 *
HC (cm)	74.9±9.8	75.5±10.1	-6.665 *
WHR (cm)	0.89±0.09	0.88±0.08	-2.379 †
4x10m shuttle run (s)	13.7±1.2	14.0±1.3	-1.319
RHHD (kg)	14.0±4.1	15.9±4.6	-1.912 †
LHHD (kg)	13.3±4.5	15.6±4.7	-2.487 †
RHHD+L (kg)	27.3±8.2	31.5±9.1	-2.157 †
SLJT (cm)	97.4±19.1	93.9±17.8	-0.855
20m shuttle run (stages)	3.0±1.4	2.1±0.9	-3.888 *
zPF-ALPHA	0.22±0.11	0.19±0.09	-1.463

WC: waist circumference; HC: hip circumference; WHR: waist-to-hip ratio; RHHD: right hand-held dynamometry; LHHD: left hand-held dynamometry; RHHD +L: right hand-held dynamometry + left; SLJT: standing long jump test; zPF-ALPHA: physical fitness-ALPHA.
* p< 0.001.
† p< 0.05.
Source: Own elaboration.

Table 3. Relationship between physical activity and physical fitness.

Variable	Physically inactive (n=74)	Physically active (n=29)	Z
Weight (kg)	37.9±11.8	34.0±8.1	-1.368
Height (cm)	137.5±11.2	136.2±10.1	-0.205
BMI (kg/m2)	19.7±3.9	18.1±3.0	-1.928 *
WC (cm)	68.1±11.0	63.2±9.4	-2.007 *
HC (cm)	76.6±10.5	71.8±7.8	-2.107 *
WHR (cm)	0.89±0.08	0.88±0.09	-0.466
4x10m shuttle run (s)	13.9±1.1	13.7±1.5	-1.005
RHHD (kg)	14.9±4.4	14.2±4.5	-0.646
LHHD (kg)	14.3±4.6	13.6±5.1	-0.660
RHHD +L (kg)	29.3±8.6	27.8±9.2	-0.623
SLJT (cm)	94.5±17.0	100.2±22.1	-1.394
20m shuttle run (stages)	2.4±1.2	3.3±1.4	-3.018 †
zPF-ALPHA	0.20±0.09	0.24±0.13	-1.628

WC: waist circumference; HC: hip circumference; WHR: waist-to-hip ratio; RHHD: right hand-held dynamometry; LHHD: left hand-held dynamometry; RHHD +L: right hand-held dynamometry + left; SLJT: standing long jump test; zPF-ALPHA: physical fitness-ALPHA.
*p<0.05.
† p<0.01.
Source: Own elaboration.

Physically active students with normal weight had higher zPF-ALPHA values. These differences were only significant in the 20m shuttle run test (p<0.001), in which lower WC, HC, (p<0.01) and WHR (p<0.05) values were also obtained (Table 4).

Table 4. Combined relationship between body mass index and physical activity and physical fitness.

Variable	A (n=34)	B (n=31)	C (n=22)	D (n=16)	χ^2
WC (cm)	62.6±7.1	60.0±6.1	77.1±11.3	74.2±8.8	47.591 *
HC (cm)	71.1±6.0	69.7±6.6	86.2±8.5	79.8±10.3	48.794 *
WHR (cm)	0.88±0.08	0.86±0.08	0.89±0.09	0.93±0.07	8.443 †
4x10m shuttle run (s)	13.8±1.3	13.5±1.1	13.7±1.1	14.4±1.4	5.091
RHHD (kg)	14.3±4.1	13.7±4.1	16.8±5.4	14.6±3.1	4.998
LHHD (kg)	13.5±4.4	13.1±4.8	16.2±5.3	14.7±3.8	7.096
RHHD +L (kg)	27.8±8.1	26.8±8.4	33.0±10.4	29.3±6.6	5.555
SLJT (cm)	94.2±18.9	100.9±18.9	94.7±21.5	92.8±11.3	3.095
20m shuttle run (stages)	2.9±1.3	3.2±1.4	2.1±0.9	2.0±0.9	15.883 *
zPF-ALPHA	0.21±0.10	0.24±0.12	0.20±0.11	0.17±0.06	2.944

A: normal weight/physically inactive; B: normal weight/physically active; C: overweight-obesity/physically inactive; D: overweight-obesity/physically active; WC: waist circumference; HC: hip circumference; WHR: waist-to-hip ratio; RHHD: right hand-held dynamometry; LHHD: left hand-held dynamometry; RHHD +L: right hand-held dynamometry + left; SLJT: standing long jump test; zPF-ALPHA: physical fitness-ALPHA.
* $p< 0.001$.
† $p< 0.05$.
Source: Own elaboration.

Discussion

The results of this study demonstrate a positive relationship between PA and PF. In this sense, physically active people have healthier BMI, WC, HC and aerobic capacity values (Table 3).

BMI and PF were directly correlated; thus, children with normal weight had healthier WC, HC and aerobic capacity values, while overweight-obese children had higher RHHD, LHHD and RHHD+L values (Table 2). Physically active participants with normal weight presented better WC, HC, WHR and aerobic capacity values in the analysis of the combined relationship between BMI, PA and PF. On the other hand, physically active schoolchildren with overweight-obesity had lower WC and HC values than their physically inactive classmates; however, they also showed worse physical performance in PF tests, which did not prove the existence of the phenotype known as *fat but fit* (Table 4).

With respect to sex, males had better physical performance in the aerobic capacity, speed-agility and upper body strength tests ($p<0.05$), so they obtained higher zPF-ALPHA scores ($p<0.01$) compared to females (Table 1). This had already been reported in previous studies,[16,17,26] with the exception of flexibility.[15,46]

Golle *et al.*,[14] in their 4-year longitudinal study, reported that girls up to age 10 achieve better scores in tests involving the upper limbs, flexibility and agility. This may indicate that sex-specific maturation processes can have a positive impact on PF in healthy schoolchildren. In this sense, genetics may reveal a part of muscular and cardiorespiratory endurance that is associated with greater capacity of skeletal muscle in relation to body weight in men due to the secretion of testosterone, and a lesser efficiency of neuromuscular coordination in women due to gynecoid fat redistribution.[47] Likewise, girls under 12 years of age reach about 85-90% of VO_2 max in terms of average absolute values compared to the boys of the same age group, which would explain these differences.[48]

The PF index increased slightly in all components (morphological, motor, skeletal muscle and aerobic) as age increased in both sexes; this result was similar to some studies[13,28] but contrary to others.[49] These differences in the results may be caused by growth (height, weight and body dimensions), absolute VO_2 max values and the level of maturation (somatic, skeletal and sexual) of schoolchildren.[47,48]

Regarding body composition, participants with overweight-obesity had better grip strength ($p<0.05$), while those with normal weight had lower WC, HC and WHR values ($p<0.05$) and healthier aerobic capacity ($p<0.05$). These better results in schoolchildren with overweight-obesity have been found in tests that require isometric force, as is the case of the hand-held dynamometry test and medicine ball overhead throws, perhaps due to a greater amount of lean mass that allows supporting this additional load and to the fact that fat mass favors inertia in the propulsion of the device and joint stabilization when gripping the dynamometer.[18] BMI, aerobic capacity, adiposity and VO_2 max are independent entities, except in tests where submaximal aerobic capacity is used.[31]

In terms of PA performance, physically active schoolchildren had lower BMI, WC and HC ($p<0.05$) and higher aerobic capacity ($p<0.05$). The available evidence coincides with these results[3,32,33]; however, Ortega *et al.*[6] state that even though there is a relationship between PA and PF in schoolchildren and young individuals, it is not consistent, and that it is, therefore, questionable what intensity, frequency and duration of PA should be taken into account to determine the effects on body composition and an improvement in PF, especially aerobic.[6] In this sense, the most recent literature review conducted by Rosa-Guillamón[50] concludes that the primary objective of intervention programs should be teaching schoolchildren to adopt an active and responsible lifestyle when acquiring other health habits.

The improvement of PF can be based on the development of at least one of its main determinants, such as cardiorespiratory fitness, muscle strength or body composition. Thus, the current recommendations established by the US Healthy People 2010 initiative[45]

(≥60 minutes/day, ≥5 days/week of moderate PA or ≥20 continuous minutes, ≥3 days/week, ≥ 6 metabolic equivalent of vigorous activity) appear to be adequate as long as adherence to PA is consolidated.

Finally, significant differences were found between WC, HC, WHR ($p<0.05$) and aerobic capacity ($p<0.001$) in favor of normal weight/physically active boys. This is consistent with Lopez-Gallego *et al.*,[15] who concluded that the results are better based on the age increase of the evaluated participants and in favor of boys (except in flexibility tests). These authors also confirmed that people who perform more PA or some training obtain better results in jumping tests than physically inactive people; however, they do not carry out an analysis of PF based on sex, age and PA together, so direct comparisons cannot be made,[15] hence the novelty of this study. Other research[6,29] indicates that schoolchildren who perform more PA have greater cardiorespiratory capacity.

A possible explanation for these results is that about 30-40% of the variance in PF measures could be attributed to factors other than changes in BMI and that more deficient nutrition and decreased PA lead to a lower training effect and PF level.[51] For this reason, it is undeniable that PF has a close link to children's health and lifestyle. In this sense, schools and physical education teachers play an important role in identifying the level of PF and in promoting an active lifestyle,[2,16] since assessing the level of PF from an early age can contribute to obtaining reports on the health status of the school population in order to encourage the adoption of healthy lifestyles.[3,50]

The lack of representativeness of the sample is one of the limitations of this study, as well as the fact that other parameters that could potentially influence PF, such as socioeconomic status, maturity stage or hormonal factors, were not included. On the other hand, one of the strengths was the administration of a battery of PF tests within the school environment, which allows teachers to know the motor needs of their students and, in this way, design educational programs aimed at developing motor skills, enjoying PA and generating adherence to it throughout their lives.

Conclusions

This study showed that schoolchildren who are active and have normal weight have a better PF and aerobic capacity and a lower BMI, WC and HC compared to their overweight and physically inactive peers; however, overweight-obese schoolchildren have higher grip strength values. In terms of sex, boys have better PF levels, but there is a slight increase in PF as age increases in both sexes.

Achieving optimal levels of PF throughout life requires adopting a healthy lifestyle from childhood, and the best strategy for achieving this is to promote the autonomous practice of PA among schoolchildren.

Conflicts of interest

None stated by the authors.

Funding

None stated by the authors.

Acknowledgements

To the teachers of the elementary schools where the study was carried out and to the school boards of these institutions for granting the corresponding permissions.

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rfm
Revista *de la* Facultad *de* Medicina

ORIGINAL RESEARCH
DOI: http://dx.doi.org/10.15446/revfacmed.v68n1.70177
Received: 01/02/2018 **Accepted:** 10/07/2018

Body mass index and cardiorespiratory fitness among public school teachers from Barranquilla, Colombia

Índice de masa corporal y capacidad cardiorrespiratoria en docentes de colegios públicos de Barranquilla, Colombia

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Abstract

Introduction: Cardiorespiratory fitness (CRF) is an excellent health status indicator, since reduced CRF values may constitute an early marker of alterations in the cardiovascular system.
Objective: To determine the relationship between body mass index (BMI) and CRF in teachers working in State schools of Barranquilla, Colombia.
Materials and methods: A descriptive, cross-sectional and correlational study was conducted from October 2015 to May 2016 in 363 teachers working in State schools of Barranquilla. Participants' sociodemographic data were collected, their BMI was calculated and their CRF was measured using the Rockport walking test (also known as 1-mile walking test).
Results: Participants' mean age was 48.1±9.4 years, 72.1% were women, and 65.55% had a BMI >25 kg/m^2. On the other hand, CRF mean was 26.4 mL/kg/min and was inversely correlated with BMI ($p<0.05$).
Conclusion: Bearing in mind the high prevalence of overweight and obesity and the low levels of CRF found in the present study it is necessary to implement health prevention programs based on physical activity and nutritional counseling aimed at encouraging public school teachers to adopt healthy lifestyles.
Keywords: Lung Volume Measurements; Oxygen Consumption; Body Mass Index; Heart Rate; School Teachers (MeSH).

Vidarte-Claros JA, Fontalvo-Navarro S, Herazo-Beltrán AY, Vélez-Álvarez C. Body mass index and cardiorespiratory fitness among public school teachers from Barranquilla, Colombia. Rev. Fac. Med. 2020;68(1):100-6. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.70177.

Resumen

Introducción. La capacidad cardiorrespiratoria (CCR) es un excelente indicador para medir la salud, pues su disminución puede ser un marcador temprano de alteraciones en el sistema cardiovascular.
Objetivo. Determinar la relación entre el índice de masa corporal (IMC) y la CCR en docentes de colegios públicos de Barranquilla, Colombia.
Materiales y métodos. Estudio descriptivo con diseño transversal y correlacional realizado entre octubre de 2015 y mayo de 2016 en una muestra de 363 docentes de colegios públicos de Barranquilla. Se recolectaron los datos sociodemográficos de los participantes, y se utilizó el test de Rockport o test de la milla para medir su IMC y CCR.
Resultados. La media de edad fue 48.1±9.4 años, el 72.1% de los participantes fueron mujeres y el 65.55% de la población tuvo un IMC>25 kg/m^2. Por otra parte, la CCR obtuvo una media de 26.4 mL/kg/min y mostró una correlación inversa con el IMC ($p<0.05$).
Conclusión. Teniendo en cuenta la alta prevalencia de sobrepeso y obesidad y la baja CCR observadas en la población estudiada, es necesario implementar programas de promoción y prevención de la salud que estén mediados por la actividad física y el componente nutricional, y que ayuden a la adquisición de estilos de vida saludables.
Palabras clave: Mediciones del volumen pulmonar; Consumo de oxígeno; Índice de masa corporal; Frecuencia cardíaca; Docentes (DeCS).

Vidarte-Claros JA, Fontalvo-Navarro S, Herazo-Beltrán AY, Vélez-Álvarez C. [Índice de masa corporal y capacidad cardiorrespiratoria en docentes de colegios públicos de Barranquilla, Colombia]. Rev. Fac. Med. 2020;68(1):100-6. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.70177.

Introduction

The incidence of cardiovascular disease increases every day and currently accounts for nearly 60% of deaths worldwide.[1] This situation may be aggravated by risk factors such as overweight and sedentary lifestyles.[2]

Overweight and obesity rates in Latin American countries are on the rise and have become a public health problem since the treatment of related comorbidities represents a high economic burden.[3,4] One of the most frequently used measure to assess body composition is body mass index (BMI), which associates weight with height; overweight is defined as a BMI of 25.0-29.9 kg/m^2, while obesity is defined as a BMI >30.0 kg/m^2.[5,6]

The 2010 *Encuesta Nacional de la Situación Nutricional en Colombia* (National Survey of the Nutritional Situation in Colombia) (ENSIN)[7] reported that the number of overweight adults increased from 45.9% to 51.2% between 2005 and 2010. The same survey showed that in the Atlantic region of Colombia, and especially in Barranquilla, there is a growing trend in overweight and obesity rates: 54.5% of adults between 18 and 64 years of age suffer from one of those conditions.[7] These data reveal a public health problem and are evidence of the need to address it.

Cardiorespiratory fitness (CRF) is an important indicator for assessing health status, as it is part of the four conditional motor capacities (strength, endurance, speed, flexibility).[8] It allows measuring endurance during activities in which the resynthesis of adenosine triphosphate is achieved mainly through aerobic metabolism.[9] Its physiological marker is the maximum rate of oxygen consumption (VO_2max), which refers to the body's ability to transport and use oxygen during exercise.[10] This is an indicator that is inversely related to cardiovascular disease morbidity and mortality,[8] and it expresses the degree or level of physical fitness of an individual; therefore, a decrease in VO_2max may be an early marker of altered cardiovascular physiology.[11]

VO_2max, which is equivalent to the maximum oxygen carrying capacity from the environment to the mitochondria,[12] is the most important parameter for quantifying the physical fitness of an individual.[13] Physical fitness can be estimated using direct and indirect methods that have different levels of accuracy and that may include surveys such as the International Physical Activity Questionnaire (IPAQ). In view of the above, functional capacity should be monitored through field tests, which are an affordable alternative[8] and have been validated in different studies.[14,15]

Teachers represent a large part of the Colombian workforce, and even though this population is subject to a series of factors that deteriorate their health status,[13] the promotion of healthy practices in their workplaces is still not satisfactory.[16] In this regard, Romero-Pérez *et al.*[17] state that there are negative relationships between workers' productivity and their level of sedentariness; moreover, Gómez *et al.*[5] argue that the presence of uncontrolled psychosocial risks in the workplace can increase the rate of cardiovascular disease. In Bogotá, García-Castro & Muñoz-Sánchez[16] have stressed the importance of understanding the relationship between the teaching practice and health and safety in the workplace given the strong impact it has on the development of society.

Due to the psychosocial factors that can trigger them, and because they not only have an impact on the personal, family and social environment but also on the working environment, cardiovascular diseases are considered as an occupational hazard for teachers.[18] This is a really concerning situation that has not been addressed adequately by any study carried out in Barranquilla. With this in mind, the aim of the present study was to determine the relationship between BMI and CRF in public school teachers in the city of Barranquilla, Colombia.

Materials and methods

A quantitative, descriptive, correlational, cross-sectional study was carried out after being approved by the Research Ethics Committee of the Physical Therapy Program of the Universidad Simón Bolívar by means of Minutes No. 0014 of 2015. For its elaboration, the dispositions of Resolution 8430 of 1993 of the Ministry of Health of Colombia[19] and the principles contained in the Declaration of Helsinki were considered.[20]

The universe consisted of 6 464 active teachers from public schools in Barranquilla aged between 18 and 65 years. The final simple size (n=363) was determined using the StatCalc application available in the Epi Info™ software, with a 95% confidence level and a 5% margin of error. Once the sample size was determined, population-based descriptive studies were conducted.

Sampling was done in 2 stages. First, 165 schools were divided/classified by location; then, the schools were randomly selected based on their location and the teachers were proportionally distributed (Table 1). The sample included teachers who had no physical limitations at the time of testing, no history of cardiovascular risk, were not on any type of medical treatment and reported not being under medical supervision.

Table 1. Distribution of the sample participating in the study according to location.

Location	Total number of schools	Percentage of schools	Number of teachers
Southeast	43	26%	95
Metropolitan	36	22%	79
Southwest	58	35%	128
North Historic Center	21	13%	46
Riomar	7	4%	15
Total	165	100%	363

Source: Own elaboration.

Before starting the study, permission was requested from the Education Department of the District of Barranquilla and a pilot test with 15 teachers was carried out, which allowed adjusting the instruments and training the evaluators according to the requirements of the instrument to be applied. Once the teachers agreed to participate, they were asked to sign an informed consent and then to fill out the questionnaires to obtain anthropometric measurements for weight and height based on the protocols proposed by the STEPS Instrument.[21]

Finally, the Rockport 1 mile walk test was applied to assess cardiorespiratory fitness.

Height was measured with a Kramer measuring device, while weight was established using a Tanita BC-585F FitScan Body Composition Monitor®. A protocol was implemented to evaluate CRF, in which the participants warmed up and then walked a mile (1 609m) as fast as possible. Aerobic capacity was estimated based on the variables age, sex, elapsed time at the end of the mile and heart rate at the end of the test, using the equation proposed by Kline *et al.* in 1987 and described by the American College of Sports Medicine in 2005: VO_2máx (mL/kg/min) = 132.85 - (0.076 x body weight) - (0.387 x age) + (6.31 x sex) - (3.264 x time) - (0.1565 x HR).[22]

The data were processed and analyzed with the statistical program SPSS version 21.0 and a univariate analysis was performed to obtain absolute and relative frequencies and central tendency and dispersion measures. Subsequently, a bivariate analysis was performed to determine the normality of the variables, which were parametric; the t-Student test was used to find mean differences for independent samples by means of correlations with the Pearson coefficient. Statistically significant differences were established based on a $p<0.05$ value.

Results

The mean age of the participants was 48.1±9.41 years. It should be noted that 82.3% of the participants were adults, mostly women, who lived in low-middle-income households (socioeconomic stratum 3, for detailed information of socioeconomic classification in Colombia, see Table 2), with bachelor's degrees and with more than 13 years of service in teaching (Table 3).

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

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

Source: Elaboration based on the data by National Administrative Department of Statistics.[23]

Table 3. Socio-demographic characteristics of the participants.

Variables		Sample		Male		Female	
		n=363		n=101		n=262	
		Frequency	%	Frequency	%	Frequency	%
Age	Youth	13	3.5	4	3.9	9	3.4
	Adulthood	299	82.3	90	89.1	209	79.7
	Old age	51	14	7	6.9	44	16.7
Socioeconomic stratum	1	20	5.5	5	5	15	5.7
	2	119	32.8	43	42.6	76	29
	3	166	45.7	40	39.6	126	48.1
	4	44	12.1	9	8.9	35	13.4
	5	8	2.2	4	4	4	1.5
	6	6	1.7	0	0	6	2.3
Educational attainment	High school	2	0.6	0	0	2	0.8
	Associate degree	12	3.3	1	1	11	4.2
	Bachelor's degree	155	42.7	53	52.5	102	38.9
	Postgraduate diploma	145	39.9	31	30.7	114	43.5
	Master's degree	46	12.7	15	14.9	31	11.8
	Doctoral degree	3	0.8	1	1	2	08
Tenure	<1 year	23	6.3	10	9.9	13	5
	1-12 years	128	35.3	39	38.6	89	34
	13-24 years	147	40.5	37	36.6	110	42
	26-36 years	34	9.4	11	10.9	23	8.8
	37-48 years	31	8.5	4	4	27	10.3

Source: Own elaboration.

The mean BMI was 27.02±4.49 kg/m^2 and it was higher in men; on the other hand, the mean CRF was 26.41 mL/kg/min^{-1}, with better values in men (30.5 mL/kg/min^{-1}) than in women (24.84 mL/kg/min^{-1}). The average time used by both men and women to perform the Rockport test was approximately 18.8 minutes (Table 4); mean weight, height and diastolic blood pressure were better in women. There was also a high prevalence of overweight and obesity among the sample, which was higher in men as well (Table 5).

Table 4. Descriptive statistics of the body mass index and cardiorespiratory capacity assessment.

Variables		n=363			Male (n=101)	Female (n=262)
		x̄±σ	Min.	Max.	x̄±σ	x̄±σ
Body mass index assessment	Age	48.1+9.4	23	65	47+8.8	48.55+9.6
	Weight (kg)	73.4+14	39.7	128	81.6+12.8	70.3+13.1
	Height (cm)	1.64+0.0	1.5	1.9	1.70+0.1	1.6+0.1
	Body mass index (kg/m^2)	27.0+4.4	16.3	41.8	27.5+4.1	26.8+4.63
Cardiorespiratory fitness assessment	Ending heart rate (beat/m)	110+15	73	165	110.4+15	111.0+15.8
	Time (min)	18.8+2.2	13.4	25.3	18.11+2.3	19.18+2.10
	Cardiorespiratory fitness (mL/kg/min^{-1})	26.4+6.9	16.21	49.83	30.50+8.4	24.84+5.55

x̄: mean; σ: standard deviation; Min: minimum; Max: maximum.
Source: Own elaboration.

Table 5. Overweight and obesity indicators.

Variable	Total	%	Male n (%)	Female n (%)
Obesity	88	24.2%	63 (24%)	25 (24.8%)
Overweight	150	41.3%	104 (39.7%)	46 (45.5%)
Normal weight	121	33.3%	91 (34.7%)	30 (29.7%)
Underweight	4	1.1%	4 (1.5%)	0 (0.0%)

Source: Own elaboration.

When applying the t-Student test, significant differences were found between men and women ($p<0.05$) in variables such as weight, height and CRF (Table 6). On the other hand, after applying Pearson's correlation coefficient, a negative correlation (-0.181) was found between BMI and CRF, which indicated that teachers with normal BMI tend to have better VO_2max; the strength of the correlation was almost zero (Table 7).

Table 6. Comparison of sex and anthropometric and physiological variables.

Variables	t	Significance (bilateral)	Mean difference	95% confidence interval	
Weight (kg)	-7.425	0.000 *	-11.384	-14.40	-8.36
Height (meters)	-14.287	0.000 *	-0.1053	-0.11	0.09
Body Mass Index (kg/m^2)	-1.318	0.188	-0.6933	-1.72	0.34
Heart rate at the end of the test (beat/m)	0.298	0.766	1.844	-3.07	4.17
VO_2máx (mL/kg/min)	-7.436	0.000 *	-5.667	-7.16	-4.16

* Significance level <0.05.
Source: Own elaboration.

Table 7. Correlation of cardiorespiratory fitness with body mass index

Variable	Pearson's Correlation	Significance (bilateral)
Body Mass Index	-0.181	0.001 *

* Significance level <0.05.
Source: Own elaboration.

Discussion

The present research sought to determine the relationship between BMI and CRF in active teachers of public schools in Barranquilla, Colombia. It found a high prevalence of overweight and obesity and low CRF in the evaluated population, as well as a significant and negative correlation between BMI and CRF.

72.20% of the population studied were women. This aspect coincides with the study conducted by García-Castro & Muñóz-Sánchez[16] in teachers from public schools in the city of Bogotá, Colombia, which suggests that the predominant presence of women in teaching activities may be explained by the fact that this is a profession with deep emotional ties.

According to their educational attainment, rank and socioeconomic stratum, most of the sample was classified in the middle-income level. In this regard, Álvarez-Castaño *et al.*[24] suggest that the probability of suffering from obesity is greater for those living in the low- or medium- class households and in families with incomes below COP 1 400 000 (about USD 400). These aspects may explain the socioeconomic gradient of overweight and obesity and the decrease in CRF, as there is an inverse relationship between these variables.[6] The relationship between socioeconomic level and the probability of developing these diseases is more evident in women since it has been found that overweight and obesity rates in this population decrease as the economic level increases.[4]

The prevalences of overweight and obesity found in the present study are similar to those reported in the 2010 ENSIN[7] and other research conducted in Latin America. For example, Bencomo *et al.*[25] reported a prevalence of overweight of 44% and obesity of 23% in university teachers, while Romero-Pérez *et al.*[17] reported a prevalence of overweight of 40.1% and obesity of 12% in women, data that is comparable to what was obtained here for the same population (39.7% and 24%, respectively).

The presence of overweight and obesity in the participants of our study is high: 24.2% were obese and 41.3% overweight. Nationwide, these data are similar to the findings of Valencia-García *et al.*[26] in Risaralda, who reported that 62.5% of the sample was overweight and obese, particularly women (64.7%) compared to men (57.4%), but contrary to the study by Fernández-Rodríguez *et al.*,[27] in which there were no significant correlations between CRF and BMI in university students in Villavicencio, Colombia.

The percentages of normal weight and underweight teachers in this study were 33% and 1%, respectively. This agrees with the findings of Mora-García *et al.*[28] in Cartagena, Bolívar, where the prevalence of underweight was 3.3%, and by Mantilla-Morrón *et al.*[29] in Barranquilla, where the prevalence of underweight was 5.7%.

In relation to sex, the frequency of overweight and obesity was higher in men than in women (70% and 63.7%, respectively). Overweight was the most common variable in both sexes (39.7% in men and 45.5% in women), which coincides with Fortich & Gutiérrez[4] and Rodríguez-Rodríguez *et al.*,[30] but differs from Navarro-Lechuga & Vargas-Moranth,[31] who reported that the prevalence of obesity was higher in women (26.80%) than in men (20.50%).

The present study is related to others that show that a better CRF is associated with a lower risk of disease and death[10,13] since there is a statistically significant relationship between the presence of overweight and obesity —which bring with them a series of associated comorbidities— and the likelihood of suffering from cardiovascular diseases.

The estimated average CRF was 26.41 mL/kg/min (standard deviation 6.9) with a minimum value of 16.21 mL/kg/min and a maximum value of 49.83 mL/kg/min, being higher in men with an average of 30.5 mL/kg/min. This coincides with the study by Ho *et al.*,[32] which described an average of 26.8 mL/kg/min in men, but differs from the averages reported by Meseguer-Zafra *et al.*[33] in men (37.1 ml/kg/min) and women (31.1 ml/kg/min), and by Aranguiz *et al.*[2] (37.4 ml/kg/min and 30.4 ml/kg/min, respectively). Moreover, the average cardiorespiratory fitness in men found in the present study is much lower than that described by Sechi & García[8] (42-49 ml/kg/min), although VO_2max was evaluated using different equations in their study.

In our study, the average CRF in women was similar to that described by Zapata-Lamana,[34] who reported worse levels of cardiorespiratory fitness and higher BMI values. These data may be related to the measurement of the waist circumference and the percentage of total and localized fat mass, variables that were not considered in the present research; however, they are endogenous variables from a physiological point of view.

A statistically significant and negative relationship between BMI and CRF was found during the investigation. This is similar to what was reported by Shazia *et al.*,[11] who reported that overweight girls had decreased cardiorespiratory fitness compared to young women with normal weight. It also differs from Aranguiz *et al.*,[2] who found a negative linear relationship like that of the present study where the strength of this correlation is zero.

Teachers in Barranquilla public schools currently have a low CRF that is associated with increased BMI and risk of cardiovascular disease. This situation is also influenced by family and personal medical history, which were found in 59.2% and 40.5%, respectively. In this sense, the results highlight the importance of creating public policies that allow the implementation of cardiovascular disease prevention and occupational health programs that include the practice of physical activity, thus raising awareness among the population about the undoubted benefits that these practices have for their health.

The authors acknowledge that the main limitation of this study was the access to teachers due to their multiple routine activities.

Conclusion

Given the high prevalence of overweight and obesity and the low CRF found among teachers in public schools from Barranquilla, there is a clear need to implement health promotion and prevention programs that include physical activity and the nutritional component to support the acquisition of healthy lifestyles.

Explanatory note: This article derives from the final work presented to obtain the Master's degree in Physical Activity and Health of the Universidad Simón Bolívar entitled *Índice de masa corporal y capacidad*

cardiorespiratoria en docentes activos del sector oficial del distrito de Barranquilla (Body mass index and cardiorespiratory fitness in active public school teachers of the district of Barranquilla.)[35]

Conflicts of interest

None stated by the authors.

Funding

The present study was financed using the economic support provided by Colciencias through its condonable educational credits program for the formation of high-level human capital for the regions - department of Atlántico. This is the result of the graduation work to obtain the degree of Master in Physical Activity and Health at the Universidad Simón Bolívar.

Acknowledgements

To the Education Department of the District of Barranquilla, to the schools and teachers taking part in the study and to the Universidad Simón Bolívar and its master's degree program in Physical Activity and Health.

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rfm
Revista *de la* Facultad *de* Medicina

ORIGINAL RESEARCH
DOI: http://dx.doi.org/10.15446/revfacmed.v68n1.71092
Received: 18/03/2018 **Accepted:** 27/06/2018

Discriminatory accuracy of serological tests for detecting *Trypanosoma cruzi* using the ROC curve and the standard methodology

Precisión discriminatoria de pruebas serológicas para Trypanosoma cruzi aplicando metodología estándar y de curva COR

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Abstract

Introduction: Serological tests are used to confirm *Trypanosoma cruzi* infection and their discriminatory accuracy depends on the established decision threshold. Both, the standard methodology and the receiver operating characteristic (ROC) curve methodology allow obtaining such threshold.
Objective: To compare the discriminatory accuracy of the standard methodology and the ROC curve methodology regarding serological tests for confirming *T. cruzi* infection.
Materials and methods: A set of anti-*T. cruzi* antibodies values from subjects previously classified as healthy or as having Chagas disease were used, and computer simulations were performed under homoscedasticity and heteroscedasticity conditions. Sensitivity, specificity, 100% sensitivity, 100% specificity, and perfect-decision were calculated.
Results: The discriminatory accuracy obtained with the standard methodology favored specificity (98.22% to 99.56%) over sensitivity (67.25% to 87.14%), while in the ROC curve methodology a balance between sensitivity (94.56% and 96.44%) and specificity (90.35% and 92.11%) was observed. Also, in the ROC curve methodology a greater perfect-decision ratio was observed, which, under homoscedasticity conditions, was >90%. Decisions thresholds were affected by heteroscedasticity conditions.
Conclusion: The ROC curve methodology showed better discriminatory accuracy, therefore its use for calculating decision thresholds in serological tests for detecting Chagas disease is recommended.
Keywords: *Trypanosoma cruzi;* Serology; ROC Curve; Sensitivity and Specificity (MeSH).

Querales M, De Lima AR, Martínez-de Cordero H, Cannova DC, Simons MI, Pérez-Ybarra L. Discriminatory accuracy of serological tests for detecting *Trypanosoma cruzi* using the ROC curve and the standard methodology. Rev. Fac. Med. 2020;68(1):107-16. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.71092.

Resumen

Introducción. Las pruebas serológicas se utilizan para detectar infección por *Trypanosoma cruzi* y su precisión discriminatoria depende del umbral de decisión establecido. La metodología estándar y la de curva característica operativa del receptor (COR) permiten obtener tal umbral.
Objetivo. Comparar la precisión discriminatoria de la metodología estándar y la metodología de curva COR en lo que respecta a pruebas serológicas para detectar infección por *T. cruzi*.
Materiales y métodos. Se utilizó un conjunto de valores de anticuerpos contra *T. cruzi* de individuos clasificados como chagásicos o sanos y se realizaron simulaciones computarizadas en condiciones homocedásticas y heterocedásticas. Se calculó sensibilidad, especificidad, sensibilidad=100%, especificidad=100% y decisión-perfecta.
Resultados. La precisión discriminatoria de la metodología estándar favoreció la especificidad (98.22% a 99.56%) sobre la sensibilidad (67.25% a 87.14%), mientras que la de la curva COR mostró un equilibrio entre sensibilidad (94.56% y 96.44%) y especificidad (90.35% y 92.11%). Esta última metodología también evidenció una mayor proporción de decisión-perfecta, la cual llegó a ser >90% en condiciones de homocedasticidad. Los umbrales de decisión fueron afectados por las condiciones de heterocedasticidad.
Conclusión. La metodología de la curva COR mostró una mejor precisión discriminatoria, por lo que se recomienda su uso para el cálculo de umbrales de decisión en pruebas serológicas para la enfermedad de Chagas.
Palabras clave: *Trypanosoma cruzi;* Serología; Curva ROC; Sensibilidad y especificidad (DeCS).

Querales M, De Lima AR, Martínez-de Cordero H, Cannova DC, Simons MI, Pérez-Ybarra L. [Precisión discriminatoria de pruebas serológicas para *Trypanosoma cruzi* aplicando metodología estándar y de curva COR]. Rev. Fac. Med. 2020;68(1):107-16. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.71092.

Introduction

Chagas disease is diagnosed using parasitological and serological methods. Parasitological methods, such as blood smear, peripheral blood smear and thick blood smear, are utilized during the acute phase, since there is a high level of parasitemia. In the chronic phase, because parasitemia is low and intermittent, serological tests such as indirect hemagglutination, indirect immunofluorescence (IFA), ELISA tests, Machado-Guerreiro reaction and Western Blot are preferred.

Although serological tests are highly sensitive, cross-reactions may occur with other parasites such as *Trypanosoma rangeli* and *Leishmania* spp. Consequently, diagnosing a patient with Chagas disease requires positivity for this condition on 2 out of 3 serological tests.[1]

The ELISA test is widely used because of its high sensitivity and good specificity depending on the antigen used.[2] This is a semi-quantitative technique that establishes a relative antibody concentration depending on the higher dilution of the patient's serum, which allows detecting the formation of immune complexes; in other words, a cut-off point or decision threshold is chosen. Results above this threshold are considered positive, while those below are considered negative.[3] However, this classification has a margin of error due to the sensitivity and specificity of the test since their values depend on the level chosen as a threshold.[4]

The traditional or standard method to establish a decision threshold consists of setting it at 2 or 3 standard deviations away from the mean of a group of patients classified as negative for a given condition or disease under the assumption of independence;[5-7] however, this method is arbitrary and inappropriate when the assumption is violated.[8] A variant of this methodology is to use the trimmed mean and 2 or 3 trimmed standard deviations, which are estimated by eliminating 5% of the extreme values, both upper and lower, from the data set of negative patients.[9]

Another methodology used to determine the threshold is the receiver operating characteristic (ROC) curve, which is widely accepted to select an optimal cut-off point for a serological test.[10,11] The curve is generated by plotting the sensitivity values for the potential test cut-off points on the y-axis as a function of the 1-specificity value on the x-axis;[10] the best cut-point provides the highest sensitivity and specificity simultaneously.[12] Both the ROC curve and the standard methodology have advantages when establishing decision thresholds,[10,12] therefore they are used interchangeably.

In this sense, the objectives of the present work were to compare the standard and the ROC curve methodologies and to determine which yields better results in the serological diagnosis of Chagasic patients. The starting point was the results of serological tests and computer-simulated samples, taking into account the influence of population variances on their efficiency.

Materials and methods

Real data populations

IgG antibody titers against *T. cruzi* measured in terms of optical density (OD) were considered as real data populations. These data were obtained from the archive of samples processed between 1992 and 2014 by the *Instituto de Biología Molecular de Parásitos* (Institute of Molecular Biology of Parasites, BioMolP by its acronym in Spanish) and the Department of Parasitology of the Universidad de Carabobo, Valencia-Venezuela. Based on these records, mean (μ) and variance (σ^2) were estimated for the results of both healthy individuals, μ_S and σ^2_S, and Chagasic patients, μ_E and σ^2_E.

Healthy individuals

This sample was made up of the OD values obtained from the sera of individuals from non-endemic areas for Chagas disease with negative IFA, ELISA, and Western Blot tests.

Chagas patients

This sample was made up of the OD values obtained from the sera of Chagasic patients from the endemic states of Carabobo and Cojedes, Venezuela, with positive results in at least 2 of the 3 tests mentioned above.[13-15]

Ethical considerations

Both healthy individuals and Chagasic patients gave their informed consent to take part in epidemiological studies on *T. cruzi*. The ethical principles for medical research involving human subjects set out in the Declaration of Helsinki were respected.[16] This research was endorsed by the Bioethics Commission of the Faculty of Health Sciences, chaired by the Directorate of Research and Intellectual Production of the Faculty of Health Sciences of the Universidad de Carabobo, which guaranteed that the bioethics and biosafety principles were applied as stated in Minutes D1-058-11 of March 14, 2011.

Enzyme-linked immunoassay

The total proteins of *T. cruzi* epimastigotes of human origin were used as the antigen, which was identified using the discrete typing unit (DTU) named TcI based on the methodology outlined by De Lima *et al.*[15] The TcI DTU was selected because it is the most common in Venezuela, representing about 95% of the isolates.[17-19]

Simulated samples

The simulated data were obtained using the add-in for producing random numbers from a normal or Gaussian distribution of the Microsoft Excel program.[20] On the other hand, the population parameters values used to generate the simulated samples were obtained from the characterization of the real data populations described above.

A population of healthy individuals (P_S) was defined using mean (μ_S) and variance (σ^2_S), as well as 3 sets of 5 populations of Chagasic patients (P_E): 1 set with the same variance of the population of healthy individuals (homoscedastic) and 2 sets with population variances different from that of the population of healthy individuals (heteroscedastic), for a total of 16 simulated populations.

As mentioned above, the variance in the homoscedastic set corresponded to that of the real data population of healthy individuals (σ^2_S). Regarding heteroscedastic sets, in the first case, the variance was obtained in the

population from real data of Chagasic patients (σ^2_E), while, for the second, the pooled or weighted variance (σ^2_c) was calculated with the population variances of healthy individuals and Chagasic patients.

The means of the simulated populations of Chagasic patients were defined as a function of the mean of healthy individuals (μ_S) and the pooled standard deviation (σ_c). Thus, the mean values for Chagasic patients were defined by P_{E1}: $\mu_{E1}= \mu_S+0.5\ \sigma_c$; P_{E2}: $\mu_{E2}= \mu_S+ \sigma_c$; P_{E3}: $\mu_{E3}= \mu_S+2\sigma_c$; P_{E4}:$\mu_{E4}=\mu_S+3\sigma_c$ y P_{E5}: $\mu_{E5}= \mu_S+4\sigma_c$, to build up populations of Chagasic patients with means increasingly distant from those of the healthy 233were generated for the population P_S and for each population P_E. Each one consisted of n_S simulated observations coming from P_S, and of n_E simulated observations coming from P_{Ei}, i=1,2, ..., 5. The size of n_S and n_E was set at $n_S= n_E=30$, because this is the most widely used sample size in practice (Table 1).

Table 1. Population parameters and variance conditions.

Population	Equal variance assumption					
	Homoscedasticity		Heteroscedasticity-1		Heteroscedasticity-2	
	Mean	Variance	Mean	Variance	Mean	Variance
Healthy	μ_S	σ^2_5	μ_S	σ^2_5	μ_S	σ^2_5
Chagas-1	$\mu_S+0.5\sigma_c$		$\mu_S+0.5\sigma_c$		$\mu_S+0.5\sigma_c$	
Chagas-2	$\mu_S+\sigma_c$		$\mu_S+\sigma_c$		$\mu_S+\sigma_c$	
Chagas-3	$\mu_S+2\sigma_c$	σ^2_5	$\mu_S+2\sigma_c$	σ^2_E	$\mu_S+2\sigma_c$	σ^2_c
Chagas-4	$\mu_S+3\sigma_c$		$\mu_S+3\sigma_c$		$\mu_S+3\sigma_c$	
Chagas-5	$\mu_S+4\sigma_c$		$\mu_S+4\sigma_c$		$\mu_S+4\sigma_c$	

Source: Own elaboration.

The set of results of healthy individuals and Chagasic patients was named scenario, and 5 scenarios were constructed for each of the variance assumptions: i=1,2, ..., 5. Scenario-1: {P_S, P_{E1}}, Scenario-2: {P_S, P_{E2}}, Scenario-3: {P_S, P_{E3}}, Scenario-4: {P_S, P_{E4}} and Scenario-5: {P_S, P_{E5}}. In this way, 15 scenarios with simulated data were obtained.

These scenarios are fundamental to simulation since the sensitivity and specificity of the tests require information from healthy and Chagasic individuals on the ROC curve. The samples of healthy individuals were the same in each simulated scenario; only the simulated samples for the Chagasic patients varied, so this method allows maintaining the same point of comparison between Chagasic patients and healthy individuals.

Decision thresholds

The standard and ROC curve methodologies were applied to obtain the decision thresholds or critical values (V^C) for the real data and the simulated samples; the calculations were made using a routine written in Excel. For the standard methodology (Std), four V^C were established: StdM1=μ+2σ, StdM2, μ+3σ, StdM3 = μ*+2σ* and StdM4=μ*+3σ*, where μ* and σ* are the trimmed arithmetic mean and the trimmed standard deviation, respectively.

The V^C of ROC curves were estimated using the minimum quadratic distance (MQD) and the Youden Index (I_γ). For MQD, V^C is min(MQD)=min{(1-sensitivity)^2+(1-specifity)^2}, and for I_γ, V^C is max (I_γ)=max{sensitivity+specifity-1}.[21,22]

Sensitivity and specificity

For the real data and the simulated scenarios, a k-th observation (y_K) was deemed healthy if $y_K \leq V_p^c$ and sick if , where V_p^c is the decision threshold of the p test. For the simulated samples, the k-th observation y_{ijk} and the decision threshold V^c_{ijp} depended on the i scenario and the simulated sample j; i=1,2,...,5; j=1,2,...,n*.

Sensitivity and specificity of a test were given by:

$$Sensitivity = \frac{True\ positives}{Total\ number\ of\ sick\ individuals} \times 100$$

$$Specificity = \frac{True\ negatives}{Total\ number\ of\ healthy\ individuals} \times 100$$

True positives are Chagasic patients declared positive through p test, while true negatives are healthy individuals declared negative through this same test.

The sensitivity and specificity of the methodologies applied in the simulated populations were compared based on the estimates given by

$$\widehat{Specificity}_{ip} = \frac{1}{n^*}\sum_{j=1}^{n^*} \%Specificity_{ijp}$$

$$\widehat{Sensitivity}_{ip} = \frac{1}{n^*}\sum_{j=1}^{n^*} \%Sensitivity_{ijp}$$

Comparison of discriminatory accuracy of applied methodologies]

To compare discriminatory accuracy, it was established how many samples of the tests had sensitivity and specificity equal to 100%. Thus, for scenario i and test p, it was obtained:

Healthy individuals: $\begin{cases} Z_{Sijp} = 1; if\ specificity_{ijp} = 100\% \\ Z_{Sijp} = 0;\ otherwise \end{cases}$

Chagasic patients: $\begin{cases} Z_{Eijp} = 1; if\ sensitivity_{ijp} = 100\% \\ Z_{Eijp} = 0;\ otherwise \end{cases}$

The proportions of samples with specificity and sensitivity equal to 100% were given by:

$$P_{\{specificity_{ip}=100\%\}} = \frac{1}{n^*}\sum_{j=1}^{n^*} Z_{Sijp}$$

$$P_{\{sensitivity_{ip}=100\%\}} = \frac{1}{n^*}\sum_{j=1}^{n^*} Z_{Eijp}$$

Similarly, the number of samples in which the tests had sensitivity and specificity equal to 100% was determined. This result was named perfect-decision and was obtained with the equations

$$W_{ijp} = 1;\ \text{if}\ specificity_{ijp} = 100\% \wedge sensitivity_{ijp} = 100\%$$

$$W_{ijp} = 0;\ \text{otherwise.}$$

The proportions of samples with perfect-decision were given by

$$P_{\{perfect-decision_{ip}\}} = \frac{1}{n^*}\sum_{j=1}^{n^*} W_{ijp}$$

Results

Real data

The population of healthy individuals was N_S=901 with the parameters μ_S=0.12226 and σ^2=0.0531. On the other hand, the Chagasic patients were N_E=342 with the parameters μ_E=0.4093 and σ_E=0.2234. The pooled standard deviation of both populations was σ_C=0.1255 The parameters were measured using the OD, and the absolute frequency distributions showed an overlapping response region for the OD of the 2 groups, with a total of 589 data (47.39%) (Figure 1).

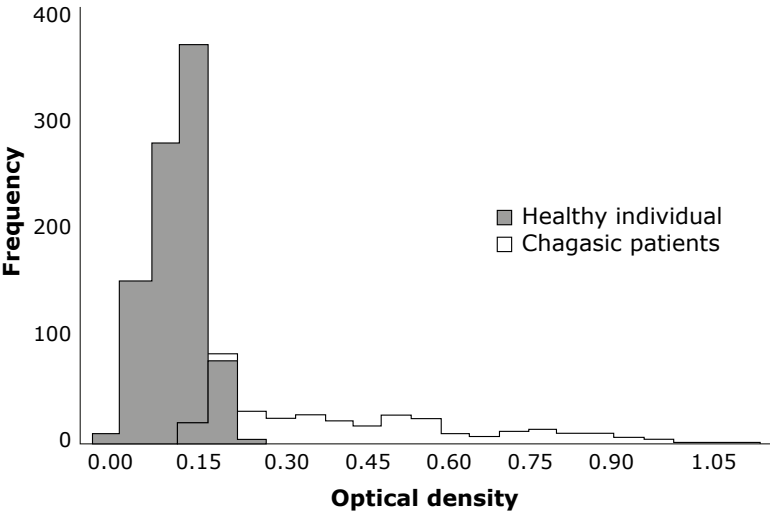

Figure 1. Optical density result of the test for immunoglobulin G against *Trypanosoma cruzi*.
Source: Own elaboration.

The thresholds of V^c for the ROC curve method were similar to each other and lower than all those of the standard method (I_Y=0.186, MQD=0.182, StdM1=0.229, StdM2=0.282, StdM3=0.194 and StdM4=0.230). Likewise, in the ROC curve, these values were located towards the center of the region of overlapping results, while they tended to be located towards the right in the standard method, favoring the specificity of the test. Sensitivity and specificity values were more balanced for the ROC curve methodology (sensitivity: 96%, specificity: 92%) than for the standard methodology (sensitivity: 67-87%, specificity: 99%). For the standard methodology, the most balanced equation was StdM3 with sensitivity of 87% and specificity of 98%.

Simulated samples

The mean of the population of healthy individuals was set at μ_S=0.1226 and the variance for the condition of homoscedasticity was σ^2_5 =$(0.0531)^2$. Under heteroscedastic conditions, the variance for healthy observations was σ^2_5 =$(0.0531)^2$, while two values were considered for Chagasic populations: the variance of real data for Chagasic patients (heteroscedasticity-1), $\sigma^2_{E1} \equiv \sigma^2_E = (0.2234)^2$, and the pooled variance for groups of healthy and Chagasic individuals (heteroscedasticity-2), $\sigma^2_{E2} \equiv \sigma^2_C = (0.1255)^2$. The population means for Chagasic patients were established at P_{E1}: μ_{E1}=0.18535 ; P_{E2}: μ_{E2}=0.2481 ; P_{E3}: μ_{E3}= 0.3736 ; P_{E4}: μ_{E4}= 0.4991 ; P_{E5}: μ_{E5}=0.6246. As for real data, all these parameters correspond to OD readings.

Decision thresholds

The mean values obtained for V^c in the standard tests showed a fixed value for all three variance assumptions since they only depend on the population of healthy individuals. On the other hand, StdM2 and StdM4 showed the highest V^c, while those obtained with StdM3 were very close to those of the ROC curve in the second and third scenarios (Table 2).

Table 2. Decision thresholds for the detection of immunoglobulin G against *Trypanosoma cruzi.* Simulated data.

Equal variance assumption	Methodology	Scenario				
		1	2	3	4	5
Homoscedasticity	I_Y	0.1492	0.1804	0.2238	0.23	0.2301
	MQD	0.1526	0.1819	0.2238	0.23	0.2301
	StdM1	0.2273	0.2273	0.2273	0.2273	0.2273
	StdM2	0.2796	0.2796	0.2796	0.2796	0.2796
	StdM3	0.1953	0.1953	0.1953	0.1953	0.1953
	StdM4	0.2316	0.2316	0.2316	0.2316	0.2316
Heteroscedasticity-1	I_Y	0.1994	0.2006	0.2057	0.2143	0.2223
	MQD	0.1719	0.1768	0.1925	0.2093	0.2215
	StdM1	0.2273	0.2273	0.2273	0.2273	0.2273
	StdM2	0.2796	0.2796	0.2796	0.2796	0.2796
	StdM3	0.1953	0.1953	0.1953	0.1953	0.1953
	StdM4	0.2316	0.2316	0.2316	0.2316	0.2316
Heteroscedasticity-2	I_Y	0.1822	0.1865	0.2059	0.2226	0.2293
	MQD	0.1608	0.1739	0.2022	0.2227	0.2293
	StdM1	0.2273	0.2273	0.2273	0.2273	0.2273
	StdM2	0.2796	0.2796	0.2796	0.2796	0.2796
	StdM3	0.1953	0.1953	0.1953	0.1953	0.1953
	StdM4	0.2316	0.2316	0.2316	0.2316	0.2316

I_Y: Youden index; MQD: minimum quadratic distance; StdM1: standard methodology 1; StdM2: standard methodology 2; StdM3: standard methodology 3; StdM4: standard methodology 4.
Source: Own elaboration.

The ROC curve methodologies showed V^c with little difference between them, which decreased when the mean of the Chagasic patients group moved away from the mean of healthy individuals and was higher under heteroscedasticity conditions. Likewise, V^c increased as a function of the mean of the Chagasic patients group (Table 2).

Discriminatory accuracy

Sensitivity and specificity

Homoscedasticity: For standard methodologies, specificity means were higher using StdM2, followed by StdM4 and Std1; StdM3 showed the lowest mean value. In addition, all estimators of this methodology revealed specificity values >90%. For ROC methodologies, I_Y and MQD showed similar specificity with a minimum of about 75% that increased as the average Chagasic patient population moved away from the mean of healthy individuals (Figure 2A).

Sensitivity in all scenarios was higher in I_Y and MQD, ranging from 75% to 100%. Regarding standard methodologies, StdM3 showed the best behavior with 42% sensitivity in scenario-1, while StdM2 showed the lowest value with sensitivity of 5.21% in the same scenario (Figure 2B).

Heteroscedasticity-1: For specificity, both methodologies showed high values in all scenarios; the highest mean value was observed in StdM2 (approximately 100%), followed by StdM4 and StdM1 (values around 98%). For the ROC curve methodologies, heteroscedasticity affected MQD more than I_Y —the latter with 95% in scenario-1 and 99% in scenario-5. However, both showed a progressive increase according to the mean values of the Chagasic patient populations (Figure 2C).

For sensitivity, although the best behavior was obtained by MQD with a minimum value of 55% in scenario-1 and 97% in scenario-5, I_Y had a similar behavior. As for the standard methodology, StdM3 provided better sensitivity values and the mean values were similar to those of I_Y. The standard methodology that showed the lowest sensitivity values was StdM2, reaching values above 60% only from scenario-4 (Figure 2D).

Heteroscedasticity-2: The mean specificity values were higher using the methodologies for StdM2 (99.95%), StdM1 and StdM4 (98% each). On the other hand, StdM3 caused a decrease in specificity by reaching an average of 92%. For the ROC methodologies, the I_Y had a better behavior than MQD (Figure 2E).

The best sensitivity values were observed with MQD, followed by I_Y and StdM3; the values were equal to MQD from scenario-3 onwards. The methodology that yielded the lowest mean sensitivity values was StdM2 (Figure 2F).

Sensitivity=100% and specificity=100

Homoscedasticity: StdM2 showed specificity=100% in almost all the simulated samples, followed by StdM4 and StdM1 with percentages around 50%. StdM3 showed specificity=100% in only 5% of cases. In the ROC curve methodologies, both showed a similar behavior, going from a low frequency of specificity=100% in the first two scenarios to a high percentage from scenario-3 onwards (87%) (Figure 3A).

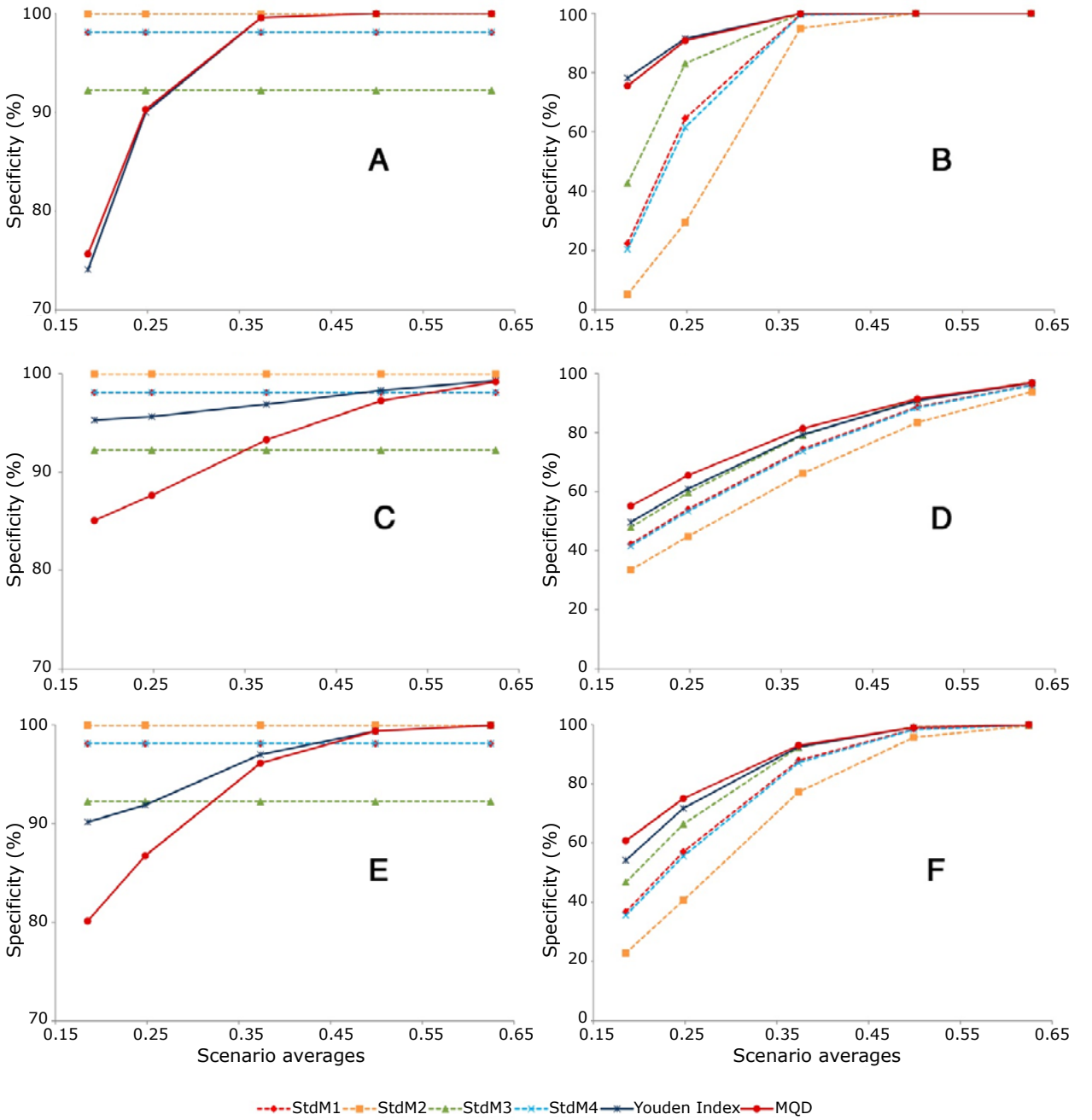

Figure 2. Specificity and sensitivity value estimators
StdM1=μ+2σ; StdM2=μ+3σ; StdM3=μ*+2σ*; StdM4=μ*+3σ*; MQD: minimum quadratic distance.
Source: Own elaboration.

All methodologies showed low frequency sensitivity=100% in the first 2 scenarios; however, the percentages shown by I_Y and MQD were higher than the others. Similarly, all methodologies showed a notable increase in sensitivity=100% from scenario-3 onwards, except StdM2, with higher I_Y and StdM3 values (95%) (Figure 3B).
Heteroscedasticity-1: The methodology that had the highest frequency of specificity=100% was StdM2 with 98.6%; the others showed percentages ≤55% and the lowest value was observed in StdM3 with 5%. Both ROC curve methodologies showed a progressive increase but I_Y was less affected than MQD by heteroscedasticity (Figure 3C).

All methodologies obtained low percentages of sensitivity=100% until scenario-4 and ≤50% in scenario-5. In the latter, the methodology that yielded the highest value was StdM3 (39.7%), followed by the ROC curve methodologies (35%); the one with the lowest value was StdM2 (Figure 3D).
Heteroscedasticity-2: The standard methodology with the highest accuracy for specificity=100% was StdM2 (98.6%); the others showed an accuracy ≤55%. Of the ROC curve methodologies, I_Y showed the best performance, although it presented low frequencies in the first 3 scenarios (42% maximum) and increased from scenario-4 onwards (Figure 3E).

With the exception of StdM2, the applied methodologies obtained values >10% sensitivity=100% from scenario-3 onwards, reaching a high percentage in scenario-5. I_Y, MQD and StdM3 showed the best behavior; the latter had the highest values (Figure 3F).

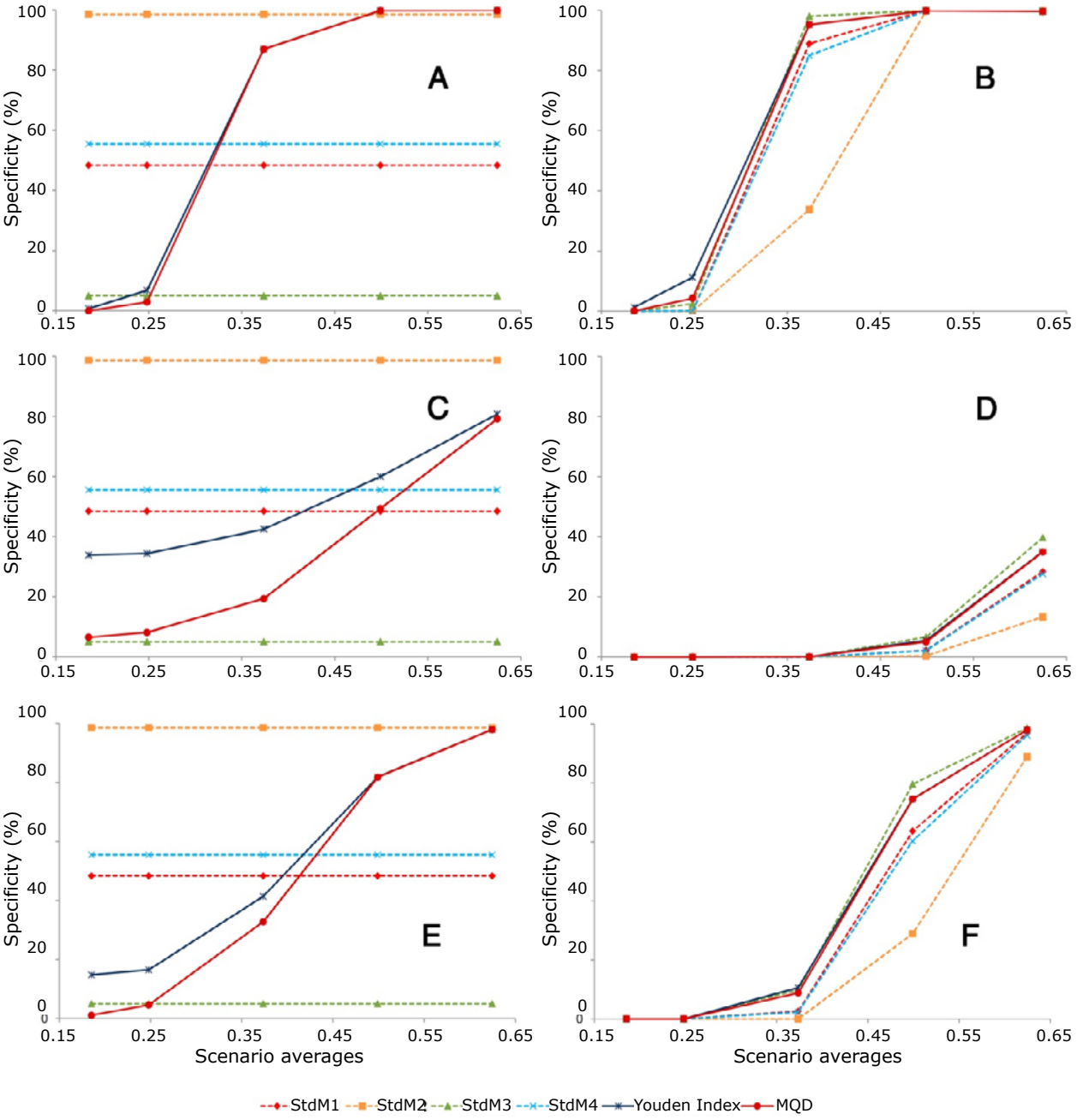

Figure 3. Estimators of specificity=100% and sensitivity=100% rates.
StdM1=μ+2σ; StdM2=μ+3σ; StdM3=μ*+2σ*; StdM4=μ*+3σ*; MQD: minimum quadratic distance.
Source: Own elaboration.

Perfect-decision

Homoscedasticity: In the first 2 scenarios, no methodology yielded perfect-decision values, and the ROC curve methodologies showed the highest percentages from scenario-3 onwards; both I_Y and MQD showed the same values (between 83% and 99%). As for standard methodologies, only StdM2 showed similar values from scenario-4 onwards; the others reached a maximum of 55% decision-perfect (Figure 4A).

Heteroscedasticity-1: From scenario-4 onwards, perfect decisions began to be observed. The highest percentages corresponded to I_Y and MQD (28%), which also showed twice the value of the methodologies StdM1 and StdM4. In addition, few cases were observed with StdM3 (2%) (Figure 4B).

Heteroscedasticity-2: Perfect-decisions could be seen from scenario-3 onwards. The highest percentages corresponded to the ROC curve methodologies (figures between 60% and 96% without distinction between I_Y

and MQD). Of the standard methodologies, only StdM2 reached figures >80%, while the lowest values were obtained by StdM3 (Figure 4C).

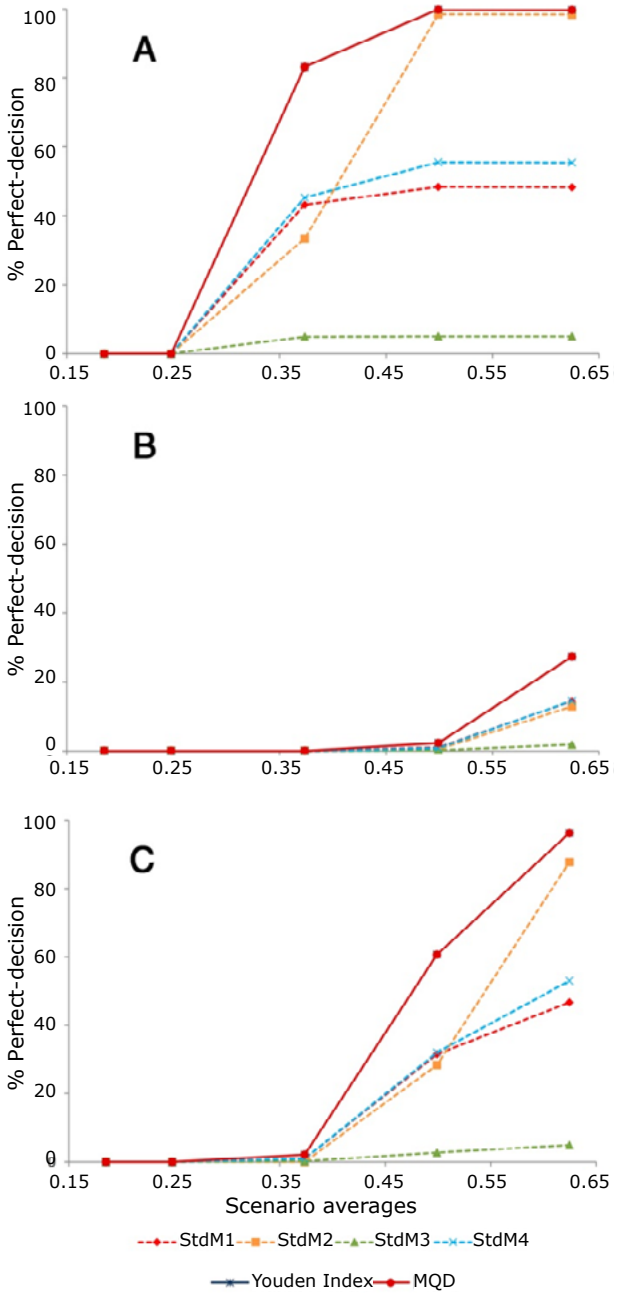

Figure 4. Decision-perfect ratio estimators StdM1=μ+2σ; StdM2=μ+3σ; StdM3=μ*+2σ*; StdM4=μ*+3σ*; MQD: minimum quadratic distance.
Source: Own elaboration.

Discussion

The ELISA cut-off points obtained through the ROC curve methodology showed a better discriminatory accuracy for *T. cruzi* serology than the standard methodology. Although it is not appropriate to diagnose a patient as Chagasic based on a single serological test, it is known that, from the three techniques recommended by the World Health Organization, the ELISA test is the most used for an initial approach, especially in epidemiological studies that evaluate a large number of patients.[1]

The discriminatory accuracy of a diagnostic test depends on its sensitivity and specificity. These values are mainly obtained due to the overlapping of the results of healthy and sick individuals.[10,23] In the present study, such OD overlapping region is observed in healthy individuals and Chagasic patients regarding real data, which evidences that this behavior is associated with the accuracy of the results in serological tests.

For V^c, the standard methodology tended towards high values, which deviated the balance from discriminatory accuracy to specificity, reaching 100% in many cases. This significantly affects sensitivity, as only patients with the most evident immune response will be diagnosed as positive. On the other hand, the V^c obtained using the ROC curve methodology, both for I_Y and MQD, generated more balanced sensitivity and specificity values, often at around 90%. This discrepancy in the decision thresholds is explained because the standard methodology, unlike the ROC curve methodology, does not consider the two populations under study to estimate the cut-off point. Therefore, the ROC curve, besides generating greater discriminatory accuracy, provides greater confidence to the analyst.[23]

Barajas-Rojas *et al.*[24] show that the application of StdM1 leads to a specificity value of about 97.5%. Greiner & Böhning[25] state that this method does not consider sensitivity, therefore it does not reflect the main function of a decision threshold, i.e., it does not differentiate subpopulations of infected individuals from those not infected. This is highly relevant since a test with low sensitivity generates a large number of false negative results.

In this regard, Sharma & Jain[26] report that the standard method tends to generate false negative results, especially in cases where 1) positive patients are receiving medical treatment, 2) antibody or antigen titers are not high enough, or 3) at the onset of infection. In this context, false negatives are a significant issue for the diagnosis of serious diseases, as misdiagnosed patients will not receive the necessary treatment, especially in the initial stages of the disease.[27]

Other studies have reported satisfactory results using the ROC curve methodology and are in line with this study. Fernández-López *et al.*[28] evaluated procalcitonin as a marker for diagnosing invasive bacterial infection in febrile infants and obtained sensitivity of 95.5% and specificity of 84.6%, while Pérez *et al.*[29] studied body mass index as an estimator of overweight and fat distribution in Venezuelan children and adolescents, finding sensitivity between 86% and 100% and specificity between 92% and 100% for different age groups.

Regarding the ROC curve methodologies evaluated, I_Y was less affected than MQD by heteroscedasticity, which coincides with studies reporting inconsistency in the decision threshold obtained by both methods.[21,22] Although both techniques give equal weight to sensitivity and specificity values, some authors recommend using I_Y because it reflects the intention to maximize the percentage of correct classification of healthy and sick patients.[21,22]

During the validation process of a diagnostic test, a correct classification of patients based on their actual health condition is expected.[30] With this in mind, the decision-perfect percentage showed a better performance

for ROC curve methodologies, as they were higher than the standard in all cases. These results support the hypothesis that, between these two methodologies, the ROC curve is the best choice for establishing decision thresholds in serological tests.

It should be noted that ROC curve methodologies identify, as was the case of this work, the decision threshold with higher joint sensitivity and specificity, which supports what is proposed by Fan *et al.*[12] However, such a threshold does not necessarily determine the potentially higher sensitivity and specificity values for the serological test, as such extreme values usually correspond to different cut-off points, one for sensitivity and one for specificity.[31] In fact, there are situations where a diagnostic test with high sensitivity or high specificity is needed; in these scenarios it is not advisable to use the decision threshold obtained by means of the ROC curve. Instead, it is appropriate to determine the specificity and sensitivity values obtained for different cut-off points and to choose the most suitable one as appropriate.[32]

McNicol[33] points out that ROC curves constructed in the presence of heteroscedasticity show a behavior different from their homoscedastic analogues. This occurs because the former, in theory, may have up to two decision thresholds: one similar to that found in the presence of homoscedasticity —that is, located at the central interception of the noise and signal distributions— and another spurious and displaced towards the end of the noise or signal distribution, depending on whether the distribution with the greatest variance is of the signal or of the noise distribution, respectively.

Although no spurious thresholds were identified in the present work, it was observed that sensitivity and specificity were affected by heteroscedasticity in the ROC curve methodologies. On the other hand, in the case of the traditional method, heteroscedasticity did influence sensitivity, but not specificity. Thus, in Figures 2, 3 and 4 it was observed that when the variance of the Chagasic patient population is greater, its influence is also greater, and that the heterocedasticity-1 assumption (greater variance) was the one that showed the worst behavior of all the methodologies. Furthermore, it was found that in ROC curve methodologies, I_Y was less affected than MQD by heteroscedasticity, which is another reason for preferring the former.

Conclusion

Bearing in mind the specific conditions of this work, the ROC curve methodology had a better discriminatory accuracy than the standard methodology in the serological testing for *T. cruzi*. Therefore, the use of the ROC curve methodology is recommended to establish the decision thresholds since it has a better performance, considering that the averages of the Chagasic patient populations move away from those of healthy individuals.

Conflicts of interest

None stated by the authors.

Funding

This research was supported by the Universidad de Carabobo through the project CDCH 2014-003.

Acknowledgements

To Professors Carlos Espino, William Quintana, José Luis Duque, Clara Nancy Gutiérrez, Wilfre Machado, Judith García, Mairett Rodríguez and Jorge Flores, for their valuable comments and suggestions.

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rfm
Revista *de la* Facultad *de* Medicina

REFLECTION PAPER
DOI: http://dx.doi.org/10.15446/revfacmed.v68n1.73456
Received: 11/07/2018 **Accepted:** 19/10/2018

Big data, pharmacoepidemiology and pharmacovigilance

Big data, farmacoepidemiología y farmacovigilancia

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Abstract

Big data is a term that comprises a group of technological tools capable of processing extremely large heterogeneous data sets, which are continuously collected and are available to be used at any time, and, therefore, constitutes a source of scientific evidence production.

In the pharmacoepidemiology field, analyses made using these data sets may result in the development of pharmacological therapies that are more efficient, less expensive, and have a lower occurrence rate of adverse reactions. Likewise, the use of tools such as Text Mining or Machine Learning has led to major advances in pharmacoepidemiology and pharmacovigilance areas, so it is likely that these tools will be increasingly used over time.

Keywords: Artificial Intelligence; Automatic Data Processing; Data Accuracy; Data Mining; Machine Learning; Registries (MeSH).

Sánchez-Duque JA, Gaviria-Mendoza A, Moreno-Gutiérrez PA, Machado-Alba JE. Big data, pharmacoepidemiology and pharmacovigilance. Rev. Fac. Med. 2020;68(1):117-20. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.73456.

Resumen

Big data es un término que comprende un grupo de herramientas tecnológicas capaces de procesar conjuntos de datos heterogéneos extremadamente grandes, los cuales se recolectan de manera continua, están disponibles para ser usados y constituyen una fuente de evidencia científica.

En el área de la farmacoepidemiología, los análisis generados a partir de estos conjuntos de datos pueden resultar en la obtención de terapias médicas más eficientes, con menor número de reacciones adversas y menos costosas. Asimismo, el uso de herramientas como el *Text Mining* o el *Machine Learning* también ha llevado a grandes avances en las áreas de farmacoepidemiología y farmacovigilancia, por lo que es probable que su empleo sea cada vez mayor.

Palabras clave: Procesamiento automatizado de datos; Minería de datos; Aprendizaje automático; Exactitud de los datos; Inteligencia artificial; Sistema de registros (DeCS).

Sánchez-Duque JA, Gaviria-Mendoza A, Moreno-Gutiérrez PA, Machado-Alba JE. [Big data, farmacoepidemiología y farmacovigilancia]. Rev. Fac. Med. 2020;68(1):117-20. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.73456.

Introduction

Big data is a term currently used by computer science to describe a range of technological tools capable of processing extensive data sets. Most such data are observational —also known as "real-world data"— and, when analyzed, can reveal patterns, trends, and associations related to human behavior and its interactions. These large-scale databases may consist of genetic, medical, environmental, economic, geographical, or social network data; for this reason, they are often so extensive and poorly organized that it is not possible to analyze them using traditional computing techniques.[1-4]

Despite its great popularity and multiple uses, there is no clear definition of the concept of big data. Therefore, its definition is based on the four "Vs": volume, velocity, variety, and veracity.[5,6] Volume refers to the availability of massive amounts of data (which requires flexible and easily expandable management, recovery, and storage systems). Velocity is the feature of the big data infrastructure that enables efficient data management. Variety means that the data comes in many formats. Finally, veracity is about reducing errors and unreliable information that affects data analysis and results. In other words, big data involves a large amount of heterogeneous data that is quickly updated and available for use, but it requires checking.[5-7]

Based on the above, this reflection article aims to describe general aspects of the current relevance of big data and its possible application in pharmacoepidemiology and pharmacovigilance. To this end, scientific literature published between 1 January 2000 and 30 November 2018 was searched. The databases consulted were MEDLINE via PubMed, ScienceDirect, and Scopus, and the search strategy included the MeSH terms ["Big data AND Pharmacoepidemiology"; "Big data AND Pharmacovigilance"].

Big data in the health area

Usually, multiple types of data are collected by different health professionals during administrative processes and clinical practice. They include, on the one hand, physicians who record the clinical history of their patients, the prescription of therapies, the results of laboratory tests and the reporting of adverse events, and, on the other hand, pharmacy personnel who record when medications are dispensed. All of this happens routinely.[7,8] Since this information is not collected for scientific research purposes, the data is not always "clean" or available for analysis by researchers; therefore, data accumulates over a long period of time, and its value is not fully recognized or exploited.[5,6] However, the usefulness of this information in health care is increasingly evident, so it is necessary to manage all this data full of scientific evidence.[7]

The use of databases in the health sector began to increase in the 1990s, particularly in Europe, North America and, more recently, Asia, where they have been widely used to assess post-marketing prescription patterns, comparative efficacy, and safety of marketed drugs.[9,10]

The ability to link databases in the health area allows integrating various sources of information to provide an overall picture of the patient's medical history and to carry out collaborative studies through international databases.[5,6,11,12] These techniques are convenient, as it would be extremely costly and time-consuming to collect such information otherwise.[13]

Large healthcare databases often contain information coded according to international classifications such as the International Classification of Diseases (ICD) and the Anatomical, Therapeutic, Chemical (ATC) classification system for drug information. They can also be found in the form of free, unstructured texts that require the use of artificial intelligence technology such as text mining.[7,14] There are two main types of machine learning that have been used in pharmacovigilance for automatic signal generation: supervised learning and unsupervised learning.

Unsupervised machine learning is a computer system that can learn associations between selected data elements on its own, i.e., without being "trained"; this approach has been used to identify complex drug safety signals and discover use patterns. In contrast, supervised machine learning requires "teaching" a computer system how to build an algorithm based on the desired result in advance.[6,15]

Another potential application for big data includes the so-called mobile health (mHealth) area. For some time, applications for smart electronic devices have been developed to help manage a large number of chronic diseases and conditions —such as diabetes and tobacco cessation— and even to improve nutritional habits.[3,16] The information collected from these devices allows for predictive modeling that can result in more efficient and cheaper medical therapies with fewer adverse reactions.[17]

Medical device manufacturers produce tools for use in routine services that monitor clinical marker levels and automatically submit information to complete electronic health records. This information, altogether, allows healthcare providers and government agencies to adjust the treatment plan by phone or applications, e-mails, or directly using the measurement device, thus promoting healthcare compliance.[2,3,5,17]

Big data for drugs in the post-marketing phase

In order to market a novel drug, researchers and manufacturers invest a great deal of time, money, and logistics. Moreover, different phases, which go from pre-clinical research to the first clinical application, must be successfully completed before they are finally approved by the regulatory bodies. Once the drugs are available to patients on the market, pharmacoepidemiology comes into play; it studies their use and effects (beneficial or adverse) in large populations in the post-marketing phase.[1,9,18]

Epidemiological surveillance has been fundamental in public health for decades, as it reports on the health status of patients based on data directly collected from healthcare institutions. These data include sociodemographic variables, clinical conditions, morbidities, laboratory reports, diagnostic and therapeutic strategies, adverse reactions, outcomes, survival, and mortality. This active surveillance is supported by intelligent electronic devices with internet access, in which patients report symptoms and other data that are updated in real time.[1,3] This can be used in the area of pharmacovigilance for reporting adverse drug events.[7,8,19]

The beginning of the technological revolution in the 1970s impacted surveillance systems by improving accessibility and increasing the speed with which data was transmitted between institutions. Similarly, there

was an increase in the number of data sources that can be used in pharmacoepidemiology and pharmacovigilance, covering spontaneous reporting systems, digitized healthcare databases, adverse reaction reports, among others.[3,6,8]

The creation of data systems that collect information on adverse event reports has been a breakthrough in the area of drug safety. Currently, there are international databases that collect such information, continually review it through signal analysis, and issue constant alerts about possible associations between an adverse event and a drug.[8,20,21] This methodology allows the continuous incorporation of data from various sources and its analysis in real time, which in turn allows the detection of possible alerts of unknown adverse reactions or whose magnitude could be greater than expected.[9,13]

Advances in pharmacoepidemiology and pharmacovigilance

Pharmacovigilance appeared more than 50 years ago in response to the harmful side effects caused by the drug thalidomide. In the early years, this science was based on anecdotal evidence and case series through systematic spontaneous reporting, so it did not provide a reliable estimate of incidence or risk. The second-generation shaped important observational studies that sought to understand the contributions of knowledge about potential adverse effects of new and old drugs. Finally, third-generation pharmacovigilance began with meta-analyses on clinical trials and made important contributions.[8]

Furthermore, in recent years, the potential for research based on healthcare databases has generated interest in the results of studies that show the risk association between the consumption of a drug and an adverse effect that could not have been identified during the follow-up time of a conventional clinical trial, such is the case of proton-pump inhibitors usage and the risk of myocardial infarction, [21] or certain drug interactions in the actual clinical context of patients treated with anticoagulants.[22]

The study of big data as a pharmacoepidemiology and pharmacovigilance strategy began in 1990, and, to date, it has proven to be cost-effective, fast, and reliable. Therefore, the Food and Drug Administration (FDA) has not only stated that this strategy has many advantages but has expanded its use to analyze the growing number of reports it receives.[7]

According to the relevant literature, there are several databases with enough information that allow conducting health studies and have a potential application in drug consumption analysis and pharmacovigilance studies. They include the Danish National Health Service Prescription Database,[23,24] the UK's Clinical Practice Research Datalink (CPRD),[25] the US FDA Adverse Event Reporting System (FAERS),[26,27] and the Scottish Prescribing Information System.[28]

In this context, there is evidence that different companies are increasingly using big data and artificial intelligence techniques to support pharmacovigilance activities. However, there is still a long way to go,[29] especially in Latin America, where this type of technology is underdeveloped in the areas of natural sciences and health.[30-32]

Even with the benefits they offer, these techniques have limitations, including the lack of quality standards and validation methods for some of their records, as they may be incomplete, inconsistent, and subject to a great deal of potential bias and confusion. On the other hand, the use of massive amounts of data may cause an existing relationship to go undetected due to the masking or dilution of a phenomenon.[7,33]

Conclusions

The availability of large amounts of healthcare data increases the power of analysis of this information and creates an opportunity to study drug use and safety. Given the high flow of information, big data techniques that allow performing various analysis procedures and obtaining results applicable to routine medical practice are required for the organization and codification of unstructured, and highly complex data. Managing and exploiting these expanding sources of information is the next challenge for the application of research methods in modern pharmacology.[1,6,17,34]

Another relevant advantage of the use of big data in pharmacoepidemiology and pharmacovigilance is the diversity of the data since medical records can be analyzed with information on hospitalization, outpatient consultations, drug prescriptions, and laboratory tests, besides opening up the possibility of continuous monitoring using intelligent electronic devices.[1,2,6]

Due to the limitations of secondary data sources, their interpretation is associated with some important challenges, such as accumulation of estimation errors and spurious correlation.[3] These massive data flows must adjust to changing conditions all the time, so the algorithmic intelligence of digital epidemiology must be harnessed. In this regard, new technologies must be regulated by public health institutions so that data is properly distributed, and high standards of accuracy are maintained.[1,6]

Conflict of interest

The authors are members of the Grupo de Investigación de Farmacoepidemiología y Farmacovigilancia (Pharmacoepidemiology and Pharmacovigilance Research Group) of the Universidad Tecnológica de Pereira in agreement with Audifarma S.A. AGM and JEMA have a contractual relationship with Audifarma S.A.

Funding

This manuscript was financially supported by Audifarma S.A.

Acknowledgements

None stated by the authors.

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rfm
Revista *de la* Facultad *de* Medicina

REVIEW ARTICLE
DOI: http://dx.doi.org/10.15446/revfacmed.v68n1.73475
Received: 12/07/2018 **Accepted:** 12/11/2018

Evidence of conflicts of interest in Medicine

Evidencia sobre conflictos de intereses en medicina

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Abstract

Introduction: Physicians' main responsibility is to practice medicine for the benefit of patients. However, there are situations where secondary interests affect this commitment and give rise to conflicts of interest.
Objective: To analyze currently available systematic reviews and meta-analyses on conflicts of interest in medicine to summarize relevant evidence in this regard.
Material and methods: A literature search was performed in the MEDLINE and LILACS databases using the following search strategy: systematic reviews and meta-analysis on conflicts of interests in medicine published in serialized scientific journals; no publication time or language limits were applied. Studies that met the inclusion criteria were grouped according to the medical activity they assessed, and information on the type and number of studies and conclusions of all publications included in the review was collected.
Results: 29 publications were included, and they were classified as follows: studies based on research articles, on clinical practice guidelines, on clinical practice, and on patient-oriented papers.
Conclusions: It was found that the authors of the original research papers included in the meta-analyses and systematic reviews analyzed here do not always state if they have conflicts of interest or not. Nevertheless, when said conflicts are reported, they tend to present results favoring the drugs or medical technologies of their sponsor.
Keywords: Conflict of Interest; Review; Medicine (MeSH).

González-Mariño MA. Evidence on conflicts of interest in medicine. Rev. Fac. Med. 2020;68(1):121-9. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.73475.

Resumen

Introducción. La principal responsabilidad de los médicos es la de actuar en beneficio de los pacientes; sin embargo, existen situaciones en las cuales surgen intereses secundarios que pueden afectar este compromiso y generar conflictos de intereses.
Objetivo. Analizar las revisiones sistemáticas y los metaanálisis actualmente disponibles en la literatura sobre el conflicto de intereses en medicina para sintetizar la información al respecto.
Materiales y métodos. Se realizó una búsqueda en las bases de datos MEDLINE y LILACS mediante la siguiente estrategia de búsqueda: revisiones sistemáticas y metaanálisis sobre conflictos de intereses en medicina publicados en revistas científicas seriadas; no se aplicaron restricciones de idioma o año de publicación. Los estudios que cumplieron con los criterios de inclusión fueron agrupados según la actividad médica evaluada; además, de cada uno de ellos se extrajo la cantidad y el tipo de estudios y las conclusiones.
Resultados. Se seleccionaron 29 publicaciones que se agruparon en estudios basados en artículos de investigación, en guías de práctica clínica, en la práctica clínica, y en publicaciones orientadas a los pacientes.
Conclusiones. Los estudios originales incluidos en las revisiones sistemáticas y los metaanálisis analizados en el presente estudio no siempre reportan los conflictos de intereses; sin embargo, cuando estos se mencionan, hay una tendencia a presentar resultados que favorecen el medicamento o la tecnología del patrocinador.
Palabras clave: Conflicto de intereses; Revisión; Medicina (DeCS).

González-Mariño MA. [Evidencia sobre conflictos de intereses en medicina]. Rev. Fac. Med. 2020;68(1):121-9. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.73475.

Introduction

Patient care, medical research, and continuing health education should be transparent processes, but this is not usually the case. It is common for physicians to receive gifts from a pharmaceutical laboratory and then prescribe the product of the company that acts as a benefactor. In this regard, some authors have reported that simple gifts, such as a meal, have led physicians to change the prescription of medicines to a particular brand.[1-3] In the case of research, scientists may be inclined to avoid publishing results that are unfavorable to the product that is funding the study.[4]

It is also common for medical societies to finance congresses with contributions from the pharmaceutical and medical technology industry. This financial support is invested not only in logistics, but in travel allowances, accommodation, and food for both speakers and attendees; this support may even go as far as sponsoring conferences as a clearly established marketing plan. This situation may also influence the presentation of outcomes that favor the sponsors.

These examples give an account of how doctors are being used as marketing agents.[5] This may constitute a conflict of interest that can be understood as a situation where a judgment or action, which should be determined by a primary value established for professional or ethical reasons (protection of research subjects, obtaining safe knowledge and adequate care for the patient in the case of health), may be influenced or appear biased to obtain a secondary benefit.[6]

In Colombia, Article 106 of Act 1438 of 2011[7] —amended through Article 133 of Act 1474 of 2011[8] and Article 17 of Act 1751 of 2015—[9] prohibits pharmaceutical companies that produce drugs and medical supplies from granting perks or gifts to professionals working in the health sector. Also, in 2018, the Ministry of Health and Social Promotion issued Resolution 2881, which requires pharmaceutical companies to report payments to any actor involved in the system.[10]

Systematic reviews are a type of scientific investigation that uses primary original studies as their unit of analysis to answer a formulated research question utilizing a systematic and explicit process of analysis of said original studies. Meta-analyses, on the other hand, are reviews that use statistical methods to combine the results of two or more studies.[11-13]

With this in mind, an analysis of the systematic reviews and meta-analyses on conflicts of interest in medicine currently available was performed to synthesize information in this regard.

Materials and methods

A search for studies on conflicts of interest in medicine published in serialized scientific journals available in MEDLINE and LILACS was done. In MEDLINE, the search was conducted on February 10, 2018, using the MeSH term "conflict of interest" and the filters "Meta-Analysis" and "Systematic Review." In turn, the search in LILACS was conducted on February 18, 2018, using the DeCS term "Conflicto de interés" (Spanish for conflict of interest) and the filter "Systematic Review." There were no language or publication date restrictions.

First, to determine whether the studies met the inclusion criteria (being a systematic review or a meta-analysis assessing conflicts of interest in some medical area), two reviewers independently scanned the title and abstract of the publications found in the initial search. The full texts of the selected publications were then analyzed by the author of this study to obtain the final sample for the review.

The publications selected during the search for analyses were grouped according to the main activity evaluated: research articles (reviews not involving direct clinical interaction), clinical practice guidelines (CPG), reviews based on clinical practice (evaluation of medical or surgical treatments), and patient-oriented publications.

Results

The search yielded 2 025 references in MEDLINE and 11 in LILACS, of which 29 were selected due to their relevance and design; all were taken from the MEDLINE database (Figure 1). The selected publications were grouped according to the activity evaluated (Tables 1, 2, 3 and 4).

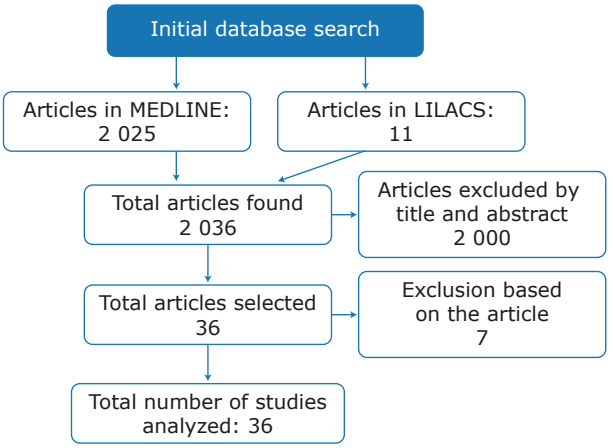

Figure 1. Selection process of articles for analysis. Source: Own elaboration.

Research articles

Nine reviews were based on research articles (Table 1), of which 4 clearly presented the association between sponsorship and outcomes; 3 did not assess the impact of having a conflict of interest; 1, which included Latin American and Caribbean publications, warns that funding for experimental studies is often ambiguous or unreported; and 1, which is a meta-analysis that analyzes preclinical trials in animals, did not find any difference between disclosing or not the financial conflict of interest.[14-22]

Clinical practice guidelines

According to the search criteria, there were 9 CPG reviews (Table 2), of which 7 concluded that there is low disclosure rates of conflicts of interest.[23-29] However, Feuerstein, in different studies and with the support of several researchers, highlights that this type of publication has multiple conflicts of interest.[23-27] The other 2 reviews do not address this issue.[30-31]

Table 1. Systematic reviews and meta-analyses on conflict of interest in research articles.

Author Year	Assessment	Number of studies	Type of study	Conclusions
Krauth *et al.*[14] 2014	Preclinical trials in animal (meta-analysis)	63	Experimental design studies.	The efficacy of statins was not altered by the disclosure of the financial conflicts of interest. Further studies are necessary to establish the possible causes of the differences between industry-sponsored and non-industry-sponsored studies, such as selective outcome reporting.
Bekelman *et al.*[15] 2003	Scope, impact, and management of financial conflicts of interest in biomedical research (meta-analysis)	37	16 cross-sectional surveys, 3 secondary data analyses, 15 systematic reviews and 3 content analyses	Financial relationships between industry, scientific researchers and academic institutions are widespread. Conflicts of interest arising from these ties can influence biomedical research in important ways.
Amiri *et al.*[16] 2014	Conflicts of interest and levels of evidence in spinal research results	864	49 level 1 studies, 200 level 2 studies, 106 level 3 studies, and 509 level 4 studies	A significant association is shown between funding source, study outcome and low levels of evidence in spinal research. A large proportion of industry-funded research was shown to provide level 4 evidence and report favorable outcomes.
Lundh *et al.*[17] 2017	More favorable outcomes and different risk of bias in industry-sponsored drug and device studies compared to studies that have other sources of funding.	75	58 clinical trials, 2 observational studies and 15 clinical and observational trials	Sponsorship of drug and device studies by the manufacturing company leads to more favorable efficacy results and conclusions than sponsorship by other sources. Analyses suggest the existence of an industry bias that cannot be explained by standard 'Risk of bias' assessments.
Reveiz *et al.*[18] 2013	Randomized clinical trials published in Latin America and the Caribbean according to funding source.	526	Randomized clinical trials	Some differences between publicly and non-publicly funded randomized clinical trials were found in clinical research for trial registration, ethic issues, conflict of interest reporting and trial settings among others.
Bes-Rastrollo *et al.*[19] 2013	Conflicts of interest in systematic reviews on sugar-sweetened beverages.	18	Systematic reviews	Systematic reviews with financial conflicts of interest were five times more likely to present a conclusion of no positive association between sugar-sweetened beverages consumption and obesity.
Alkhaled *et al.*[20] 2014	Effects of interventions that assess the relationship between physicians and pharmaceutical companies	4	1 randomized trial, 2 cohorts and 1 linear regression model	Available evidence suggests a potential impact of policies aiming to reduce interaction between physicians and drug representatives on physicians' prescription behavior. There was no evidence concerning interventions affecting other types of interaction with pharmaceutical companies.
Hui *et al.*[21] 2012	Conflict of Interest in supportive and palliative oncology literature	848	429 case series, 72 cohort studies, 149 cross-sectional studies, 56 qualitative studies, 47 randomized trials and 95 studies with other designs.	A majority of supportive/palliative oncology studies did not report funding sources and conflict of interest, raising the need for standardization.
Schoenthaler *et al.*[22] 2014	Clinical trials on urolithiasis	110	16 level 1 studies, 15 level 2 studies, 23 level 3 studies and 56 level 4 studies.	90% of the publications declared conflicts of interest, whereas sponsoring of studies was declared only by one-third. A considerable number of trials involved issues of high commercial impact.

Source: Own elaboration.

Table 2. Systematic reviews of conflict of interest in clinical practice guidelines.

Authors Year	Assessment	Number of studies	Type of studies	Conclusions
Feuerstein *et al.*[23] 2016	Overall quality of recommendations and conflict of interest in CPGs for Barrett's esophagus	8	CPG on Barrett's esophagus.	Half of the guidelines disclosed whether there was a conflict of interest; 75% of them reported potentially relevant conflicts of interest. There was evidence of the need to improve the process of CPG development, which are fundamental to maintaining a reliable health system.
Feuerstein *et al.*[24] 2013	Quality of scientific evidence and conflicts of interest in gastroenterology CPGs.	81	CPG	Most guidelines failed to disclose the conflicts of interest, but when they became known, they were numerous.
Feuerstein *et al.*[25] 2016	Determination of the validity of hip and knee osteoarthritis guidelines	13	CPG	Half of CPGs' recommendations for hip and knee osteoarthritis are based on poor-quality evidence. Almost as many fail to reveal relevant conflicts of interest, but they are evident when they are disclosed.
Feuerstein *et al.*[26] 2013	CPG	19	CPG	Most guidelines do not disclose any conflicts of interest, but they are numerous when commented upon. In addition, they are not often updated and there is a lack of consensus among medical societies among the guidelines reviewed.
Feuerstein *et al.*[27] 2014	Validity of the CPGs published by the interventional medical societies	149	CPG	Most of the intervention CPGs did not disclose conflicts of interest or level of evidence, but when they did, it was of low quality.
Norris *et al.*[28] 2011	Conflict of interest in CPGs development	12	CPG	There is little information on the high prevalence of conflict of interest among CPG authors, and there are only case studies on their effect on guideline recommendations. Further research is needed to explore this potential source of bias.
Khalil *et al.*[29] 2012	CPG	126	CPG	There is a substantial variation in the percentage of authors with potential conflicts of interest among guideline writing groups in the different medical societies selected by convenience sampling. However, several of these CPGs do not include potential conflicts of interest in their published guidelines.
Raftery *et al.*[30] 2008	CPGs in the United Kingdom	3	Cross-sectional surveys: 2 RCTs and 1 mixed study (ACE-cohort study)	There was a low level of evidence about whether payments to health professionals increase their involvement in testing or patient recruitment.
Tibau *et al.*[31] 2015	CPG	142	91 CPGs and 51 consensus meetings.	Support for a specific drug is more common when the authors have financial conflicts of interest with the company marketing that drug. However, there is not enough evidence supporting an association between the funding of CPGs or consensus by the industry and said support.

RCT: randomized controlled trials; CPG: clinical practice guidelines.
Source: Own elaboration.

Reviews based on clinical practice

The search yielded 8 reviews based on clinical practice (Table 3), of which 7 highlight the tendency to present results that favor the drug or commercial sponsor. The other review shows that conventional treatment is favored over the experimental metal-on-metal hip prosthesis arm.

Table 3. Systematic reviews on conflict of interest in reviews based on clinical practice.

Authors Year	Assessment	Number of studies	Type of studies	Conclusions
Fickweiler *et al.*[32] 2017	Prescription	49	43 cross-sectional studies, 2 cohort studies, 3 RCTs and 1 case-control study.	The interaction between physicians, the pharmaceutical industry, and its sales representatives, as well as the acceptance of gifts from the company's sales representatives, have been found to affect physicians' prescribing behavior and are likely to contribute to irrational prescribing of the company's drug.
DeGeorge *et al.*[33] 2015	Surgical technique	124	69 retrospective studies, 1 high-quality study, 12 low-quality studies and 42 poor-quality or unclassified studies.	Studies disclosing an industry conflict are significantly associated with reporting lower postoperative complications
Hsu *et al.*[34] 2012	Surgical technique	64	No level 1 studies, 10 level 2 studies, 7 level 3 studies, and 47 level 4 studies	Authors with financial conflicts have contributed to the increase in negative outcomes reported in the literature regarding the experimental treatment of metal-on-metal total hip arthroplasty; that is, the standard treatment is better than the experimental treatment.
Sung *et al.*[35] 2013	Drug	66	56 RCTs, 9 cohort studies and 1 pseudo-experimental study.	About half of studies on the effect of botulinum toxin A in cerebral palsy were sponsored by the industry. Qualitative conclusions in those studies are more favorable to the use of the botulinum toxin A than the non–industry-sponsored studies. Therefore, clinicians should be aware of an industry-related conflict of interest regarding reports on the efficacy of botulinum toxin A injections in patients with cerebral palsy.
Riaz *et al.*[36] 2016	Cardiovascular clinical trials (phase 2 and 3)	114	RCT	Authors' conflicts are associated with favorable outcomes in cardiovascular outcome trials.
Printz *et al.*[37] 2013	Conflicts of interest in the evaluation of hyaluronic acid injections for osteoarthritis of the knee	48	RCT	None of the studies with a reported financial conflict of interest of at least one author had an unfavorable conclusion; 11 (35%) of the 31 studies with no industry-affiliated authors indicated that hyaluronic acid injection for knee osteoarthritis was no more effective than a placebo injection.
López *et al.*[38] 2015	Association between funding and findings in plastic surgery	568	119 cohort studies, 3 cross-sectional studies, 39 case-controls, 22 RCTs, 256 case series and 129 conducted under another design.	Investigators with a financial conflict of interest are significantly more likely to publish plastic surgery studies with a positive conclusion compared with investigators with no conflicts of interest.
Lee *et al.*[39] 2012	Thromboprophylaxis after total joint arthroplasty	66	53 prospective studies with a comparison group and 13 without a comparison group	Most studies on thromboprophylaxis after total joint arthroplasty are sponsored by the industry. Moreover, the qualitative conclusions in those studies are favorable to the use of the sponsored prophylactic agent.

RCT: randomized clinical trial
Source: Own elaboration.

Patient-oriented research

The search yielded 3 reviews that assess conflict of interest from the patients' perspective (Table 4). The first study reviews websites that describe payments to physicians, analyzes them, and makes recommendations for improvement; the second concludes that, for patients, conflicts of interest do not appear to be important, and the third evaluates conflict of interest in

the development of tools designed to help people participate in decision-making about health care options and makes recommendations about various methods of presenting information about conflict of interest.

Table 4. Systematic reviews and meta-analyses on conflict of interest in patient-oriented research.

Authors	Assessment	Number of studies	Type of studies	Conclusions
Hwong *et al.*[40] 2014	Websites that present data on payments to doctors.	21	List of ProPublica's disclosure websites (www.propublica.org), court investigation orders and public disclosure announcements	The development of a national disclosure website is only the first step to ensure transparency in physician-industry interactions. A central location for payment would allow more rigorous research into the effects of industry payments on patient care and the medical profession.
Fadlallah *et al.*[41] 2016	Patients and general public.	20	15 convenience sampling studies, 2 stratified random sampling studies, 1 systematic random sampling study, 1 simple random sampling study and 1 cluster random sampling study	Regarding physicians' receipt of personal gifts, awareness of participants and the general public was low. However, participants also reported greater acceptability and fewer perceived influence for office-use gifts compared to personal gifts.
Barry *et al.*[42] 2013	Support to patient decisions.	4	Meta-analysis	Disclosure of the conflict of interest alone is not sufficient, so it is recommended that the source of funding be disclosed in plain language.

Source: Own elaboration.

Discussion

Conflicts of interest can occur in any professional activity.[43] In medicine, for example, one of the areas in which conflict of interest and outcome bias can have the greatest impact is research, because the results of a biased study can put a large number of people at risk.[44]

Even though there are different methodological procedures to reduce conflicts of interest (e.g. Cochrane's), these strategies focus on study design and development rather than on funding sources.[44] This is a serious problem since many researches around the globe are financed by the industry; in fact, this is the most common source of funding in the USA.[45]

Some of the analyzed systematic reviews and meta-analyses report a tendency to favor the sponsoring entity.[15-17,19] For instance, Bekelman *et al.*[15] found that clinical trials funded by the drug manufacturer or in which the researchers have financial relationships with the manufacturers are 3.6 times more likely to report that the drug tested is effective compared to studies without such relationships.

There is also a low level of disclosure of conflicts of interest in CPGs, as the groups that develop them often do not make public their policies on the subject, their sources of funding for the development of guidelines, or the financial relationships of the members of the drafting panel. This lack of transparency makes it difficult for readers and users of the guidelines to assess undue influence and bias and, according to several studies, numerous conflicts of interest are evident when information is disseminated.[23-27] However, it is necessary to highlight the effort made by some groups or entities developing CPGs to reduce the possibility of developers having conflicts of interest. This is an effort in which transparency (understood as a way of operating so that the public can see clearly what actions are carried out) and accessibility have been cited as the most important aspects to assess conflict of interest policies in health organizations.[46]

The conclusions of the clinical practice-based reviews presented in Table 3 showed that most found an association between the sponsored product and favorable research outcomes. Thus, in the review by Riaz *et al.*,[36] the declaration of financial conflicts of interest by at least one investigator was associated with a significantly higher probability of favorable outcomes for the drug or intervention under investigation ($p<0.005$). On the other hand, DeGeorge *et al.*[33] found that studies that report conflict of interest are more likely to show a favorable outcome regarding infections ($p<0.01$), wound complications ($p<0.01$), overall morbidity ($p<0.07$) and mortality ($p<0.05$).[33]

Finally, the review by Fadlallah *et al.*[41] showed that patients and the general public care very little about the personal gifts their physicians receive from the pharmaceutical industry, and that when studies focus on surgeons, patients believe that professionals decide what is best for their health, regardless of their financial relationship with the industry.

Relationships between physicians and the industry are common and vary according to the specialty, type of practice and professional activity.[47] In the USA, of 850 000 active physicians, 616 567 received some type of payment in 2015[48] (average payment per physician: USD 3 242; median payment per physician: $157); of these, 589 042 received food and drinks,[1] which was associated with a greater tendency to prescribe brand name drugs, even when there are equally effective generic drugs.[48-53]

In all medical activities, it is important to establish policies that reduce the influence of secondary interests,

clearly communicate the financial link with the industry, prohibit the acceptance of gifts or entertainment, and seek alternatives to industry funding of continuing medical education activities.[54,55] Careful policy setting regarding conflicts of interest helps maintain confidence in academics.[56]

The relationship between the industry and researchers has been the subject of intense debate worldwide. Such is the case of the organization Cochrane, a very respected organization in the academic field, and the studies on the effectiveness and safety of the human papillomavirus vaccine, which have been at the center of controversy due to the quality of the review conducted by Arbyn *et. al,*[57] the sponsorship of these studies,[58] and the existing conflict of interests of the reviewers.[59]

The main limitation of the present review is that the search was conducted only in two databases, had broad inclusion criteria and its findings were descriptive.

Conclusions

There are relationships between the pharmaceutical industry and physicians that can affect professional practice since interests, different from clinical research, may arise.

The publications analyzed in this review showed that the original studies included in the systematic reviews and meta-analyses do not always report conflicts of interest. However, when they are mentioned, the results tend to favor the sponsor's drug or device.

Conflicts of interest

None stated by the author.

Funding

None stated by the author.

Acknowledgements

None stated by the author.

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rfm
Revista *de la* Facultad *de* Medicina

REVIEW ARTICLE
DOI: http://dx.doi.org/10.15446/revfacmed.v68n1.72108
Received: 10/05/2018 **Accepted:** 29/07/2018

Oral tolerance induction in organ and tissue transplantation. Literature review

Inducción de tolerancia por vía oral en trasplante de órganos y tejidos. Revisión de la Literatura

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Abstract

Introduction: Oral tolerance is defined as the suppression of the immune response to antigens that have been previously administered orally. The purpose of inducing oral tolerance is to avoid using immunosuppressive drugs since, considering that they are not antigen-specific, they make the host more susceptible to acquire infections and develop neoplasms.
Objective: To carry out a literature review on the most relevant theoretical references regarding oral tolerance induction in organ and tissue transplantation to prove that oral tolerance is a viable alternative therapy in transplant patients.
Materials and methods: A literature review was conducted in the PubMed, MEDLINE, LILACS and Embase databases using the following search strategy: publication time: no limits; publication language: English and Spanish; type of studies: case-control studies, literature and systematic reviews; search terms: "T-Lymphocytes, Regulatory", "Autoimmunity", Immunosuppression", "Immune system" and "Immune Tolerance", and their equivalents in Spanish.
Results: After the initial search was completed, 719 records were retrieved; however, only 99 addressed oral tolerance induction. Once duplicate records and articles without full-text access were removed, 75 studies were included for analysis.
Conclusions: Oral administration of antigens is an effective way to induce immune tolerance in transplant patients (murine models) as it eliminates the adverse effects associated with immunosuppressive therapy, which currently is the standard therapy to treat these patients worldwide.
Keywords: T-Lymphocytes, Regulatory; Autoimmunity; Immunosuppression; Immune System; Immune Tolerance (MeSH).

Rivillas-Reyes JF, Hernández-Duran EF, Morales-Manrique JL, Rivillas MP, Lozano-Marquez E, Lozano-Marquez H. Oral tolerance induction in organ and tissue transplantation. Literature review. Rev. Fac. Med. 2020;68(1):130-42. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.72108.

Resumen

Introducción. La tolerancia oral es la supresión de la respuesta inmune a antígenos administrados con anterioridad por vía oral; su inducción tiene el propósito de evitar el uso de fármacos inmunosupresores, los cuales, dado que son poco específicos a antígenos, vuelven al huésped más susceptible de contraer infecciones y desarrollar neoplasias.
Objetivos. Realizar una revisión de la literatura sobre los referentes teóricos más relevantes de la inducción de a tolerancia oral en lo que respecta al trasplante de órganos y tejidos para demostrar que el uso de esta alternativa terapéutica es viable en pacientes trasplantados.
Materiales y métodos. Se realizó una revisión de la literatura en PubMed, MEDLINE, LILACS y Embase mediante la siguiente estrategia de búsqueda: periodo de publicación: sin límites; idiomas: Inglés y Español; tipo de artículos: estudios caso-control, revisiones sistemáticas y de la literatura; términos de búsqueda: "T-Lymphocytes, Regulatory", "Autoimmunity", Immunosuppression", "Immune system" and "Immune Tolerance", y sus equivalentes en español.
Resultados. La búsqueda inicial arrojó 719 registros, sin embargo solo 99 abordaban la inducción de la tolerancia oral. Una vez los registros duplicados y los artículos sin acceso a texto completo fueron removidos, se incluyeron 72 estudios en la revisión.
Conclusiones. La administración oral de antígenos es una opción efectiva para inducir tolerancia inmunológica en pacientes trasplantados (modelos murinos), pues elimina los efectos adversos que conlleva la terapia inmunosupresora actualmente utilizada.
Palabras clave: Linfocitos T reguladores; Autoinmunidad; Inmunosupresión; Sistema inmune; Tolerancia inmunológica (DeCS).

Rivillas-Reyes JF, Hernández-Duran EF, Morales-Manrique JL, Rivillas MP, Lozano-Marquez E, Lozano-Marquez H. [Inducción de tolerancia por vía oral en trasplante de órganos y tejidos. Revisión de la Literatura]. Rev. Fac. Med. 2020;68(1):130-42. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.72108.

Introduction

Organ transplantation is an alternative for the treatment of patients suffering from certain chronic end-stage diseases. Immunosuppressive drugs help prevent transplant rejection, but they may have multiple side effects, including an increased risk of infection and the development of cardiovascular diseases and neoplasms. Therefore, attempts to achieve transplant tolerance since the beginning of the procedure have always been considered to reduce the harmful effects of immunosuppressors and make grafts last longer.[1]

The key to determining the molecular processes of the immune system is to identify how an antigen first comes into contact with it. One form of contact is the oral route, in which it has been observed that, upon recognition of the antigen, the cells of the gastrointestinal tract generate a milder immune response than if the antigen entered the body by a different route; this is known as oral tolerance.[1]

Bartman *et al.*[2] have reported the success of oral tolerance in certain autoimmune diseases such as arthritis. Likewise, several authors have pointed out its efficacy in organ transplants made in murine and human models.[2-21]

A literature review on the induction of oral tolerance, immunological mechanisms, the regulatory cell response against exposed antigens and the experimental results of oral tolerance in organ and tissue transplants was conducted to demonstrate that this therapeutic alternative is viable in transplant patients.

Materials and methods

A literature review was conducted between February and April 2018 in PubMed, MEDLINE, LILACS and Embase. The search was made using the following DeCS Bireme terms: "linfocitos T reguladores", "autoinmunidad", "inmunosupresión", "sistema inmune" and "tolerancia inmunológica", and the MeSH terms "T-Lymphocytes, Regulatory", "Autoimmunity", Immunosuppression", "Immune system" and "Immune Tolerance". Boolean operators were not used to conduct the search. The review included original research articles, case–control studies, and narrative and systematic reviews in humans and animals, published in Spanish and English, and with no publication time limit.

The search yielded 719 results; two co-authors simultaneously and independently reviewed abstracts and titles to determine if they met the inclusion criteria (studies on oral tolerance and human transplantation). In case of disagreement, a third author resolved the discrepancy. After this review, it was determined that 99 articles met the inclusion criteria; 24 of them were excluded because the full text was not available and 3 because they were duplicated. In total, 72 relevant articles were selected for this review (Figure 1).

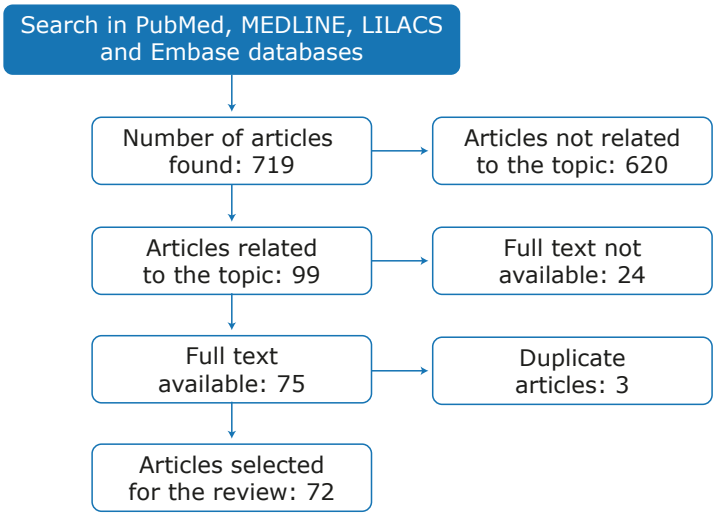

Figure 1. Flow chart of the study. Article selection process. Source: Own elaboration.

Results

Of the studies selected for analysis, 52 (72%) were published between 2005 and 2018 and the country with the largest number of publications was the United States with 39 (54%), followed by Japan with 8 (11%). The predominant language was English (65 articles) and most publications were review articles (56%) and case-control studies (31%) (Table 1).

Discussion

The main motivation for carrying out this research was the need to identify the available literature on the treatment provided to patients receiving solid organ transplants, the associated side effects and the new therapies to solve these problems. The results of this review show that, even though there are no human clinical trials on new post-transplant therapies, there are several laboratory animal studies that describe different types of intervention related to this issue.

To better understand these new works, it is necessary to revisit the physiological foundations of immunological tolerance and its relationship with solid organ transplantation, considering that oral tolerance induction is discussed in this work as an alternative therapy to the one currently used.

Table 1. Methodology and findings of the selected studies.

Study/Year	Type of article	Findings
Bartman *et al.*[2] 2015	Review	Commensal microbes can modify the immune response to organ transplantation locally (in the gastrointestinal tract) and throughout the organism. For example, T cell response to viral infections in the bone marrow varies depending on the commensal microbiota. The cell wall molecules from commensal microorganisms enter the circulation and modify the expression of neutrophils or their precursors in the bone marrow. It seems that transplant rejection may be influenced by microbiota in the immune system.
Faria & Weiner[3] 2005	Review	Epithelial cells and gastrointestinal flora modify the function of dendritic cells, which induce the production of Treg cells, responsible for regulating the autoimmune and inflammatory response. Although there are some satisfactory results in animal and human models, their clinical application has not been possible.
Hershberg & Mayer[4] 2000	Review	Intestinal epithelial cells function as APCs. They also have antigen receptors that can generate the internalization of antigens through endocytosis. Unlike the M cells in Peyer's patches, the glycocalyx of the epithelial cells restricts the exposure between them and the antigen; on the other hand, the large surface area of microvillus allows the epithelial cells to play a key role in antigen uptake. Enzymes or pH changes in the lumen of the gastrointestinal tract modify the chemical properties of the antigens, allowing them to destroy the epitopes before they are processed by the APCs and change the cellular stimulus.
Miron & Cristea[5] 2012	Review	The best-known function of enterocytes is the chemical processing of food, but they can also induce immunological oral tolerance since they cooperate with cells of the intestinal mucosaassociated lymphoid tissue to maintain a nonreactivity state toward dietary and microbial antigens. The microenvironment of the intestinal lamina propria triggers the events that polarize APCs and activated T-lymphocytes; for this reason, the contribution of enterocytes modifies this microenvironment and maintains the balance between suppression and stimulation of the inflammatory response.
Chan *et al.*[6] 2004	Review	Immune tolerance is divided into central and peripheral tolerance. In central tolerance, the ectopic antigens expressed in the thymus medulla produce Treg cells and eliminate self-reactive cells. However, in the thymus, there is no 100% negative selection of self-reactive thymocytes, so peripheral tolerance becomes a secondary mechanism of tolerance induction. In the periphery, tolerance is mainly induced by the interaction between dendritic cells and regulatory T cells.
Jiang & Chess[7] 2006	Review	3% of the T-cell precursors entering the thymus survive positive and negative selection (cells with high avidity for self-peptides). CD4+ regulatory T cells express a large amount of FOXP3 transcription factor, whose mutation in humans generates autoimmune diseases and inflammatory disorders such as immune dysregulation, polyendocrinopathy, enteropathy, and X-linked syndrome (IPEX). However, the overexpression of this factor has an immune response suppressing activity, which is evidence of its involvement in immune regulation.
Sakaguchi *et al.*[8] 2008	Review	The regulatory T cell marker CD25 is a component of the high-affinity IL-2 receptor, which promotes high levels of FOXP3 and activated T cell apoptosis. In humans, CD25 deficiency is associated with severe autoimmunity and allergies, and its manifestations are indistinguishable from IPEX syndrome, which is generated by the FOXP3 mutation.
Jaramillo *et al.*[9] 2006	Review	In infections, regulatory T cells (Treg) limit the immune response against pathogens and are activated directly by the pathogen or products of the infection. In cases of HIV infection, in the periphery, decreased levels of FOXP3 mRNA and regulatory T cells are observed, as well as an inverse relationship between the amount of Treg cells and the appearance of the immune reconstitution inflammatory syndrome. On the other hand, in the case of infections caused by human T- lymphotropic virus-1 (HTLV-1), the tax gene may exert an inhibitory effect on the expression of FOXP3, which generates alteration in the function of Treg cells.
Dubois *et al.*[10] 2009.	Case-control	Oral tolerance initiates in gut-associated lymphoid tissues by dendritic cell-mediated deletion of Ag-specific T cells and is completed systemically by CD4+CD25+ T cells. This suggests that orally administered biotherapies that increase the susceptibility of effector T cells to the suppressive response of Treg may be of great value for the treatment of autoimmune and inflammatory diseases.
Scalea *et al.*[11] 2016	Review	The inhibitory mechanism of Treg cells is believed to be mediated mainly by 4 actions: release of soluble inhibitory factors, cytolysis, metabolic dysregulation, and altered dendritic cell function.
Coombes *et al.*[12] 2007	Review	A population of CD103+ mesenteric lymph node dendritic cells induces the development of FOXP3+ Treg cells.

Table 1. Methodology and findings of the selected studies. (Continued)

Study/Year	Type of article	Findings
Ashton-Chess *et al.*[13] 2007	Review	Tolerance biomarkers are necessary to measure the susceptibility of patients to respond to tolerance-inducing regimes, to diagnose tolerance after induction or weaning patients from immunosuppressive drugs, and to predict when they will no longer be effective. Techniques such as ELISA, flow cytometry and polymerase chain reaction and DNA microarrays are used to detect biomarkers that predict the risk of graft rejection.
Koelman *et al.*[14] 2000	Case-control	Oral exposure to HLA molecules in seminal fluid in pregnant women who have practiced oral sex reduces the risk of preeclampsia, as there is a correlation between swallowing sperm during oral sex and a lower incidence of preeclampsia. Since pregnancy and transplantation have several similarities, it is proposed that the induction of allogeneic tolerance to the fetus' paternal HLA molecules may be critical for reducing the risk of pre-eclampsia. Recent studies suggest that exposure, particularly oral exposure, to soluble HLA (sHLA) or HLA-derived peptides may induce tolerance to transplantation. Similarly, sHLA antigens present in seminal plasma may induce tolerance to the father's antigens in the mother.
Yin *et al.*[15] 2018	Case-control	Oral administration of Tsumura Japan (TJ-35) increases survival time in heart transplantation in murine models and may induce the production of CD4+CD25+Foxp3+regulatory T cells in these models.
Yokoyama *et al.*[16] 2005	Case-control	Administration of a cyclooxygenase 2 inhibitor (NS-398) in murine models induced indefinite survival of most fully mismatched cardiac grafts and generated CD4+T regulatory cells.
Jin *et al.*[17] 2014	Case-control	Of 34 kinds of Japanese medicinal herbs studied in murine models, 12 prolonged allograft survival. The administration of Sairei-to (TJ-114) and Tokishakuyaku-san (TJ-23) allowed achieving allograft survival indefinitely (MST>100 days). Patients that received Seisinrensiin (TJ-111), Tokishigyakukagoshuyushokyoto (TJ-38), Rikkunshito (TJ-43), Maobushisaishinto (TJ-127), Ninjin-yoei-to (TJ-108), Ryokan-kyomi-shinge-nin-to (TJ-119), Inchingorei-san (TJ-117), Hochuekkito (TJ-41), Kihi-to (TJ-65) and Sinbu-to (TJ-30) also obtained prolonged survival times (MSTs of 28, 22, 16, 14, 14, 13, 12, 9.5, 9 and 9 days, respectively).
Ilan *et al.*[18] 2010	Case-control	Oral OKT3 antibody enhances T-cell proliferation, suppresses Th1 and Th17 lymphocyte response, and increases TGF-β and IL-10 factors expression. Accordingly, oral OKT3 antibody offers a new mechanism for the treatment of autoimmune diseases.
Ilan *et al.*[19] 2000	Case-control	Chronic graft-versus-host disease (cGVHD) is a serious complication after bone marrow transplant. Murine models that received bone marrow transplants and were previously sensitized with donor splenocytes by mouth showed improved signs of cGVHD.
Taur *et al.*[20] 2012	Case-control	After stem cell transplantation, intestinal microbiota changes and there is an increased risk of developing bacteremia. After allogeneic hematopoietic stem cell transplantation, the diversity and stability of the intestinal flora is disturbed, resulting in the proliferation of bacteria associated with the subsequent development of bacteremia. The evaluation of fecal microbiota allows identifying the patients at greater risk of bloodstream infection after transplantation.
Tawara *et al.*[21] 2013	Case-control	After analyzing the effect of donor microbiota on the severity of GVHD induced by T cells from germ-free and pathogen-free donors in murine models, it was found that donor microbiota does not alter the expansion and differentiation of alloreactive T cells nor the severity of the disease.
Stonc *et al.*[22] 1990	Case-control	Administration of 16,16-dimethyl prostaglandin E_2 ($DMPGE_2$), a stable prostaglandin E_2 analogue, significantly prolonged survival time of heterotopic cardiac grafts from ACI to LBN rats. It is concluded that $DMPGE_2$ suppresses solid-organ graft rejection, inhibits allogeneic mixed lymphocyte response, and induces donor-specific in vitro hyporesponsiveness.

Treg: regulatory T-cells; HLA: human leukocyte antigen; IL: interleukin; APC: antigen-presenting cells; MST: median survival time; TGF-β: Transforming Growth Factor Beta.
Source: Own elaboration.

Oral tolerance

The adaptive immune system is found in vertebrate organisms and is composed mainly of antibody-secreting cells (B cells) and specialized T cells (which have distinct functions in immune response) and can eliminate pathogens and generate tolerance to antigens. Antigens are useful for avoiding attacks against the body's own cells and preventing excessive responses against external antigens.[23]

Oral tolerance is defined as the suppression of the immune response to antigens that have been previously administered orally.[1] This is a form of peripheral tolerance in which attempts are made to treat external agents that come into contact with the body through the mouth as if they were internal components, thus

making them part of the individual.[3] In other words, it is a method to induce immune tolerance systemically.[24]

The term oral tolerance was first used in 1911 when Wells fed chicken egg proteins to guinea pigs and saw that they were resistant to anaphylaxis.[25] Although many researchers have tried to reproduce these results,[26] they have not succeeded because tolerance is an active immune event that involves multiple factors such as the dosage of the antigen, the human microbiota, and the co-stimulation of these components.[3]

Mechanisms of action of oral tolerance

When given orally, an antigen is initially found in gut-associated lymphoid tissue (GALT), which is the largest immune organ in the human body.[27] The function of this system is the ingestion and recognition of dietary antigens to avoid unwanted immune responses and protect the body against pathogens,[3] thus allowing for a tolerogenic environment.[28] GALT comprises epithelial cells, intraepithelial lymphocytes and lamina propria lymphocytes in the form of lymphoid nodes (known as Peyer's patches) located in in the lowest portion of the small intestine and in the mesenteric lymph nodes (Figure 2).

Another important part of GALT is intraepithelial lymphocytes, which regulate intestinal homeostasis, maintain barrier function, respond to infection, and modify the adaptive and innate immune response. The most important intraepithelial lymphocytes are CD8+T cells.[3]

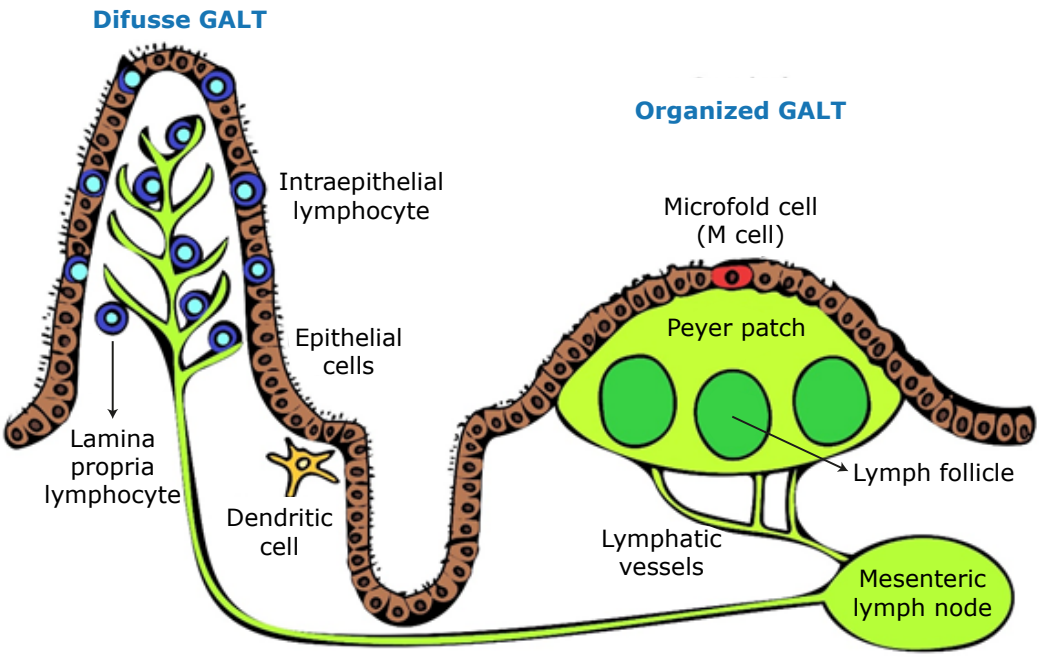

Figure 2. Gut-associated lymphoid tissue system. Source: Own elaboration.

To induce a mucosal immune response, the antigen must gain access to antigen-presenting cells (APCs) by penetrating the mucus layer and the epithelial cell barrier. These antigens are transported through mechanisms, most commonly M cells associated with Peyer's patches,[29] which internalize antigenic proteins through phagocytosis and endocytosis, taking them to the extracellular space where they are processed and presented by lymphocytes and macrophages.[30] Other mechanisms used by antigens to access APCs is dendritic cell extension into the intestinal lumen[31] and through enterocytes (located in Peyer's patches), which capture soluble antigens, processing them and presenting them to the effector cells.[4]

The induction of the immune response occurs after processing the antigen captured in the intestinal lumen. To this end, APCs express the antigen through molecules of the major histocompatibility complex, allowing T lymphocytes to recognize it. In addition, depending on the microenvironment, T-lymphocytes can be classified as regulators or effectors; the former are responsible for oral tolerance, while the latter are involved in cytolytic activity[32] (Figure 3).

Role of enterocytes

Enterocytes play a key role in immune tolerance because, besides being a mechanical barrier against foreign substances, they react intelligently to the heavy antigenic load of the gastrointestinal mucosa.[5] This type of cell has specialized receptors that recognize pathogens such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs), which are sensors of molecular patterns of bacteria and stimulate the inflammatory mechanisms that activate the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB).[33]

With respect to the maintenance of immune tolerance, enterocytes express a limited variety of TLRs (subtype TLR-2) in their apical region,[5] which activate the 3-phosphokinase pathway when stimulated with peptidoglycans, which in turn stimulates a negative regulation of NF-kB.[34,35]

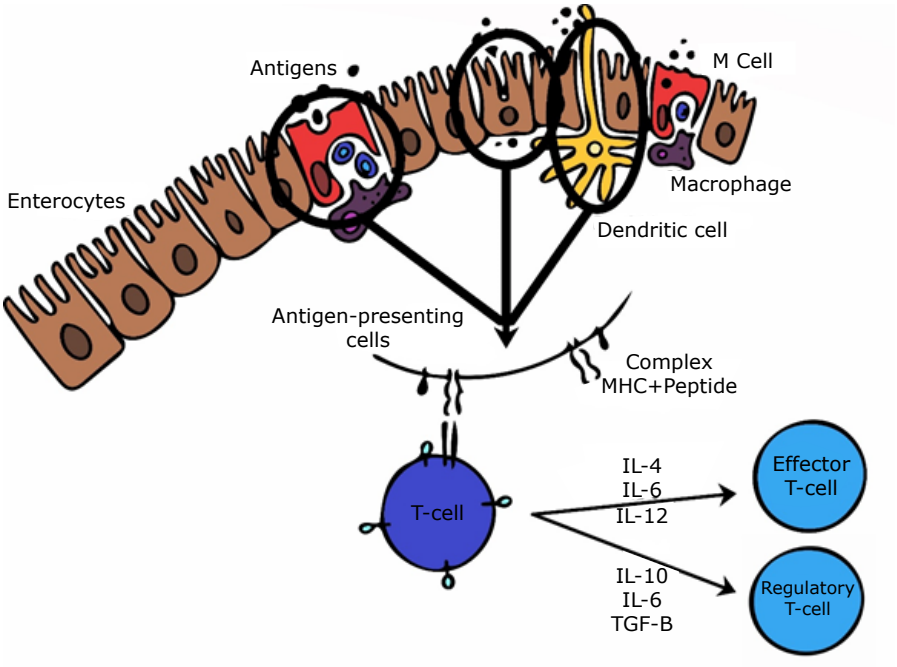

Figure 3. Antigen presentation and cell selection.
ACP: Antigen-Presenting Cell; MHC: Major Histompatibility Complex; IL: Interleukins; TGF-β: Transforming Growth Factor Beta; TL: T Limphocyte or T Cell.
Source: Own elaboration.

Enterocytes have two main proinflammatory cascades, one mediated by NF-kB, as mentioned above, and the other by p38, a mitogen-activated protein kinase. The inhibition exerted by both pro-inflammatory cascades on the enterocytes is the mechanism that maintains immune tolerance in the intestine. This way, NF-Kb activation produces the downregulation of p38 because the former induces the activation of a protein phosphatase kinase-1 (MKP-1) that dephosphorylates the latter[36] and promotes tolerance by inhibiting one of the major pro-inflammatory cascades.

Basic mechanisms of immune tolerance

Immune tolerance is defined as the absence of a specific response against specific actively acquired antigens. Tolerance mechanisms occur via T cells and B cells and can be established centrally (central tolerance) during cell genesis and differentiation, and peripherally (peripheral tolerance) on already differentiated adult cells:[6,7]

T-cells

Central tolerance. During the embryonic stage and neonatal period, immature cells migrate from the bone marrow to the thymus to express receptors that recognize peptides of the major histocompatibility complex. T cells that recognize these complexes with high avidity survive; this process is known as positive selection.[37] In contrast, T cells that weakly recognize such complexes die, and this is known as negative selection,[38] which is the main mechanism for regulating self-tolerance;[39] the surviving T-cells migrate to secondary lymphoid organs.[6] An additional mechanism of immune tolerance is the modification of the T cell receptor to allow it to bind to interleukine-7 (IL-7)-like cytokines, which induces the formation of regulatory T cells (Treg) or lymphocytes.[8]

Peripheral tolerance. Mechanisms of peripheral tolerance include: anergy, immunological ignorance, clonal deletion, active suppression and Treg cells.

1. Anergy: It occurs when, despite the existence of the first signal (CD3) to trigger T-lymphocyte response — in other words, the recognition of the MHC+ peptide junction—, there is no second signal (co-stimulation), which causes no response from the T-lymphocytes.[8]
2. Immunological ignorance: It occurs in the absence of T-cell activation due to low concentrations of the antigen, which does not induce the first signal.[40]
3. Clonal deletion: It refers to lymphocyte apoptosis by caspase activation.[41]
4. Activa suppression: Cell activity is suppressed through the secretion of inhibitory cytokines such as transforming growth factor B (TGF-β) and interleukin 10 (IL-10) by Treg cells.[8]
5. Treg cells: They are dominantly responsible for controlling the immune response.[9]

B cells

Central tolerance. B cells are formed, expressed, and matured in the bone marrow; however, they can be highly avid (leading to clonal deletion) or moderately avid (leading to receptor editing) due to autoantigens.[42]

Peripheral tolerance. Surviving B cells migrate to the periphery and those that are highly avid for autoantigens are eliminated through the intrinsic apoptosis pathway. Low-affinity B cells enter into partial anergy because if they are exposed to high doses of the antigen, they can be re-recruited.[43] It should be noted that

the dose of antigen taken orally is a fundamental determinant of the immune response: low doses induce tolerance via Treg lymphocytes, while high doses induce anergy or clonal deletion.[25,44,45]

One of the best ways to understand oral tolerance is the identification of the role of dendritic cells, retinoic acid and CD103+ lymphocyte differentiation cluster in their induction.[3] The expansion of dendritic cells in vivo improves oral tolerance, since they induce the expression of Treg FOXP3+ cells when found in the mucosa by means of TGF-β and retinoic acid signaling pathways.[3] Dendritic cells in the mucosa can be divided into two types: CD103+ (tolerogenic) and CD103- (non-tolerogenic). Tolerogenic cells produce retinoic acid and induce FOXP3+ Treg cells if given TGF-β.[12,46]

There are other innate immune cells that are relevant for oral tolerance. On the one hand, macrophages are found in the lamina propia of the intestine and produce IL-10. On the other hand, dendritic cells are found in the gut; they produce β-catenin, which stimulates the production of retinoic acid, IL-10 and TGF-β; trigger the proliferation of Treg cells; and inhibit the response of effector T cells.[3]

The importance of the tolerance mechanisms in the intestinal mucosa described above lies in understanding that regulatory lymphocytes do not travel from other lymphatic organs to the site of response, but that oral antigens induce the formation of Treg cells.

When dendritic cells recognize antigens in the gastrointestinal tract, the inflammatory response is triggered, resulting in up to 80% anergy and deletion for each antigen. This is known as primary response and its effector organ is the liver; the secondary immune response occurs in the mesenteric nodules with the presentation of antigens by the tolerogenic dendritic cells.[10]

Role of Treg cells in oral tolerance

Treg cells are the most widely studied cells in relation to oral tolerance induction.[11,47] Currently, operational tolerance after transplantation, which is understood as the long-term survival of a graft in the absence of maintenance immunosuppressive therapy,[13,48] is mediated by an antigen-specific response caused by FOXP3 expressing CD4+ CD25(high) regulatory T cells. These cells control the immune response against the donor's alloantigens.[49]

Of all Treg cells, the most relevant for transplantation are CD4+ CD25+ regulatory T cells[22] and FOXP3+ transcription factor expressing cells.[50] The introduction of this transcription factor into CD4+ CD25+ T cells gives them the ability to suppress and amplify the transcription of specific regulation genes.[49]

Type 3 and 4 immunoglobulin transcriptase enzymes favor the induction of co-stimulatory molecules in CD4+ CD25+ Treg cells. This makes the latter tolerant to donor antigens by stimulating CD4+ T cells and natural killer cells, which produce positive feedback on CD4+ CD25+ Treg cells to express the FOXP3 protein. As a result of this expression, an antigenic microchimerism is formed, and it allows immune tolerance and prevents rejection of the transplanted organ (Figure 4).[51]

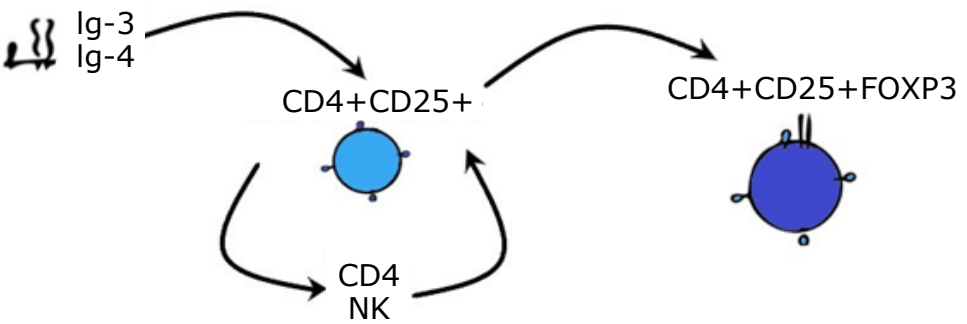

Figure 4. Antigenic microchimerism.
Ig: immunoglobulin; CD: cluster of differentiation; NK: natural killer cell; FOXP3: forkhead box P3.
Source: Own elaboration.

The main advantage of immune tolerance is its specificity since it maintains the immune response against neoplasms and microorganisms. However, there is a decreased response to alloantigens in the transplanted organ.[49]

It is known today that the administration of oral antigens induces the production of Treg cells, particularly, induced CD4+ CD25+ FOXP3+ Treg cells, natural CD25+ FOXP3+ Treg cells, Tr1 and CD8+ cells.[3] Regarding these subclasses, Tr1 cells act through cell contact, unlike the others, which do so through suppressive cytokines such as IL-10 and TGF-β. Tr1 cells suppress the response of virgin T cells, the expression of co-stimulatory cells, and the secretion of pro-inflammatory cytokines by APCs (Figure 5).[49]

Because Treg cells are known to mediate tolerance induction and maintenance of their effect over time, researchers such as Scalea *et al.*[11] state that adoptive transfer of this type of receptor-derived cells may lead to stable graft tolerance.

During solid organ transplantation, the immune system generates a response that is attributed to rejection, which is mediated by antibodies, T cells or vascular disturbances; in this response, antibody rejection is the worst prognosis.[52,53]

Immunosuppressive drugs used in transplants produce a large number of side effects,[54] including nephrotoxicity, malignancy, hypertension, diabetes and infections. Cytomegalovirus infection is one of the most common.[55-57]

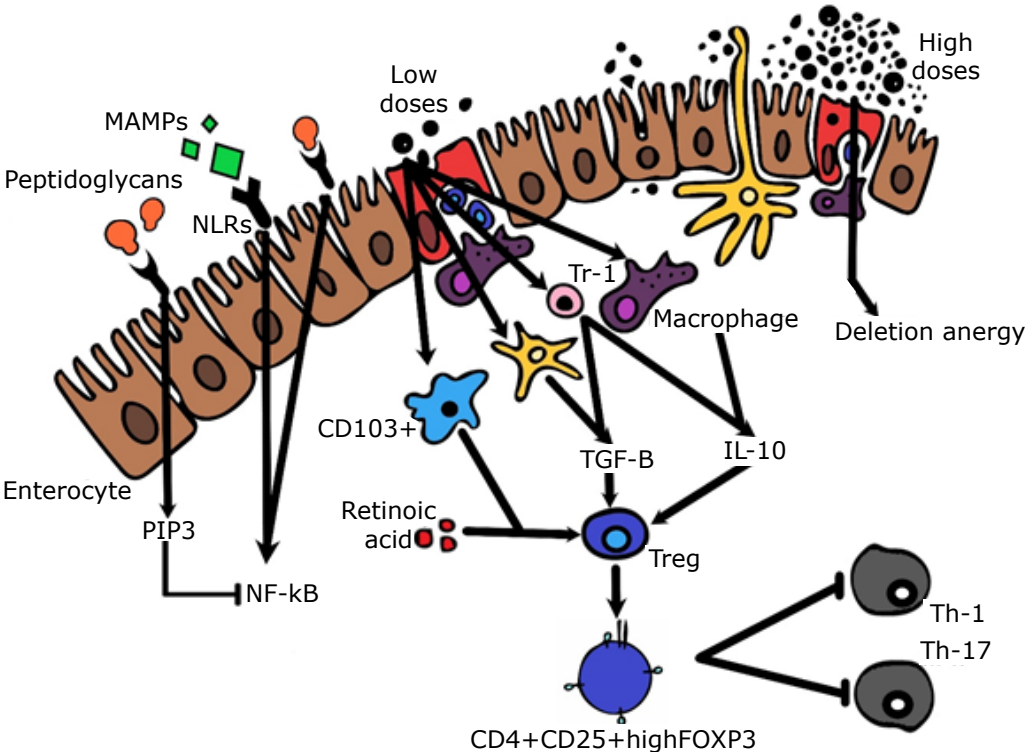

Figure 5. Mechanisms of immunological tolerance.
CD: cluster of differentiation; TGF-β: transforming growth factor-beta; IL: interleukin; Treg: regulatory T lymphocyte; Th: helper T lymphocyte; MAMPs: microorganism associated molecular pattern; TLR: Toll-like receptor; FOXP3: fork-head box P3; PIP3: phosphatidylinositol 3-phosphate; NF-Kb: nuclear factor kappa-light-chain-enhancer of activated B cells; NLRs: NOD-like receptors.
Source: Own elaboration.

Studies and usefulness in transplants

In Colombia, the first kidney transplant was performed at the Hospital San Juan de Dios in Bogotá in 1963.[58] Since then, transplantation surgeries and the amount of places where these procedures are performed have increased, and today there are about 25 hospitals authorized to perform solid organ transplantations in the country.[59] Nevertheless, several obstacles must be faced to achieve successful transplants, for example, graft rejection due to lack of immunological tolerance.

As described above, one of the methods for achieving immunological tolerance is the oral route since the intake of alloantigens or soluble human leukocyte antigen from the donor allows the immune system to make an initial recognition through the APCs and the major histocompatibility complex in the gastrointestinal tract. This way, when the transplant is done, the recipient's immune system will not trigger a rejection response, as tolerance to the donor's antigens will already have been generated.

One of the most promising results in induction of immune tolerance to a transplanted graft was found in a study by Kelman *et al.,*[14] which describes what happens to the immune system during pregnancy. These authors state that there is tolerance between the molecules of the human leukocyte antigen system of the fetus and the immune system of the mother and report a correlation between oral sex and swallowing sperm and a lower incidence of preeclampsia. Said results allow us to presume that the oral route is a useful mechanism to induce tolerance.

Most of the evidence found comes from murine models with heart, kidney, cornea, and bone marrow transplants, as shown in Table 2.

Probiotics, herbal medicine, COX-2 inhibitors, monoclonal antibodies and CD4 lymphocytes from the donor are some of the antigens that have been used to induce immunological tolerance.

Table 2. Studies of oral tolerance induction and their results.

Sample	Trasplanted organ	Intervention	Results	Findings	Ref.
Murine	Cornea	Corneal epithelial cells (2x10^6 cells/dose)	Not reported	Increase in IL-10 and decrease in IL-2 and IFN-y	[60]
		Corneal and splenic epithelial cells (2x10^6 cells/mL)	20 days	Not reported	

Table 2. Studies of oral tolerance induction and their results. (Continued)

Sample	Trasplanted organ	Intervention	Results	Findings	Ref.
Murine	Heart	Control *	13 days	Not reported	61
		Sairei-to (TJ114) (2 g/kg/day)	>30 days		
Murine	Heart	Control *	7 days	Not reported	15
		Tsumura Japan (TJ-35) (2 g/kg/day) + Licorice	18 days		
		Tsumura Japan (TJ-35) (2 g/kg/day)	20.5 days	Increase in CD4-CD25 FoxP3	
		Splenic cells sensitized with Tsumura Japan (TJ-35)	63 days		
Murine	Bone marrow	Splenic cells + *Lactococcus lactis*	Not reported	Increase in FoxP3	62
Murine	Bone marrow	Ciprofloxacin (50 mg/kg)	77 days	Decrease in inflammation and markers in the liver and intestine in 40% of the patients who received Ciprofloxacin and in 70% of those who received *Lactobacillus rhamnosus*	63
		Lactobacillus rhamnosus	77 days		
Murine	Heart	Control *	8 days	Increase in IL-4	16
		COX-2 inhibitor (20 mg/kg)	11 days	Increase in IL-10	
		Sensitized spleen tissue (20 mg/kg)	>100 days	Increase in IL-4 e IL-10	
		Sensitized spleen tissue (2 mg/kg)	18 days	Increase in Treg cells	
		Sensitized spleen tissue (0.2 mg/kg)	0 days	Not reported	
Murine	Heart	Tokishakuyaku-san (TJ-23) (2 g/kg)	>100 days	Not reported	64
		Tokishakuyaku-san (TJ-23) (0.2 g/kg)	27 days		
		Tokishakuyaku-san (TJ-23) (0.02 g/kg)	8 days		
Murine	Heart	Inchingorei-san (TJ-117) (0.5 g/kg/day)	16 days	Increase in CD4, CD25 and Foxp3	17
		Inchingorei-san (TJ-117) (1 g/kg/day)	>100 days		
		Inchingorei-san (TJ-117) (2 g/kg/day)	12 days		
Humans	NA	Anti-CD3 (0.2 mg)	Not reported	Increase in TGF-β	18
		Anti-CD3 (1 mg)		Increase in IL-10	
		Anti-CD3 (5 mg)			
		Anti-CD3 (0.2 mg) + b-glucosylceramide (7.5 mg)		43% TH1 lymphocyte suppression	
		Anti CD3 (1 mg) + b-glucosylceramide (7.5mg)		41% TH17 lymphocyte suppression	
Murine	Heart	Sairei-to (TJ114) (2 g/kg/day)	>100days	Leukocyte infiltrates and mild obliterative vasculopathy	65
		Sairei-to (TJ114) (0.2 g/kg)	41 days		
		Sairei-to (TJ114) (0.02 g/kg)	7 days	Not reported	
		Sairei-to (TJ114) (0.002 g/kg)	7 days		
		Distilled water	7 days		
		Splenic cells sensitized with Sairei-to (TJ114) (2 g/kg)	>100 days	Leukocyte infiltrates and mild obliterative vasculopathy	
		Control *	7 days	Not reported	
Murine	Spleen	Splenic cells (50 mcg)	Not reported	Increase in IL- 10	19
		Splenic cells ($1.9x10^6$ cells/dose/day)	18 days	Decrease in IFN	
Murine	Cornea	Corneal epithelium	20 days	Decrease in IL-4 and increase in IL-10	66
		Corneal epithelium + endothelial cells	18 days	Increase in TGF-β	
Murine	Kidney	Splenic cells ($1x10^8$ cells/ 300 mcL)	46 days	Increase in CD4 and CD8	67

Table 2. Studies of oral tolerance induction and their results. (Continued)

Sample	Trasplanted organ	Intervention	Results	Findings	Ref.
Murine	Kidney	Splenic cells infused into the portal vein	33.6 days	Not reported	68
		Control *	8 days		
Murine	Heart	Splenic cells single dose (1x10^7 cells)	13 days	Not reported	69,70
		Splenic cells multiple dose (1x10^7 cells)	20 days		
		Anti-CD4 monoclonal antibody (200 mcg/ dose) + Splenic cells	18 days		
		Anti-CD4 monoclonal antibody (15 days before) + Splenic cells	26 days		
		Anti-CD8 monoclonal antibody (200 mcg/dose)	100 days		
		CD8 Antibody (200 mcg/dose) + Splenic cells	52 days		
Murine	Skin	Anti-CD4 monoclonal antibody (200 mcg/ dose) + Splenic cells (1x10^7 cells/ dose)	62 days	Not reported	71
		Anti-CD4 monoclonal antibody (200 mcg/ dose)	18 days		
		Splenic cells	19 days		
		Control *	12 days		

IL: interleukin; COX: cyclooxygenase; Treg: regulatory T lymphocyte; CD: cluster of differentiation; FOXP3: forkhead box P3; NA: not applicable; IFN: interferon; TGF-β: transforming growth factor-beta; TH: helper T lymphocyte.
* No intervention.
Source: Own elaboration.

The use of probiotics in transplant recipients was considered an alternative when changes in the microbiota were evident in the subjects (humans and mice) that rejected the graft. In this regard, Finney *et al.*[72] found increased *Bacteroides* and *Ruminococcus* colonies in specimens that rejected liver transplantation in murine models; in contrast, Taur *et al.*[20] observed decreased *Bacteroides* colonies in human models that presented acute rejection to kidney transplantation. Therefore, the use of probiotics has been proposed as a way to modify the microbiota and the immune system, not only at a local level but also at a systemic level.[2,21]

Probiotics have demonstrated good survival rates after bone-marrow transplantation in murine models because its administration stimulates both anti-inflammatory and pro-inflammatory signals.[62] These microorganisms are responsible for maintaining the integrity of the epithelial barrier of the gastrointestinal tract by stimulating immunoglobulin A and the secretion of mucus and defensins, and by altering the adhesion of bacteria to the epithelium.

In 2004, Gerbitz *et al.*[63] found that the administration of *Lactobacillus rhamnosus* before transplantation improved long-term survival and reduced rejection associated with decreased CD3 levels.

The COX enzyme is responsible for prostaglandin secretion, which has two isoforms: COX-1, a constitutive enzyme, and COX-2, induced by the action of cytokines and tumor promoters. In 1990, Stonc *et al.*[22] proved that the use of COX-2 inhibitors prolongs the survival time of cardiac grafts in mice, and in 2005, Yokayama *et al.*[16] noted that its use prolongs transplant survival beyond 100 days versus 11 days in the control group.

Given their immune system modulating characteristics, medicinal plants are another type of antigen used throughout history to sensitize the donor to transplants.[64] For example, in Asia, these plants have been used as alternative therapy for different diseases in humans for more than 3 000 years; in the case of transplants, it has been reported that their use in murines with heart transplants increases the survival time of the graft.[17]

Medicinal plants have been studied at the molecular level, finding that they are made up of multiple components. For example, the administration of Tokishakuyaku-san, also known as Tsumura TJ-23, at a minimum dose of 2 g/kg in murine models has yielded good results in terms of cardiac graft survival.[64]

Oral tolerance induction studies in humans also include the use of anti-CD3 monoclonal antibodies (OKT3). Its immunological effects in peripheral blood were the suppression of Th1 and Th17 lymphocyte response, increased expression of Treg cell markers, increased TGF-β/IL-10 and decreased expression of IL-23/IL-6 in dendritic cells without side effects.[18] Likewise, studies in mice have shown how the intake of CD4 lymphocytes from the donor decreases the induction of pro-inflammatory cascades and increases IL-10 levels in cases of spleen transplantation.[19,65-67]

Finally, combined therapy of CD4 lymphocytes and anti-CD3 orally demonstrated promising results in kidney and heart transplantation in murine models by prolonging the survival of the grafts by more than 100 days.[68,69,71] None of the interventions described above have been studied in humans, so despite having a physiological basis, these results cannot be extrapolated or presumed to be safe in a human context. However, the use of oral immunological tolerance induction strategies opens a door to the study of new practices to treat chronic diseases and manage side effects of immunosuppressive drugs, immune transplant rejection, autoimmune diseases, among others, which may generate high-quality evidence to create novel strategies in the field.

Conclusions

There are many immunological mechanisms that underlie transplantation tolerance. The oral route is an alternative for inducing tolerance in transplant patients, since it eliminates the adverse effects that current immunosuppressive therapy entails.

Although it is possible to demonstrate the viability of oral tolerance for immunological induction and its possible usefulness in the transplant field, it should be noted that, according to the literature, there are no human clinical trials to ensure that oral immunological tolerance induction strategies are safe. Therefore, there is no high-quality evidence to infer that these strategies are safe in humans.

Conflicts of interest

None stated by the authors.

Funding

None stated by the authors.

Acknowledgements

None stated by the authors.

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rfm
Revista *de la* Facultad *de* Medicina

CASE REPORT
DOI: http://dx.doi.org/10.15446/revfacmed.v68n1.71380
Received: 01/04/2018 **Accepted:** 07/06/2018

Bulluos Henoch-Schönlein Purpura in pediatrics. Case report

Púrpura Henoch-Schönlein bullosa en pediatría. Reporte de caso

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Abstract

Introduction: Henoch Schönlein purpura (HSP) is the most common type of vasculitis in childhood. HSP affects small blood vessels, and it rarely leads to serious complications such as bullous small vessel vasculitis, as it occurred in the case presented here.
Case presentation: 5-year-old male who was brought to a primary healthcare center due to having arthralgia and purple skin lesions on his lower limbs. After the patient was diagnosed with HSP, he developed bullous lesions, so he was hospitalized and analgesic and topical management was started. During his hospital stay, the patient's renal function was monitored, and since he did not experience other complications, he was discharged.
Conclusion: The available literature on HSP suggests that its cutaneous bullous manifestation rarely occurs in pediatric population and that, unlike normal HSP cases, it is not always associated with renal and/or gastrointestinal involvement. However, regardless of the dermatological severity of this type of vasculitis, the function of the gastrointestinal and renal systems must be always monitored in these patients.
Keywords: Purpura; Purpura, Schoenlein-Henoch; Vasculitis; Immunoglobulin A; Blister (MeSH).

Quimbayo-Romero AI, Camargo-Rodríguez KJ, Lozano-Triana CJ, Landínez-Millán G. Bulluos Henoch-Schönlein Purpura in pediatrics. Case report. Rev. Fac. Med. 2020;68(1):143-7. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.71380.

Resumen

Introducción. La púrpura Henoch-Schönlein (PHS) es la forma más común de vasculitis en la infancia; esta se da en pequeños vasos sanguíneos y no es frecuente que genere complicaciones graves como la vasculitis bullosa, tal como sucedió en el caso que se presenta a continuación.
Presentación del caso. Paciente masculino de cinco años que fue traído a un centro de atención primaria con un cuadro clínico consistente en artralgias y aparición de lesiones purpúricas en miembros inferiores. Luego de ser diagnosticado con PHS, presentó lesiones bullosas, por lo que fue hospitalizado y se inició manejo analgésico y tópico; durante su estadía en el hospital se vigiló su función renal y, ya que no presentó otras complicaciones, se dio de alta.
Conclusión. Las publicaciones disponibles sobre PHS sugieren que su presentación cutánea bullosa en pediatría no es frecuente y que no siempre se relaciona con un compromiso renal y/o gastrointestinal como la variante clásica; sin embargo, siempre debe vigilarse la función de estos sistemas sin importar la gravedad dérmica de esta vasculitis.
Palabras clave: Púrpura; Púrpura de Schoenlein-Henoch; Vasculitis; Inmunoglobulina A; Ampolla (DeCS).

Quimbayo-Romero AI, Camargo-Rodríguez KJ, Lozano-Triana CJ, Landínez-Millán G. [Púrpura Henoch-Schönlein bullosa en pediatría. Reporte de caso]. Rev. Fac. Med. 2020;68(1):143-7. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.71380.

Introduction

Henoch-Schönlein purpura (HSP) is the most common form of vasculitis in childhood. It is an immunoglobulin A (IgA)-mediated disorder characterized by palpable small-vessel vasculitis. About 90% of HSP cases occur during the first 10 years of life, and the most common age range is 3-5 years.[1,2] Lesions are usually observed on the lower limbs and sometimes on the upper limbs, face and chest. Moreover, most patients have petechial or purpuric lesions or a combination of both; also, some individuals have bull's eye lesions consisting of concentric rings surrounded by pale and hemorrhagic rings.

The most common gastrointestinal symptoms in HSP are abdominal pain, vomiting, diarrhea, and paralytic ileus. However, non-erosive arthritis can also occur without permanent deformity in the ankles, knees, and feet.[2] As for skin lesions, blisters are the least frequent and are found in about 5% of cases: Saulsbury[3] found 2 patients with hemorrhagic bullous lesions in a series of 100 patients.

This case report describes an atypical presentation of a skin condition in a patient treated at a tertiary pediatric hospital in Bogotá D.C., Colombia.

Case presentation

A five-year-old male patient, with a history of bronchiolitis and pneumonia, was taken by his parents to a primary care center due to arthralgia in hands, feet, and knees associated with the appearance of painful and erythematous lesions in the skin of the lower limbs; these symptoms appeared three days before consultation. The child was diagnosed with HSP. Laboratory tests were performed, including urinalysis, renal function, and urinary tract ultrasound, all of which were normal and therefore treated on an outpatient basis.

Two days after discharge, the parents took the child once again to the medical center due to a complication of his symptoms, so he was referred to a tertiary care center. The skin lesions turned into multiple phlyctenae containing translucent blood-like fluid, with variable sizes and located exclusively in the lower limbs. The physical examination revealed stable vital signs and grade 2 edema in the lower limbs accompanied by multiple palpable purpuric lesions extending to the buttocks; in addition, some of these lesions appeared in isolation in the upper limbs. Many of the skin lesions joined together and formed phlyctenae with serohematic fluid (Figure 1), mainly in the feet and legs, which generated pain on palpation and as a result of mobilization of the lower limb joints.

After the physical examination, the diagnosis of HSP was reconfirmed, and the patient was hospitalized given his symptoms, mainly a severe skin condition; laboratory tests were performed, and intravenous analgesia with opioids was adjusted. The tests (Table 1) revealed low-grade proteinuria with a urine protein/creatinine ratio of 0.43, urea nitrogen of 25.8 mg/dL, and creatinine of 0.45 mg/dL, showing a BUN/creatinine ratio of 57.3. Acute kidney injury in pregnancy secondary to dehydration was considered, so intravenous fluids were adjusted, and kidney function tests and abdominal ultrasound were requested.

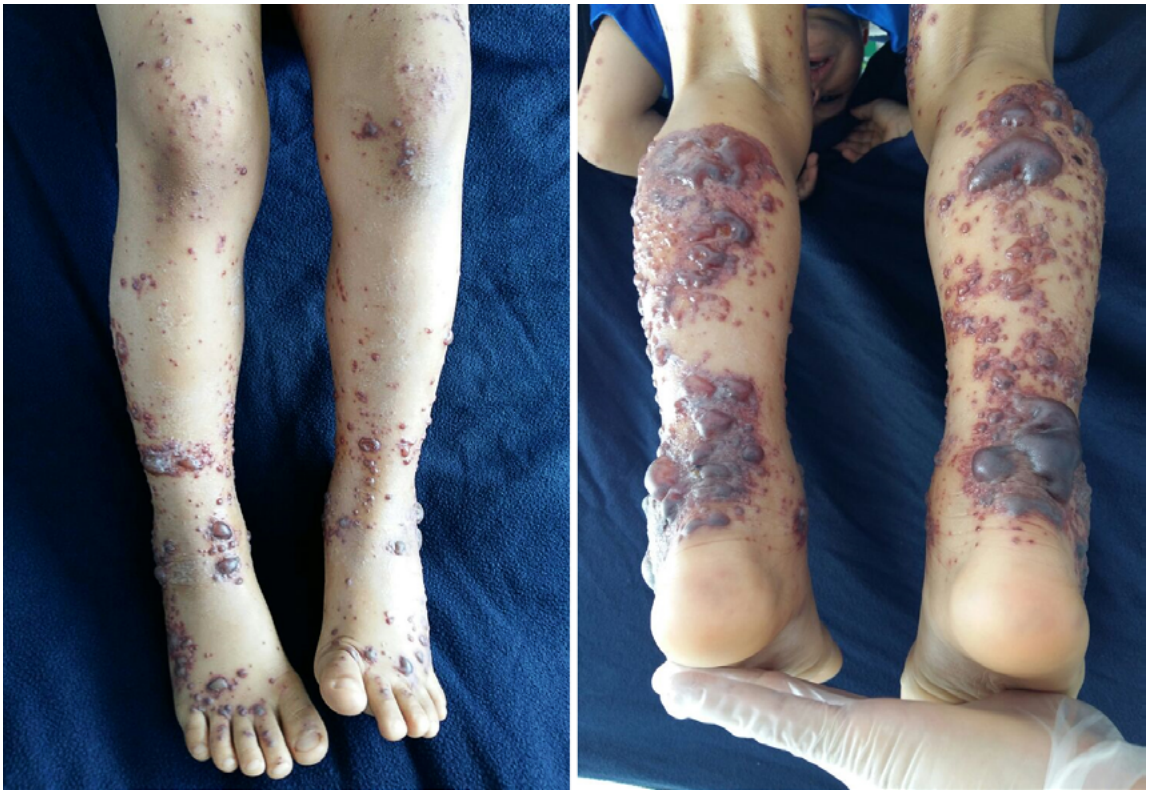

Figure 1. Purpuric lesions and phlyctenae on the lower limbs.
Source: Document obtained during the study.

Table 1. Lab test results.

Test \ Date	13/04/2016	15/04/2016	19/04/2016	20/04/2016	22/04/2016	23/04/2016	25/04/2016
Creatinine (mg/dL)	0.44		0.45	0.44		0.45	0.28
BUN (mg/dL)	11.4		25.8	8.7		12.6	
Albumin (g/dL)	4.2						
Isolated creatinine in urine (mg/dL)			124.4				
Isolated proteinuria (mg/dL)			54.7				
Blood count							
Leucocytes (/mm^3)				12 870	10 600		
Neutrophils				55%	57%		
Lymphocytes				33%	31%		
Hemoglobin (g/dL)				12.2	11.8		
Hematocrit				35.80%	35.10%		
Platelet (/mm^3)				384 000	518 000		
PT/control (seconds)					15/14.4		
PTT/control (seconds)					26.4/29.4		
INR					1.04		
IgA (mg/dL)							355
C3 (mg/dL)							162
C4 (mg/dL)							24
Partial urine test		Density: 1 010, pH: 8, negative proteins, sediment: epithelial cells 0-2 per FoV, leukocytes 0-2 per Fov			Density: 1 020, pH: 6, sediment: leukocytes 2-5 per FoV, red blood cells 0-2 per FoV, scarce bacteria, mucus +++		
Abdominal ultrasound		No obvious alterations					

BUN: blood urea nitrogen; PT: prothrombin time; PTT: thromboplastin time; INR: international normalized ratio; IgA: immunoglobulin A; C3: complement component 3; C4: complement component 4; FoV: field of view of microscope. Source: Own elaboration.

Kidney function test, glomerular filtration rate, kidney ultrasound, complement test, and coagulation times were normal during hospitalization; only a discrete elevation in IgA levels was found. The patient was assessed by the plastic surgery and dermatology services, which agreed with the HSP diagnosis. Given the large skin involvement, a skin biopsy was performed, finding neutrophilic intradermal vesicles that involved the dermis; immunofluorescence was not reported in the pathology results.

The patient recovered satisfactorily and received support treatment with a vaseline gauze dressing over the bullous lesions, analgesia, and intravenous hydration for the pain. Subsequent kidney function tests were normal, so he was discharged.

Discussion

Among systemic vasculitides, HSP is the most frequent in the pediatric age, but its diagnosis is questioned when the clinical presentation does not match the classic expression of the disease.[1,2,4] HSP is an IgA-mediated systemic small blood vessel vasculitis and may result from a response of immune complexes to various antigenic stimuli in susceptible individuals.[1]

The most common symptoms of HSP are purpura, arthritis, abdominal pain, gastrointestinal bleeding, and nephritis;[2] only 2% of patients develop bullous hemorrhagic lesions.[1]

According to González *et al.*,[5] the incidence of this pathology is 135 cases per million inhabitants in the population under 14 years of age, being 100 times lower in adults.[5] In turn, Rabelo *et al.*[6] reported an annual incidence that ranges from 13.5 to 18 cases per 100 000 inhabitants for the year 2000 in Brazil.

The etiology of HSP is not clear, but some association has been found with a history of group A beta-hemolytic streptococcal infections, *Salmonella spp, Bartonella spp, Yersinia* or *Mycoplasma spp.* Other germs related to this disease are the hepatitis B virus, human immunodeficiency virus, Epstein-Barr virus, Coxsackie virus, chickenpox virus, and adenovirus. The onset of HSP has also been associated with the use of some antibiotics such as penicillin or macrolides, or angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and non-steroidal anti-inflammatory drugs.[3,7]

HSP is a leukocytoclastic vasculitis that sometimes presents with increased IgA levels; it may be caused by microorganisms that share an antigenic determinant with small-caliber blood vessel endothelial cells. In this sense, after pathogen invasion, the antigen-specific IgA antibodies cross-react with the antigens of some pathogens and are deposited in the endothelial cells, mainly in the skin and kidney, although they can also be deposited in the joints and the intestine, causing the symptoms and signs of the disease. However, this is only a theory, since no association has yet been found between a specific antigen and the development of HSP.

Another hypothesis that could explain the presence of HSP is related to the alteration of oligosaccharide glycosylation in the hinge region of IgA1, which generates abnormal IgA1 levels that are not completely catabolized in the liver and are deposited in various tissues, such as in the kidney mesangium. After this process, the complement system is activated alternately, generating damages in the endothelial lining; at this point, an increase in IgA and C3 complement in the endothelial cells of the skin and kidney mesangium is evident.

The clinical signs of HSP occur in the organs where the largest deposits of immunoglobulin are found. Therefore, four main clinical manifestations have been established: 1) *Purpuric skin lesions*, which are palpable and predominantly present in the lower limbs but can be also be found in other body areas to a lesser extent;[1,8,9] 2) *arthralgia or arthritis*, which are generally oligoarticular (predominantly in the ankles, feet, knees, and hips and to a lesser extent in the upper limbs) and migratory; 3) *abdominal pain*, which may be related to gastrointestinal bleeding; and 4) *kidney impairment*, which may lead to acute kidney failure in severe cases.[3,10]

Given the presence of multiple etiological agents and non-specific prodromes, it is necessary to make a correct initial diagnosis of HSP, since kidney and gastrointestinal involvement may exist in 40% and 33% of cases, respectively, although most clinical presentations are found in the skin. It is worth noting that 2% of patients with skin lesions may develop bullous or blistering lesions without a clear trigger, as in the present case, in which the patient presented with typical lower limb HSP lesions that progressed to bullous lesions.

Despite the self-limiting course of the disease, significant sequelae and risk of short- and long-term complications can be observed, such as nephritis, kidney failure, massive gastrointestinal bleeding, and relapse.[3] Saulsbury[3] also reported alterations in some kidney function tests such as urine protein/creatinine and BUN/creatinine ratio, which, in this patient, were related to a prerenal problem caused by dehydration and not to a frank kidney injury, since the laboratory tests, once dehydration was corrected, were normal during hospital stay until discharge.

Since the bullous presentation of HSP is rare, it is essential to differentiate it from other types of vasculitis and other skin pathologies since their management is different, and the sequelae and complications may be severe. Based on this, in the present case, the diagnosis was confirmed by the dermatology service, which ruled out other possible differential diagnoses.

According to the experience and the literature reviewed by Chen *et al.*[8] and Liu *et al.*,[9] severe cutaneous presentations are associated with a very low probability of kidney or gastrointestinal involvement, as is the case reported here. Conversely, mild skin involvement can lead to significant kidney or gastrointestinal involvement, making a correct diagnosis necessary, as evidenced by Saulsbury[3] in his case series.

Conclusions

The available literature suggests that the cutaneous presentation of bullous HSP is rare in pediatrics and is not always related to kidney and/or gastrointestinal involvement, as is the case of the classic variant. However, the function of these systems should be monitored regardless of the severity of this vasculitis on the skin, as life-threatening complications could arise in the short or medium term. Therefore, outpatient follow-up should be performed in the first months after the diagnosis, requesting laboratory tests such as complete blood count, urinalysis, and kidney function and keeping adequate blood pressure, height, and weight levels to evaluate the evolution and status of the patient.

Ethical considerations

This case report was prepared with the informed consent of the patient's legal guardian.

Conflicts of interest

None stated by the authors.

Funding

None stated by the authors.

Acknowledgements

To the patient, his family, and the Fundación Hospital Pediátrico de la Misericordia, since writin this paper would not have been possible without their help.

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rfm
Revista *de la* Facultad *de* Medicina

CASE REPORT
DOI: http://dx.doi.org/10.15446/revfacmed.v68n1.72674
Received: 05/06/2018 **Accepted:** 10/09/2018

Precocious puberty due to congenital adrenal hyperplasia. Case report

Pubertad precoz por hiperplasia adrenal congénita. Reporte de caso

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Abstract

Introduction: Premature pubarche occurs in girls before the age of 8 or boys before the age of 9 and is a sign of precocious puberty associated with increased growth acceleration. Precocious puberty can be caused, among others, by nonclassic congenital adrenal hyperplasia (CAH).
Case presentation: This is a case of a 4 1/2-year-old who developed premature pubarche six months before consultation, and whose parents were first-degree cousins. She had advanced bone age, her external genitalia were normal and her height was inconsistent with her mid-parental height. After performing an adrenocorticotropic hormone test (ACTH test) and other hormone tests, it was found that she had high levels of 17-hydroxyprogesterone (17-OHP), which allowed diagnosing her with nonclassic CAH. Based on this diagnosis, glucorticoid therapy was ordered, and after one year of starting the treatment she had a favorable clinical outcome and did not show any secondary sex characteristics or bone age progression.
Conclusion: Nonclassic CAH is the most frequent cause of precocious puberty. Considering that this type of hyperplasia may be asymptomatic during the early days or years of life, its diagnosis must be suspected in children with precocious puberty, increased growth acceleration and advanced bone age.
Keywords: Puberty; Precocious Puberty; Adrenal Hyperplasia, Congenital; 17-alpha-Hydroxyprogesterone (MeSH).

Dallos-Lara MF, Mendoza-Rojas VC. Precocious puberty due to congenital adrenal hyperplasia. Case report. Rev. Fac. Med. 2020;68(1):148-52. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.72674.

Resumen

Introducción. La pubarca antes de los 8 años en niñas y de los 9 años en niños, es una manifestación de la pubertad precoz asociada al aumento en la velocidad de crecimiento. La hiperplasia adrenal congénita (HAC) no clásica es una de las causas de pubertad precoz.
Presentación de caso. Paciente femenina de 4 años y medio y con padres consanguíneos (primos hermanos) quien inició pubarca 6 meses antes de ser llevada a consulta. La niña presentaba edad ósea avanzada, talla discordante con la talla media parental y sus genitales externos eran normales. Luego de realizar el test de estimulación con hormona adrenocorticotropa y otros exámenes hormonales, se encontró que sus niveles de 17-hidroxiprogesterona eran elevados, lo que permitió diagnosticarla con HAC no clásica. Con base en este diagnóstico, se inició tratamiento con glucocorticoides y luego de un año de tratamiento la paciente tuvo una buena evolución clínica, ya que no se observó progresión de los caracteres sexuales secundarios ni de la edad ósea.
Conclusión. La HAC no clásica es la causa más frecuente de la PPP. Ya que este tipo de hiperplasia puede ser asintomática durante los primeros días o años de vida, se debe sospechar su diagnóstico en la infancia cuando haya pubarca precoz, mayor velocidad de crecimiento y edad ósea avanzada.
Palabras clave: Pubertad; Pubertad precoz; Hiperplasia suprarrenal congénita; 17-alfa-hidroxiprogesterona (DeCS).

Dallos-Lara MF, Mendoza-Rojas VC. [Pubertad precoz por hiperplasia adrenal congénita. Reporte de caso]. Rev. Fac. Med. 2020;68(1):148-52. English. doi: http://dx.doi.org/10.15446/revfacmed.v68n1.72674.

Introduction

Precocious puberty is defined as the appearance of secondary sexual characteristics before the age of 8 in girls and 9 in boys.[1-3] It is classified into *central precocious puberty* (CPP), which is caused by the early activation of the hypothalamic–pituitary–gonadal axis, and *peripheral precocious puberty* (PPP), which occurs when there is no activation of the gonadotropic axis.

PPP is characterized by the production of sex hormones that may be caused by genetic factors (congenital adrenal hyperplasia (CAH), McCune-Albright syndrome, mutation of the DAX1 gene and familial testotoxicosis), or acquired factors (functional ovarian cysts, gonadal or adrenal tumors, β-hCG-secreting tumor and consumption of exogenous sex steroids).[2,4] The following is the case of a girl diagnosed with PPP secondary to non-classic CAH.

Case presentation

A 4 1/2-year-old female patient was assessed by the pediatric endocrinology service due to the appearance of pubic hair six months before the consultation, without thelarche or acne. Her parents were first-degree cousins, and, given their heights, the mid-parental height would be 150cm (less than 2 standard deviations).

At birth, her weight was 3340g, length 50cm, and head circumference of 34cm. She presented early symptomatic neonatal hypoglycemia that required intravenous administration of dextrose, and jaundice that was treated with phototherapy. The patient also presented left spastic hemiplegia secondary to left lateral ventriculomegaly, which had been identified on prenatal ultrasound.

The physical examination revealed: height: 105.3 cm (0.5 standard deviations, according to the growth charts from the Centers for Disease Control and Prevention, USA); weight: 17 kg; body mass index: 15.4 kg/m^2; bone age: 6 years according to Greulich and Pyle method; normal blood pressure; absence of goiter, abdominal masses and acne; Tanner breast 1 and pubic 2; and female genitals without clitoromegaly.

Based on these findings, the patient was diagnosed with PPP secondary to non-classic CAH. An adrenocorticotropic hormone (ACTH) stimulation test was requested (Table 1), finding normal renin and electrolyte levels in blood, as well as high levels of 17-hydroxyprogesterone (17-OHP), which are clinical signs of CAH.

Table 1. Laboratory tests.

Test		Result		Reference values
ACTH Test	17-hydroxyprogesterone	Pre-stimulation	0.7 ng/mL	<2 ng/mL
		Post-stimulation	25.1 ng/mL	<15 ng/mL
	Cortisol	Pre-stimulation	212.1 nmol/L	276-552 nmol/L
		Post-Stimulation	921.9 nmol/L	>848.4 nmol/L
Free testosterone		1.3 pg/mL		<0.5 pg/mL
DHEA		947.3 ng/mL		0.32-5.84 ng/mL
Delta 4-androstenedione		2.35 ng/mL		<0.5 ng/mL

ACTH: adrenocorticotropic hormone; DHEA: dehydroepiandrosterone.
Source: Own elaboration.

In the absence of hydrocortisone, prednisolone was administered at a dose equivalent to 15 mg/m^2/day of hydrocortisone, thus lowering the levels of dehydroepiandrosterone (DHEA), androstenedione, testosterone, and 17-OHP. During a follow-up consultation, her chronological age (9 years) was consistent with her bone age and height in less than 2 standard deviations (Figure 1), which coincided with her mid-parental height.

Discussion

The onset of puberty, which may be early, in clinical terms, occurs when the breast bud appears in girls and when the testicular volume is >4mL in boys.[5] In CPP, the appearance of secondary sexual characteristics occurs sequentially, contrary to what happens in PPP.

The appearance of pubic hair before age 7 in white girls, before age 6 in African American girls, and before age 9 in boys is defined as early puberty.[6,7] Also, the presence of pubic hair in the absence of breast growth in girls suggests adrenal and ovarian disorders or exposure to androgens.[5] In the reported patient, pubarche, as the first finding of puberty added to the advanced bone age and the lack of concordance of height compared to mid-parental height, indicated the presence of PPP.

One of the causes of PPP is CAH, an autosomal recessive disease characterized by an alteration of adrenal steroidogenesis that leads to a decrease in the synthesis of cortisol and aldosterone. Such decrease generates negative feedback in the pituitary gland with a consequent ACTH overproduction and subsequent stimulation of the adrenal gland, which in turn causes hyperplasia.[8]

About 95% of CAH cases are caused by a 21-hydroxylase deficiency[8,9] due to the mutation of the CYP21A2 gene. There are 2 forms of presentation: classic and non-classic. The prevalence of the former is 1 case per 16 000 births, while the prevalence of the latter is 1 case per 1 000 births.[6,10,11]

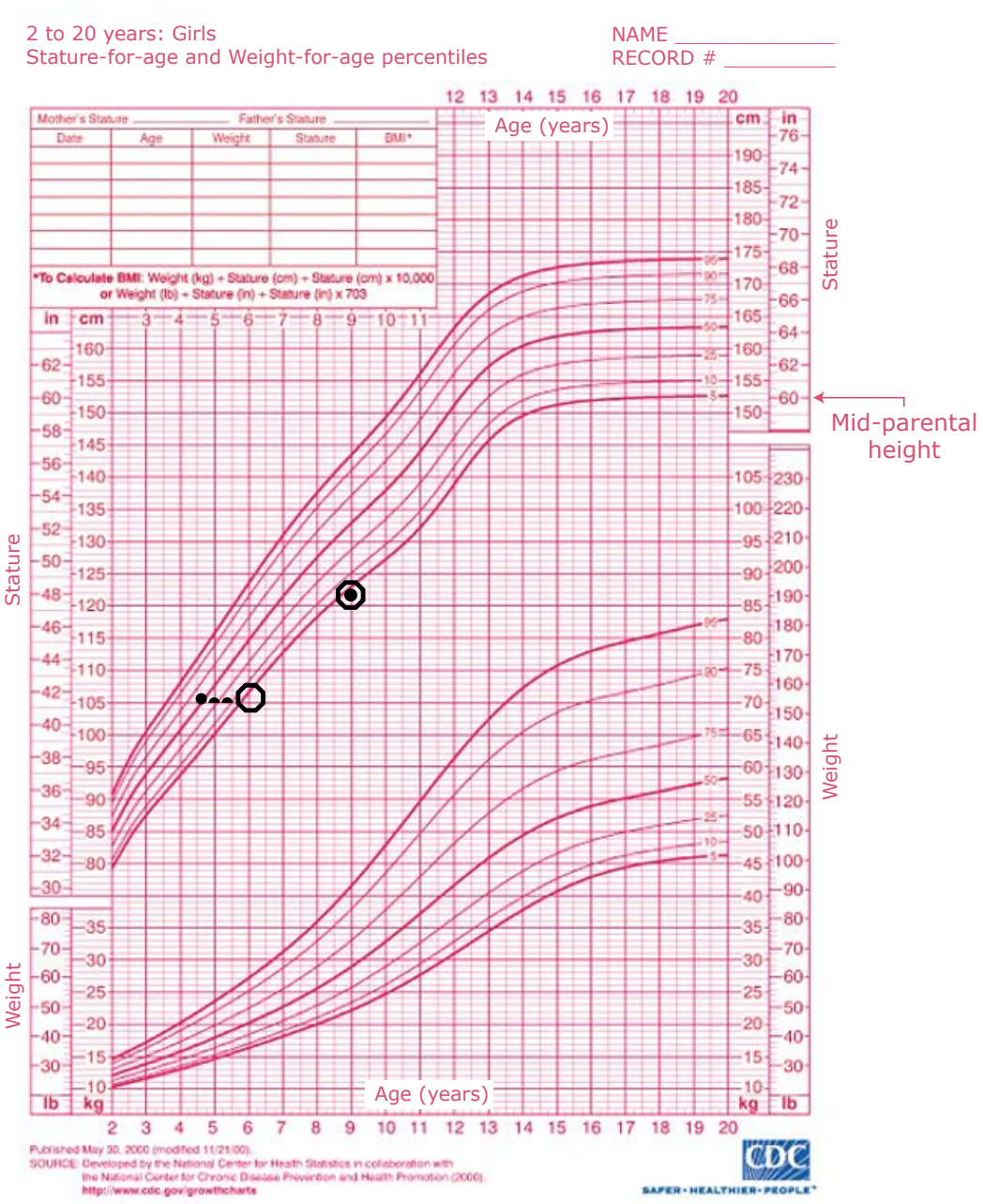

Figure 1. Centers for Disease Control and Prevention growth chart plotted according to chronological age
• Height
O Bone age.
Source: Own elaboration.

Most patients with non-classic CAH are asymptomatic or have mild manifestations that may be expressed as precocious puberty, hirsutism, acne, clitoral hypertrophy, menstrual irregularities, or polycystic ovary.[8,12,13] In this regard, Moral *et al.*[14] conducted a multicenter study in 220 girls with non-classic CAH and found that 92% of the girls under 10 years of age had early puberty.

Hypoglycemia may also be present in non-classic CAH due to cortisol deficiency, a counter-regulatory hormone that increases blood glucose levels through gluconeogenesis and glycogenolysis.[15,16] In the reported case, it was present in the neonatal stage, a time of adaptation with high metabolic demands that include an increase in counter-regulatory hormones, which went unnoticed, as in many cases.

The diagnosis of non-classic CAH is made by determining the concentrations of 17-OHP, a metabolite that builds up as a result of the steroidogenesis disruption caused by the 21-hydroxylase deficiency. Therefore, Speiser *et al.*,[17] in their 2010 consensus, suggest measuring 17-OHP in blood in the morning and performing a full adrenocortical profile after an ACTH stimulation test to differentiate 21-hydroxylase deficiency from other enzyme defects, or in case of doubtful diagnosis.

For non-classic neonatal CAH screening, a blood sample on filter paper is collected by pricking the baby's heel between the second and fourth day of life, which is tested to obtain 17-OHP levels using mainly immunoassay techniques. The result is considered abnormal when levels are above the 97th percentile for age.[6,8,11]

Unlike classic CAH, random 17-OHP levels in non-classic CAH may be in the normal range; therefore, the ACTH stimulation test is the gold standard for diagnosis[18,19]. It´s considered positive when pre-stimulation levels are >5 ng/mL (15nmol/L) and post-stimulation levels are >15 ng/mL (45 nmol/L).[8,17,18] In the reported patient, the baseline 17-OHP level was normal, and was only elevated on the ACTH test, which indicated non-classic CAH. Testosterone and delta 4-androstenedione values were higher than expected for the pre-pubertal stage, which contributed to the diagnosis of CAH and its corresponding decrease after treatment.

Since CAH is an autosomal recessive disease, some research[12,13,17] suggests that genetic studies should always confirm the CYP21A2 gene mutation and that phenotype-genotype correlation should be made to provide genetic counseling for the family. However, in the present case, it was not possible to carry out such studies and, therefore, counseling was not provided due to problems related to the patient's social security coverage.

Glucocorticoids are administered for the treatment of non-classic CAH in patients with accelerated bone age, virilization, and premature or rapid progression pubarche.[9,17,18] Some of the objectives of this treatment in girls are achieving adequate growth rate and the proper onset of puberty, as well as avoiding accelerated skeletal maturation, the reduction of the expected mid-parental height, and psychological alterations. In adolescents, the treatment aims to avoid irregular menstrual cycles, hirsutism, and acne. Likewise, long-term corticosteroid use can prevent frequent situations caused by this pathology, such as infertility, abortions, fetal death, psychiatric problems, decreased bone density, obesity, dyslipidemia, insulin resistance, hypertension, diabetes, among others.[18,19]

It is worth mentioning that the growth rate increases in precocious puberty. Therefore, one of the best ways to assess whether the treatment is appropriate is by evaluating this aspect. In the case presented here, the girl initially had a difference of more than 2 standard deviations from the mid-parental height, but upon receiving treatment, she returned to her normal growth rate and her bone age did not progress. 17-OHP and delta 4-androstenedione values should be reviewed during follow-up to confirm if normal levels have been achieved, as is the case of this patient.

Conclusions

Non-classic CAH is the most common cause of PPP. Since this type of hyperplasia may be asymptomatic during the first days or years of life, this diagnosis should be suspected when there is early puberty, increased growth rate, and advanced bone age. Early treatment of CAH helps avoid loss of final genetic height and prevent cardiometabolic diseases in adulthood.

Ethical considerations

For this case report, the girl's mother was asked to sign an informed consent form. The patient's assent was also obtained.

Conflicts of interest

None stated by the authors.

Funding

None stated by the authors.

Acknowledgements

To the patient and her family, the Hospital Universitario de Santander and Universidad Industrial de Santander.

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rfm
Revista *de la* Facultad *de* Medicina

LETTER TO THE EDITOR
DOI: http://dx.doi.org/10.15446/revfacmed.v68n1.74937
Received: 16/09/2018 **Accepted:** 29/03/2019

English language and Peruvian medical programs

El inglés en la medicina académica peruana

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Dear Editor:

After reading the article entitled "*English proficiency level in Colombian undergraduate students of medical programs,"*[1] published in your prestigious journal and with whose conclusions we agree, we would like to delve into the subject and highlight some aspects mentioned in that editorial.

The study by Alonso *et al.*[1] is the first in Colombia to report that only about 20% of graduates from different medical schools have an intermediate or high level of English. This figure must improve not only in Colombia but also in other Latin American countries such as Peru, since mastery of the English language would optimize access to useful tools related to technological development and research for medical students, even though Spanish is the official language in most countries of the region.[2]

Therefore, medical graduates should be better prepared in English, paying special attention to technical language, communication skills, and critical reading for facilitating their entry into an increasingly competitive national and international labor market.[3] A common disadvantage of the lack of English proficiency is the poor access to new bibliographic references, which exposes the students to not having relevant information for their training and has clinical repercussions that are already evident in some graduates.[4]

Although many medical journals published in Spanish are currently making their transition to English, Peruvian journals have not yet entirely made such transition.[5] This is described in the Mayta-Tristan study *et al.*[6] published by a Peruvian journal of medicine and public health, which reports that scientific production regarding cancer in Peru increased significantly between 2000 and 2011 and that about 25 articles, of which 82.1% were in English, were published every year during this period. However, in most of these publications, the corresponding author was a foreigner, and the Peruvian researchers were co-authors.[6] For this reason, and considering that a large number of indexed biomedical journals accept material in English only, we consider that educational institutions must encourage the learning of that language, particularly reading and writing skills.[7]

In summary, it is necessary to make a call to prioritize the incorporation of the English language in the learning process of medical students as part of their academic programs in Latin America taking Colombia as an example, as it reached the goal set for 2014 regarding the proficiency level in this language. Concerning Peru, we have the challenge of exceeding the expectations of the "English: Doors to the World" plan, a proposal that set goals exclusively for schoolchildren for the year 2021. According to this plan, young people must graduate from high school having already an intermediate English level. If this goal is achieved, it will serve as an incentive to develop similar strategies for university students.[8]

Conflicts of interest

None stated by the authors.

Funding

None stated by the authors.

Acknowledgements

To Universidad Científica del Sur for providing us with comprehensive scientific training.

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Rev. Fac. Med. 2020 Vol. 68 No. 1: 155-7

rfm
Revista *de la* Facultad *de* Medicina

LETTER TO THE EDITOR
DOI: http://dx.doi.org/10.15446/revfacmed.v68n1.79864
Received: 23/05/2019 **Accepted:** 17/07/2019

Intra-individual somatic variation of the rs669 polymorphism in the A2M gene in patients with colorectal cancer

Variación somática intraindividual del polimorfismo rs669 del gen A2M en pacientes con cáncer colorrectal

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Dear Editor:

An intra-individual somatic variation (ISV) is described as the genetic difference among different tissues of the same individual. ISV increases with age, may not manifest a defined phenotype, and is associated with neurological, hematological, and immune disorders, especially with cancer.[1]

To analyze possible ISV in Mexican patients with colorectal cancer (CRC), we studied the polymorphism rs669 (c.2998 A>G, p.Ile1000Val) of the *A2M* gene, which encodes for the alpha-2 macroglobulin protein, a protease inhibitor involved in tumor progression and proliferation.[2] This variant is located near a thioester site, which is necessary for the inhibitory function of the protein.

For the present study, the variant was selected based on previous research conducted by Ramirez-Plascencia.[3] She determined that the frequency of the G allele in peripheral blood was 0.35 in 146 healthy individuals from western Mexico, who had an average age of 42 years within a range of 19 to 48 years; 62% of the participants were men. The variant was found to be in equilibrium according to the Hardy-Weinberg assumption that analyzes the distribution pattern of genotypes (p=0.098).

Prior informed consent and immediately after surgical resection, tumor tissue, healthy tissue adjacent to the tumor and peripheral blood were obtained from 62 patients with CRC that had not received chemotherapy or radiotherapy treatment (Table 1). The average age in this group was 63 years with a range of 34 to 96 years.

After histopathological diagnosis, DNA was extracted from the tumor tissue and the healthy tissue adjacent to the tumor using the High Pure PCR Template Preparation kit, and from peripheral blood using the DTAB-CTAB method (dodecyltrimethylammonium bromide - cetyltrimethylammonium bromide).[4] The variant was identified by PCR-RFLP (polymerase chain reaction - restriction fragment length polymorphism) with the primers Forward 5'-GGAGACATATTAGGCTGC-3' and Reverse 5'-CTGAAACCTGGGAAATCC-3', and with the enzyme *MboI.* Enzyme digestion products were analyzed in 6% polyacrylamide gel stained with silver nitrate.

Table 1. Clinical-pathological characteristics of 62 patients with colorectal cancer.

Variable		n=62 (%)
Average age in years (range)		63 (34-96)
Sex	Male	38 (61%)
	Female	24 (39%)
Tumor location	Colon	35 (56%)
	Rectum	25 (40%)
	No information	2 (4%)
Degree of differentiation	Well differentiated	2 (3%)
	Moderate	40 (64%)
	Poorly differentiated	7 (11%)
	No information	13 (20%)
Metastasis	Positive	24 (38%)
	Negative	17 (27%)
	No information	21 (33%)

Source: Own elaboration.

The AA, AG and GG genotypic frequencies in peripheral blood were 0.40, 0.52 and 0.8, respectively, and 0.40, 0.53 and 0.7, respectively, in tumor tissue. Statistical comparison with Fisher's exact test between the groups showed no statistically significant difference (p=0.96), but 3 (5%) patients with different genotype between tumor and blood were identified. This result was the same after repeating the test twice.

The genotype in the healthy colorectal tissue adjacent to the tumor was identified to determine if the variation corresponded to the somatic alterations associated with the tumor tissue. This led to establish that the peripheral blood and healthy tissue genotypes were identical, as opposed to what was found in the tumor tissue; this also confirmed the ISV exclusive of the tumor in the 3 patients with different genotypes (Figure 1).

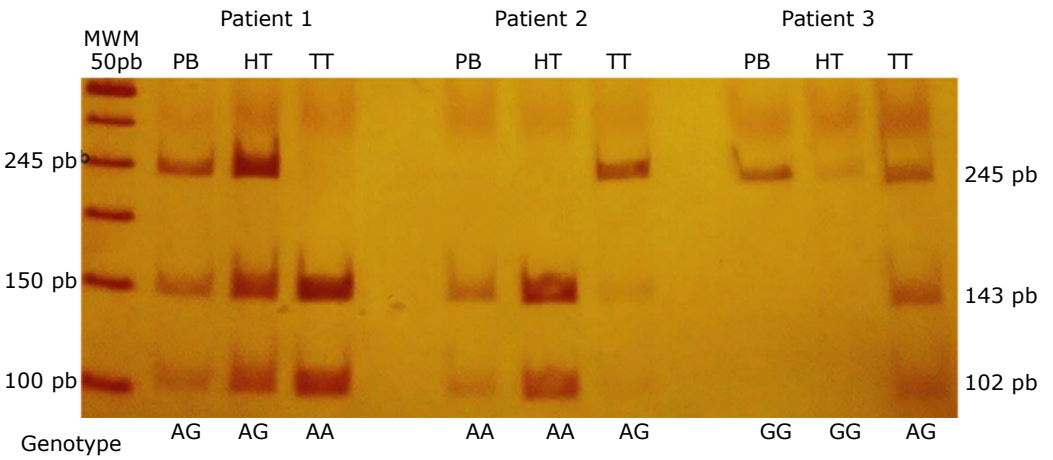

Figure 1. Intra-individual somatic variation in 3 patients with colorectal cancer evidenced by a different genotype in tumor tissue. Polyacrylamide gel at 6% stained with silver nitrate.
PB: peripheral blood; HT: healthy tissue; TT: tumor tissue; MWM: molecular weight marker.
Source: Own elaboration.

After analyzing the clinical data of ISV patients, it was found that all were male, and 2 were under 40 years of age and their cancer had not been diagnosed as hereditary. However, finding ISV in only 3 of the 62 participants was, due to their small number, a limitation to establish a relationship with age, sex, tumor location and degree of progression.

The difference of the tumor genotype in patient 1 (Figure 1) can be explained by hemizygosity, which means that the genotype interpreted as homozygous AA in tumor tissue may be only one allele A instead, i.e. loss of the allele G in the tumor since the peripheral blood and healthy tissue show the AG genotype. At this point, it should be noted that hemizygosity frequently originates from chromosome segment deletion or total chromosome loss, alterations that are part of the chromosomal instability pathway, considered the most frequent molecular pathway in CRC development.[5]

Regarding alterations of chromosome 12, according to the Mitelman database,[6] monosomy 12 is one of the main findings in adenocarcinomas, which supports the feasibility of hemizygosity for rs669 polymorphism in patients with CRC. Nevertheless, the genotype in the tumor tissue of the 3 patients with ISV could have originated from the incorrect incorporation of nucleotides during DNA replication or from the effect of endogenous or exogenous mutagens with inadequate DNA repair, facts that have been described as the most frequent routes of de novo mutations.[7] Continuous exposure to toxic agents and their high cell proliferation is also influential in the case of colorectal tissue, as demonstrated in the study in human autopsies by O'Huallachain *et al.*,[8] where ISV was determined based on the great variety of findings in tissues of constant division such as the intestine.

This research shows how the study of ISV enriches the knowledge of genetic diversity among tissues by changing the concept of identical genome in somatic cells for a dynamic model, which can impact on genetic diseases such as cancer.[9] It should be noted that ISV have been described in patients with neoplasms, mainly in relation to variants associated with drug responses. Thus, the analysis of variants of the *MTHFR* gene in patients with colon cancer published by Rai *et al.*[10] shows that the A1298C polymorphism only had identical genotypes in 45.81% of patients when the tumor and normal tissue adjacent to the tumor were compared. However, other authors describe ISV in cancer in terms of genotype discrepancy between peripheral blood and tumorous colorectal tissue: Marsh *et al.*[11] report frequencies of 1.1% in 1 139 comparisons made in 44 patients in which 28 polymorphisms were analyzed, Van Huis-Tanja *et al.*[12] report frequencies of 1.4% in 1 418 genotypes of 11 genotyped single nucleotide polymorphisms in 149 patients, and Balboa *et al.*[13] claim that the frequencies are up to 22% among the genotypes of 10 variants studied in 65 patients.

The 5% ISV finding for the rs669 polymorphism of the *A2M* gene in CRC patients did not show significant differences between the tissues analyzed, but contributed to show the genetic variation associated with cancer, even in passenger genes or "low-penetrance" genes such as *A2M*. Future research on other variants with a larger sample are expected to provide more representative evidence of ISV in CRC.

Conflicts of interest

None stated by the authors.

Funding

None stated by the authors.

Acknowledgements

To doctors VM Maciel, MW Centeno and J Valenzuela from the Colon and rectum service of Hospital Civil de Guadalajara "Dr. Juan I. Menchaca".

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Author Guidelines

The Revista de la Facultad de Medicina (Journal of the Faculty of Medicine) adheres to the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals del International Committee of Medical Journal Editors (ICJME) (http://www.icmje.org/icmje-recommendations.pdf).

General guidelines

A. Submission of articles to the Revista de la Facultad de Medicina (Journal of the Faculty of Medicine)

Articles shall only be received at our OJS (Open Journal System) website (http://goo.gl/rsVzGU). Submission must include: article, metadata and complementary files (assignment of copyright https://goo.gl/EfWPdX and authorship responsibility https://goo.gl/6zztk4)

B. Languages of submission and language of publication

As of January 10, 2018 and in accordance with what the editorial of V65N2 (https://goo.gl/HaZ37B) states, all articles received shall begin a transition process for being published in English. In consequence, articles shall be received in English, Spanish and Portuguese, provided that the following terms are fulfilled:

I. Submissions in English

Articles written in English prior to its submission must be accompanied by a letter signed by an official translator or an English Language specialist (professional level) with a certified English language proficiency (C2) in which he or she states that the article has been reviewd or checked by him/her and that it complies with the minimum academic standards of language. Each submission will be reviewed and may be rejected if the journal staff concludes that it does not meet the minimum language requirements.

II. Submissions in Spanish and Portuguese

Authors shall attach (step 4 of the submission process) the **Publication in English Commitment Letter** (https://goo.gl/4rhxxh) signed by them in which they commit to translate the text into English, if the article is approved for publication. The project will be undertaken by one of the official translators of the journal, whose contact details will be provided by the Journal staff in a timely manner when the document reaches this stage of the process. Once the selected translator has received the payment (all of them will charge the same fee), the journal will be notified in order to submit the final version of the article for translation, after being proofread. Such version will be reviewed and approved by both the authors and the Journal. Current translation rate is 120 Colombian pesos per original word to be translated (roughly 0.06 USD per word), the list of references will not be included in this service as it does not require to be translated. Exceptions will be considered for those authors who prove to experience difficulties regarding the payment of this service, for example, authors residing in countries such as Venezuela or Cuba due to the exchange rate in theese countries.

C. Authorship

Those appointed as authors of articles submitted to our Journal must fully comply with the authorship criteria established in the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals del International Committee of Medical Journal Editors (ICJME), setction II, subsections A and B (http://www.icmje.org/icmje-recommendations.pdf)

D. Structure of articles – General sections

In accordance with the ICJME recommendations, before submitting an article, authors must verify it has the following general structure (please, keep in mind that according to the type of article an specific structure will also be required, for further details please see Section E of these guidelines)

I. Title page:

1. Provide a title in the language in which the article is written
2. Provide a title in a second language (English or Spanish depending on which language is written the article)
3. Provide a short title no longer than 40 characters (including blank spaces)
4. All authors' full names and last names must be stated; their institutional affiliation must be identified with superscript Arabic numerals.
5. Institutional affiliation for each author must be presented without specifying positions, only institutions and sections/departments within them shall be included.
6. Provide the ORCID number for each author.
7. Complete contact details of the main author or the corresponding author must be provided (name, institutional address, telephone, city, country, email).
8. Word count: please state the total number of words that make up the article without taking into account words included in titles, abstracts, acknowledgments, tables, figures, and the list of references. The number of words

must not exceed the maximum allowed for each the type of article (see Section F)
9. Number of figures and tables: please state the total number of tables and figures included in the article. The maximum numbers of tables and figures allowed is 6.

II. Abstract (in Spanish)

1. It must not exceed 200 words.
2. References must not be included.
3. In case of experimental studies, protocol (clinical trial) registry number must be included in the last line of the abstract, example: https://www.ncbi.nlm.nih.gov/pubmed/29791437
4. Original research articles, review articles and short communications must have an abstract made up the following sections: "introduction", "objective", "materials and methods", "results" and "conclusions".
5. For case reports, abstracts shall be presented in accordance with the CARE checklist of information to include when writing a case report (http://www.care-statement.org/resources/checklist), item 3, Abstract.
6. Keywords (in Spanish): Include 3 to 6 exact descriptors from DeCS Bireme (http://decs.bvs.br/).

III. Abstract

1. It must not exceed 200 words.
2. References must not be included.
3. In case of experimental studies, protocol (clinical trial) registry number must be included in the last line of the abstract, example: https://www.ncbi.nlm.nih.gov/pubmed/29791437
4. Original research articles, review articles and short communications must have an abstract made up the following sections: "introduction", "objective", "materials and methods", "results" and "conclusions".
5. For case reports, abstracts shall be presented in accordance with the CARE checklist of information to include when writing a case report (http://www.care-statement.org/resources/checklist), item 3, Abstract.
6. Keywords: Include 3 to 6 exact MeSH descriptors (http://www.nlm.nih.gov/mesh/).

IV. Introduction

The summarized rationale of the study must be included in this section. Furthermore, at the end of this section, the purpose of the study must be clearly stated. Only the references required to support the ideas depicted here are to be included.

V. Materials and methods

The type of study and the methodology used (sample identification, selection criteria, statistical methods, etc.) shall be described here. If the procedures performed during the study involved humans or animals, authors must explicitly state that they followed the ethical principles for medical research on humans of the Declaration of Helsinki (2013) and any other applicable national regulations, said documents must be duly referenced. Additionally, it must be clearly expressed that the study was approved by the ethics committee of the institution or institutions where it was carried out, and the corresponding letter of approval from the ethics committee must be enclosed.

In case of experimental studies, registration of clinical trials in a public trials registry at or before the time of first patient enrollment as a condition of consideration for publication is mandatory. An example of a public trial registry can be found at https://clinicaltrials.gov. The clinical trial registration number must be included in the last line of the abstract.

VI. Results

The results obtained in the study must be presented in a logical and coherent way. Data can be shown in tables or figures, but not simultaneously in both. Avoid repeating the data presented in tables and figures within the body of the article, and do not combine the presentation of results with your discussion, as the latter has its own section.

VII. Discussion

In this section, results obtained in the study must be addressed without making a general review of the subject. Authors must only discuss the new and most relevant aspects presented by the study and the conclusions proposed from them. Limitations of the research and the agreement or disagreement of findings reported in the article with other studies on the subject, duly referenced, must be reported.

VIII. Conclusions

Conclusions must be related to the objectives of the study described in the "introduction" section. Do not draw conclusions that are not supported by the findings of your study or that are supported by a work that has not yet been finalized. If appropriate, create new hypotheses but present them as such. Propose your recommendations.

IX. Conflict of interests

Please state, based on the funding sources of the study or any other reason, whether the authors have a conflict of interest or not. Authors must complete and sign the Conflict of Interest Disclosure Form of the ICJME (http://www.icmje.org/about-icmje/faqs/conflict-of-interest-disclosure-forms) and attach it to the submission (step 4).

X. Funding

Please state if the study was funded by external sources and if they influenced its completion.

XI. Acknowledgment

Express your gratitude only to people and institutions that have contributed substantially to your work. Authors are responsible for acknowledging the people or institutions that could be recognized as contributors to the results of the work and its conclusions by the readers.

XII. Tables, figures and references

1. Tables

A maximum of 6 tables and/or figures is allowed. Tables shall be editable, have a title, be listed in order of appearance, be mentioned within the body of the article and be included immediately after the paragraph in which they are first mentioned. If abbreviations are used, they must be clarified in table footers. If a table already published is partially or totally reproduced, the corresponding reference must be added and a letter of permission for its reproduction must be attached. If a table is created by the authors, the legend "Source: own elaboration." must be included.

2. Figures

A maximum of 6 tables and/or figures is allowed. Figures must be editable and have a minimum 72 dpi resolution. Figures include any type of illustration other than tables (graphics, x-rays, photographs, etc.) and must be listed in order of appearance. Every figure shall be mentioned within the body of the article and included immediately after the paragraph in which it is first mentioned. If abbreviations are used, they must be clarified in figure footers. Titles and legends must not be included in the figure but below it. If a figure already published is partially or totally reproduced, the corresponding reference must be added and a letter of permission for its reproduction must be attached. If a table is created by the authors, the legend "Source: own elaboration." must be included.

Please refrain from including any description in figures footers, such explanations shall only be included in the main text of the article.

XIII. References

Both in-text and end references must conform strictly to the Vancouver style adopted by the ICJME in its recommendations. References must be introduced in order of appearance and identified by Arabic numerals in parentheses, without superscripts, at the end of the sentence or paragraph where they are alluded to. For a complete guide on the Vancouver system, please go to https://goo.gl/XdCdmS or https://goo.gl/8DJ5Er.

E. Type of articles accepted – Specific structure

In addition to the general structure described above, each type of article must meet the following requirements:

I. Editorial

An editorial is a paper written by the editor, by a member of the Editorial Board or by a guest researcher on orientations in the subject domains of the journal.

The maximum number of words allowed for Editorials, excluding abstracts, tables and figures, and references, is 1000.

II. Original research

Original research articles are papers that present in detail the original results of both research projects already finished and biomedical researches. It is an unpublished text that provides new information on specific aspects, as well as relevant contributions to scientific knowledge.

Original research articles shall have a structured abstract and must comply with the general structure for writing articles required by the Revista de la Facultad de Medicina (see Section D).

If the procedures performed during the study involved humans or animals, authors must explicitly state that they followed the ethical principles for medical research on humans of the Declaration of Helsinki (2013) and any other applicable national regulations, said documents must be duly referenced. Additionally, it must be clearly expressed that the study was approved by the ethics committee of the institution or institutions where it was carried out, and the corresponding letter of approval from the ethics committee must be enclosed.

In case of experimental studies, registration of clinical trials in a public trials registry at or before the time of first patient enrollment as a condition of consideration for publication is mandatory. An example of a public trial registry can be found at https://clinicaltrials.gov. The clinical trial registration number must be included in the last line of the abstract, for example: https://www.ncbi.nlm.nih.gov/pubmed/29791437

Articles reporting results of clinical trials in "Materials and methods" must include a data sharing statement that complies with the provision of the ICMJE recommendations, Section II, Subsection L, paragraph ii (Data Sharing).

The maximum number of words allowed for Original Research articles, excluding abstracts, tables and figures, and references, is 3500.

III. Short communication

It's a brief article reporting final, partial or preliminary original results of a technologic or scientific research that usually requires a rapid dissemination.

Short communications shall have a structured abstract (in English and Spanish) and must comply with the general structure for writing articles required by the Revista de la Facultad de Medicina (see Section D).

If the procedures performed during the study involved humans or animals, authors must explicitly state that they followed the ethical principles for medical research on humans of the Declaration of Helsinki (2013) and any other applicable national regulations, said documents must be duly referenced. Additionally, it must be clearly expressed that the study was approved by the ethics committee of the institution or institutions where it was carried out, and the corresponding letter of approval from the ethics committee must be enclosed.

The maximum number of words allowed for Short communications, excluding abstracts, tables and figures, and references, is 1500.

IV. Systematic Review

Review articles are the result of a research where the results of published or unpublished researches on a field of science or technology are analyzed, systematized and integrated in order to report development trends and the progresses that have been made in the field the review addresses. This type of paper is characterized by a careful literature systematic review

of at least 50 references.

- Only systematic reviews are to be submitted. Narrative or literature reviews will not be accepted anymore, unless the editor asks authors to submit this type of article to start the publication process
- Systematic reviews shall have a structured abstract and must comply with the general structure for writing articles required by the Revista de la Facultad de Medicina (see Section D).
- At least 50 references shall be included.
- Systematic reviews must strictly comply with all the items established in the PRISMA checklist: http://prisma-statement.org/PRISMAStatement/Checklist
- Systematic reviews must comply with the following structure: Introduction, Materials and methods, Results (where the PRISMA based studies selection flowchart (https://goo.gl/hD7PWq) should be included), Discussion and Conclusions, this in line with the structure established in the PRISMA checklist: http://prisma-statement.org/PRISMAStatement/Checklist

The maximum number of words allowed for Systematic reviews, excluding abstracts, tables and figures, and references, is 4000.

V. Reflection paper

When writing reflection papers authors shall present the results of a research from their analytical, interpretative or critical perspective on a specific topic and using original sources. Essays and reflection papers s on topics related to medicine and health areas are to be included in this section.

Reflection papers must have the following structure: "Introduction", "other sections of the article", "conclusions".

The maximum number of words allowed for Reflection papers, excluding abstracts, tables and figures, and references, is 3500.

VI. Case report

A case report is an article where the results of a study on a particular situation are presented in order to make known the technical and methodological experiences considered in a specific case. It includes a brief review of the literature related to the condition being reported.

Case reports submitted to the Journal must follow all the items of the CARE checklist for writing case reports (http://www.care-statement.org/resources/checklist).

When submitting a case report, the informed consent signed by the patient(s), or legal representative(s), whose data and/or experience was used for writing the report must be uploaded as a supplementary file in step 4 of the submission process.

The maximum number of words allowed for Case reports, excluding abstracts, tables and figures, and references, is 2000.

VII. Letter to the editor

A document presenting critical, analytical or interpretative stances on documents published in the Journal that, in the opinion of the Editorial Board, constitute an important contribution to the subject discussion by the scientific community of reference.

The maximum number of words allowed for Letters to the editor, excluding abstracts, tables and figures, and references, is 1000.

F. Assignment of rights, responsibility of authorship and translation commitment letter

All submissions must be accompanied by the assignment of rights, responsibility of authorship and translation commitment letter forms, duly completed and signed by all authors. The forms are available in https://goo.gl/EfWPdX, https://goo.gl/6zztk4 and https://goo.gl/4rhxxh, respectively. These forms can be loaded during step 4 of the submission.

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Once received, articles will be analyzed, using the TurnItin Software, to generate a similarity and plagiarism report. If the article exceeds 15% of similarity, and if said similarity is not derived from a thesis (be aware this report does not take into account references and less than 7 words matches), it will be sent back to the authors for modification or rejected as appropriate.

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When procedures have been carried out on humans or animals, the ethical principles for medical research on humans of the Declaration of Helsinki 2013 (https://goo.gl/C5BPi3) and any other applicable national regulations must be explicitly stated and duly referenced. Additionally, the study must be approved by the ethics committee of the institution or institutions where it was carried out, and the respective letter of approval issued by the ethics committee must be enclosed.

If personal images or data are used during the study, the identity and the privacy of the people involved must be protected by editing the images included in the article and using terms and conventions to refer to their data or names.

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As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. The article (or most of it) has not been published, is not in the process for publication in another journal and will not be sent to other journals while waiting for acceptance or rejection.
2. The text is typed and double-spaced on letter-sized sheets, with margins of 2.5x2.5x2.5x2.5, and 12-point Verdana font. Unless the paper is an Editorial or Letter to the Editor, its writing style does not use any first person (plural or singular) form of conjugation.
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5. All the indications for the submission of articles, as established in the "Guidelines for authors", have been met. In case of breaching 4 or more items, the article will be rejected.
6. The article is organized according to the structure required for each type of article, as established in the "Guidelines for authors".
7. The references strictly follow the Vancouver style, as required by the journal, and were chosen as recommended in the "Guidelines for authors", including DOI where applicable. For further examples, please visit https://goo.gl/XdCdmS.
8. References include all material published in widely circulated journals, books, official information available online and other types of information that can be cited according to the Vancouver system. Abstracts of papers presented at congresses or symposia can only be referenced when they are published in widely circulated journals.
9. If this study involved humans or experimental animals, the "Materials and methods" section explicitly states that the applicable international ethical standards were met and that the study was approved by the ethics committee of the institution or institutions where it was made. The respective letter of approval issued by the ethics committee is enclosed.
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A. Envío de artículos a la Revista de la Facultad de Medicina

Solo se recibirán artículos a través del portal OJS (Open Journal System) en el link http://goo.gl/rsVzGU, donde se deberá realizar el envío completo: artículo, ingreso de todos sus metadatos y archivos complementarios (cesión de derechos https://goo.gl/EfWPdX y responsabilidad de autoría https://goo.gl/6zztk4)

B. Idiomas de recepción e idioma de publicación

A partir del 10 de enero de 2018 y de acuerdo con en el editorial del V65N2 (https://goo.gl/HaZ37B), se empezará un proceso de transición de publicación en inglés, por lo cual se recibirán artículos en inglés, español y portugués siempre que se cumplan las siguientes condiciones:

I. Envío en inglés

Deberá ir acompañado de una carta firmada por traductor oficial o personal especializado (certificado este último con nivel C2 en inglés) en la que afirme que ha escrito o ha revisado el artículo y que el mismo cumple con las reglas de redacción de dicho idioma. Todo envío será revisado de forma y de concluirse que no cumple con los requisitos mínimos de idioma, será rechazado.

II. Envíos en español y portugués

Los autores adjuntarán firmado el oficio de compromiso de publicación en inglés (https://goo.gl/4rhxxh) en el que, siempre que el artículo apruebe el proceso editorial de publicación, se comprometen a traducirlo al inglés con uno de los traductores oficiales de la revista, cuyos datos les serán suministrados. Este proceso estará a cargo de la Revista y los detalles se informarán cuando documento llegue a esta etapa del proceso. Una vez los autores realicen el pago al traductor seleccionado (quienes manejarán una misma tarifa), este último informará a la revista para proceder al envío final del artículo con corrección de estilo para realizar su traducción al inglés, versión que revisarán y aprobarán los autores y la revista. La tarifa actual de la traducción es de 120 pesos colombianos por palabra original traducida (aproximadamente 0.06 usd por palabra), no se contará la lista de referencias para estos efectos. Se tendrán en cuenta excepciones para quienes demuestren dificultades para el pago de este servicio, por ejemplo autores que residan en países como Venezuela o Cuba debido a la compleja tasa cambiaria.

C. Autoría

Quienes figuren como autores de los artículos enviados deberán cumplir en su totalidad con los criterios de autoría establecidos en Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals del International Committee of Medical Journal Editors (ICJME), sección II, subsecciones A y B, http://www.icmje.org/icmje-recommendations.pdf.

D. Presentación del artículo - Secciones generales

De acuerdo a las recomendaciones de ICJME los artículos deben cumplir con la siguiente estructura general (según el tipo de artículo se requerirá una estructura específica, al respecto ver la sección F de estas indicaciones):

I. Página de portada

1. Título en el idioma en que se presente el artículo (Español, Inglés, Portugués)
2. Título en segundo idioma (inglés o español según idioma de presentación del artículo)
3. Título corto que no exceda 40 caracteres contando espacios (inglés y español).
4. Nombres completos de autores con filiación identificada por número arábigo en superíndice
5. Filiación completa de cada autor sin especificar cargos, solo instituciones y secciones dentro de las mismas
6. Identificación ORCID de cada autor. Esta información también debe incluirse en los metadatos del envío (paso 2 del envío en el portal OJS).
7. Correspondencia completa del autor principal (nombre, dirección institucional, teléfono, ciudad, país, correo electrónico).
8. Recuento de palabras: indique el número total de palabras en el texto sin tener en cuenta las palabras de títulos, resúmenes, agradecimientos, tablas y figuras, ni listado de referencias. El número de palabras no debe exceder el máximo permitido según tipo de artículo (ver Sección E)
9. Número de figuras y tablas: indique el número total de tablas y figuras en el artículo. No debe exceder el máximo permitido: 6.

II. Resumen

1. No debe superar las 200 palabras.

2. No debe incluir referencias.
3. En caso de estudios experimentales, incluir el registro del protocolo (ensayo clínico) en la última línea del resumen, ejemplo: https://www.ncbi.nlm.nih.gov/pubmed/29791437
4. Para Investigación original, Artículo de revisión, y Comunicación breve debe estructurarse en "Introducción", "objetivo", "materiales y métodos", "resultados", "conclusiones".
5. Para reportes de caso debe estructurarse de acuerdo con los lista de comprobación CARE para presentación de reportes de caso (http://www.care-statement.org/resources/checklist), ítem 3 Resumen.
6. Palabras clave: Incluir 3 a 6 descriptores exactos que se encuentren DeCS Bireme (http://decs.bvs.br/).

III. Abstract

1. No debe superar las 200 palabras.
2. No debe incluir referencias.
3. En caso de estudios experimentales, incluir el registro del protocolo (ensayo clínico) en la última línea del resumen, ejemplo: https://www.ncbi.nlm.nih.gov/pubmed/29791437
4. Para Investigación original, Artículo de revisión, y Comunicación breve debe estructurarse en "Introduction", "objective", "materials and methods", "results", "conclusion".
5. Para reportes de caso debe estructurarse de acuerdo con los lista de comprobación CARE para presentación de reportes de caso (http://www.care-statement.org/resources/checklist), ítem 3 Resumen.
6. Keywords: Incluir 3 a 6 descriptores exactos que se encuentren en MeSH (http://www.nlm.nih.gov/mesh/).

IV. Introducción

Sintetice la racionalidad del estudio y, al final de esta sección, indique el objetivo del mismo. Cite solo las referencias estrictamente necesarias.

V. Materiales y métodos

Describa el tipo de estudio y la metodología empleada en la realización del artículo (identificación de la muestra, criterios de selección, métodos estadísticos, etc.). Si se realizaron procedimientos en seres humanos o animales debe expresarse de forma explícita que se respetaron los principios éticos para las investigaciones médicas en seres humanos de la Declaración de Helsinki (2013) y cualquier otra normativa nacional que aplique, debidamente referenciadas, y que el estudio fue aprobado por el comité de ética de la institución o instituciones donde fue realizado, acompañando el envío con la respectiva carta de aprobación por parte del comité de ética. En caso de estudios experimentales se requiere que el protocolo del estudio (ensayo clínico) haya sido registrado previamente en una base de datos de registro de protocolos, se sugiere consultar https://clinicaltrials.gov, Incluir el registro en la última línea del resumen.

VI. Resultados

Presente de forma lógica y coherente los resultados obtenidos. Los datos se pueden mostrar en tablas o figuras, pero no de forma simultánea en ambas. Evite repetir en el texto los datos presentados en tablas y figuras y no combine la presentación de los resultados con su discusión, pues esta última tiene su propia sección.

VII. Discusión

Aborde los resultados obtenidos en el estudio sin realizar una revisión del tema en general. Discuta únicamente sobre los aspectos nuevos e importantes que aporta su trabajo y las conclusiones propuestas a partir de los mismos. Indique las limitaciones de la investigación y las concordancias o discordancias de sus hallazgos con los obtenidos en otros estudios sobre el tema, debidamente referenciados.

VIII. Conclusiones

Deben estar relacionadas con los objetivos del estudio que fueron descritos en "introducción". No formule conclusiones que no estén respaldadas por los hallazgos del estudio o que se apoyen en otros trabajos aún sin finalizar. Si lo considera pertinente, plantee nuevas hipótesis pero califíquelas como tales. Cuando sea apropiado, proponga sus recomendaciones.

IX. Conflicto de intereses

Indique si a partir de la financiación del estudio o por otro motivo los autores presentaron o no conflicto de intereses en la realización del artículo. Debe diligenciarse el formato de divulgación de conflicto de intereses del ICJME (http://www.icmje.org/about-icmje/faqs/conflict-of-interest-disclosure-forms) y adjuntarse como archivo complementario (paso 4 del envío).

X. Financiación

Señale si el estudio contó con financiación externa y si esta influenció su realización.

XI. Agradecimientos

Agradezca solo a personas e instituciones que hayan contribuido sustancialmente a su trabajo. Los autores son responsables por la mención de personas o instituciones a quienes los lectores podrían atribuir un apoyo a los resultados del trabajo y sus conclusiones.

XII. Tablas, figuras y referencias

1. Tablas

Deben ser editables. Se permitirá un máximo de 6 tablas y/o figuras. Deberán tener título, enumerarse en orden de aparición, mencionarse en el texto e incluirse inmediatamente después del párrafo en que son nombradas. Si se utilizan abreviaturas han de ser aclaradas en forma de pie de tabla. Si una tabla ya publicada es reproducida parcial o totalmente indíquelo referenciándolo y adjuntando en el envío carta de permiso para la reproducción de la misma. Si una tabla es creación de los autores indíquelo con la leyenda Fuente: elaboración propia.

2. Figuras

Deben ser editables y tener una resolución mínima de 30 dpi. Denomine como figura cualquier tipo de ilustración que no sea tabla (gráficos, radiografías, fotografías, etc.) y enumérelas en orden de aparición. Toda figura deberá mencionarse en el texto e incluirse inmediatamente después del párrafo en que es nombrada. Si se utilizan abreviaturas, las mismas tienen que ser aclaradas en forma de pie de figura. Los títulos y leyendas no deben aparecer en la figura, sino abajo de la misma. Si una figura ya publicada es reproducida parcial o totalmente indíquelo referenciándolo y adjuntando en el envío carta de permiso para la reproducción de la misma. Si una figura es creación de los autores indíquelo con la leyenda Fuente: elaboración propia.

No incluir descripciones en los pies de figura, estas explicaciones deben incluirse en el cuerpo del documento.

XII. Referencias

La citación de referencias, tanto in texto como en el listado final, debe ajustarse estrictamente al formato Vancouver aprobado por el ICJME en sus recomendaciones . La enumeración debe realizarse en orden de aparición y debe identificarse mediante números arábigos entre paréntesis, sin superíndice, ubicados al final de la frase o párrafo en donde se les alude. Para una guía sobre el sistema Vancouver ir a https://goo.gl/XdCdmS o https://goo.gl/8DJ5Er.

E. Tipos de artículo, estructura y máximo de palabras

Además de la estructura general antes descrita, cada tipo de artículo debe cumplir con los siguientes requisitos:

I. Editorial

Documento escrito por el editor, un miembro del Comité Editorial o un investigador invitado sobre orientaciones en las áreas de especialidad de la revista.

Máximo permitido de palabras 1000, sin contar títulos, resúmenes, tablas y figuras y referencias.

I. Investigación original

Artículo que presenta, de manera detallada, los resultados originales de proyectos de investigación ya terminados, así como de investigaciones biomédicas. Es un trabajo inédito que aporta nueva información sobre aspectos específicos y contribuye de manera relevante al conocimiento científico.

Debe incluir resumen estructurado y cumplir con la estructura general requerida por la revista (ver Sección D).

Si se realizan estudios en o con datos de seres humanos o animales deben haberse tenido en cuenta los principios éticos de investigación de la Declaración de Helsinki y la normativa nacional que aplique (debidamente referenciadas), indicar que fue aprobado por comité de ética institucional y acompañar el envío con la carta de aprobación por parte de dicho comité.

En caso de estudios experimentales se requiere que el protocolo del estudio haya sido registrado previamente en una base de datos de registro de protocolos, se sugiere consultar https://clinicaltrials.gov, Incluir el registro en la última línea del resumen, ejemplo: https://www.ncbi.nlm.nih.gov/pubmed/29791437.

Si la investigación reporta resultados de ensayos clínicos debe incluirse (en materiales y métodos) una declaración sobre la divulgación de datos que cumpla con lo establecido por en las recomendaciones del ICMJE, Sección III, Subsección L, literal ii (Data Sharing).

Máximo permitido de palabras 3500, sin contar títulos, resúmenes, tablas y figuras y referencias

III. Comunicación breve

Documento breve que presenta resultados originales finales, preliminares o parciales de una investigación científica o tecnológica que, por lo general, requiere de una pronta difusión.

Debe incluir resumen estructurado y cumplir con la estructura general requerida por la revista (ver Sección D).

Si se realizan estudios en o con datos de seres humanos o animales deben haberse tenido en cuenta los principios éticos de investigación de la Declaración de Helsinki y la normativa nacional que aplique (debidamente referenciadas), indicar que fue aprobado por comité de ética institucional y acompañar el envío con la carta de aprobación por parte de dicho comité.

Máximo permitido de palabras 1500, sin contar títulos, resúmenes, tablas y figuras y referencias

IV. Artículo de revisión sistemática:

Documento resultado de una investigación donde se analizan, sistematizan e integran los resultados de investigaciones publicadas o en prensa sobre un tema específico con el fin de dar cuenta de los avances y tendencias de desarrollo en este campo. Se caracteriza por presentar una cuidadosa revisión sistemática de la literatura médica de por lo menos 50 referencias.

- Solo se aceptarán revisiones sistemáticas. Las revisiones narrativas no serán aceptadas, a menos que exista invitación previa por parte del Editor para su presentación a proceso de publicación
- La revisión sistemática debe incluir resumen estructurado y cumplir con la estructura general requerida por la revista (ver Sección D)
- Mínimo de referencias a incluir: 50
- Debe cumplir estrictamente con todos los ítems de la lista de comprobación PRISMA: http://prisma-statement.org/PRISMAStatement/Checklist
- Debe estructurarse en Introducción, Materiales y métodos, Resultados (donde debe incluirse el flujograma formato PRISMA https://goo.gl/hD7PWq), Discusión y conclusiones, esto en línea con la estructura de la lista de comprobación PRISMA: http://prisma-statement.org/PRISMAStatement/Checklist
- Máximo permitido de palabras: 4000, sin contar títulos, resúmenes, tablas y figuras y referencias

V. Artículo de reflexión

Documento que presenta los resultados de una investigación, desde una perspectiva analítica, interpretativa o crítica del autor, sobre un tema específico en el que se recurre a fuentes

originales. En esta sección también se incluyen aquellos ensayos y artículos de reflexión sobre temáticas relacionadas con la medicina y el área de la salud.

Deberá estructurarse en "Introducción", "texto del artículo", "conclusiones". Máximo permitido de palabras 3500, sin contar títulos, resúmenes, tablas y figuras y referencias

VI. Reporte de caso

Documento que presenta los resultados de un estudio sobre una situación particular con el fin de dar a conocer las experiencias técnicas y metodológicas consideradas en un caso específico; incluye una revisión breve de la literatura relevante.

La estructura y presentación de los reportes de caso deben cumplir todos los ítéms del checklist de los líneamientos CARE (http://www.care-statement.org/resources/checklist) para presentación de casos.

El envío debe estar acompañado del consentimiento informado del o los pacientes o sus representantes objeto del caso (paso 4 del envío, archivos complementarios)

Máximo permitido de palabras 2000, sin contar títulos, resúmenes, tablas y figuras y referencias

VII. Carta al editor

Texto en el que se expresan posiciones críticas, analíticas o interpretativas sobre los documentos publicados en la Revista que, a juicio del Comité Editorial, constituyen un aporte importante a la discusión del tema por parte de la comunidad científica de referencia.

No requiere estructura.

Máximo permitido de palabras 1000, sin contar títulos, resúmenes, tablas y figuras y referencias

F. Formatos de cesión de derechos, responsabilidad de autoría y compromiso de traducción

Todo envío deberá ir acompañado de los oficios cesión de derechos, responsabilidad de autoría y compromiso de traducción debidamente diligenciados y firmados por todos los autores, los cuales están disponibles para descarga en https://goo.gl/EfWPdX, https://goo.gl/6zztk4 y https://goo.gl/4rhxxh, respectivamente. Dichos oficios podrán cargarse en el paso 4 del envío.

G. Informe de similitud y plagio

Una vez recibidos, los artículos serán analizados con el Software TurnItin, donde se generará un informe de similitud y plagio, en caso de superar 15% de similitud y no derivarse de un trabajo de grado o tesis de postgrado dicha similitud (no se tienen en cuenta referencias ni coincidencias menores a 7 palabras), el artículo será devuelto para modificación o rechazado según sea el caso.

H. Declaración de ética y transparencia

La Revista de la Faculta de Medicina acepta y se adhiere a las "Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals" del International Committee of Medical Journal Editors (ICMJE) (www.icmje.org) y a los lineamientos establecidos por Equator (Enhancing the QUAlity and Transparency Of health Research) Network (http://www.equator-network.org/) y por el Committee on Publication Ethics (COPE) (http://publicationethics.org/) con el fin de garantizar la calidad de las publicaciones científicas, su transparencia, integridad y debido respeto de los principios éticos que rigen la investigación biomédica. De acuerdo a lo anterior, los trabajos enviados a la Revista de la Facultad de Medicina se deben ajustar a dichos lineamientos.

Además, cuando se hayan realizado procedimientos en seres humanos o animales debe expresarse de forma explícita que se respetaron los principios éticos para las investigaciones médicas en seres humanos de la Declaración de Helsinki de 2013 (https://goo.gl/C5BPi3) y cualquier otra normativa nacional que aplique, debidamente referenciadas, y que el estudio fue aprobado por el comité de ética de la institución o instituciones donde fue realizado, acompañando el envío con la respectiva carta de aprobación por parte del comité de ética.

En caso de utilizarse imágenes o datos personales en la realización del estudio se debe proteger la identidad y privacidad de estas personas mediante la edición de las imágenes incluidas en el artículo y el uso de términos y convenciones para referirse a sus datos o nombres.

Los artículos (o partes importantes de los mismos) enviados a la Revista de la Facultad de Medicina deben ser documentos inéditos que no corresponden a traducciones ni a adaptaciones de otras fuentes ya publicadas. Al enviarlo junto con los oficios de cesión de derechos de publicación (https://goo.gl/EfWPdX) y de responsabilidad de autoría (https://goo.gl/6zztk4) debidamente diligenciados, los autores expresan que:

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Lista de comprobación para la preparación de envíos

Como parte del proceso de envío, los autores/as están obligados a comprobar que su envío cumpla todos los elementos que se muestran a continuación. Se devolverán a los autores/as aquellos envíos que no cumplan estas directrices.

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2. El texto está escrito a doble espacio en hojas tamaño carta márgenes 2.5x2.5x2.5x2.5, letra Verdana 12 puntos. No está escrito en primera persona (singular o plural), si no se trata de una carta al editor o editorial.
3. Respeta el límite máximo de palabras permitido por la revista, sin contar resúmenes, tablas, figuras y referencias: 4 000 para "Revisión sistemática", 3 500 para "Revisión de la literatura", 3 500 para "Investigación Original" y "Artículo de reflexión"; 2 000, para "Reporte de caso" y 1 000 para "Carta al Editor" y "Editorial".
4. Incluye un resumen en español y uno en inglés de máximo 200 palabras cada uno. Se indican 3 a 6 palabras claves, tanto en español, como en inglés, tomadas de los descriptores DeCS y MeSH, respectivamente.
5. Cumple con todas las indicaciones para la presentación y envío de artículos informadas en las "Directrices para autores". En caso de incumplir 4 o más ítems el artículo será rechazado.
6. Está organizado de acuerdo con las estructura exigida para cada artículo y establecida en las "Directrices para autores".
7. Las referencias están ajustadas estrictamente al formato Vancouver exigido por la revista y se eligieron según se recomienda en las "Directrices para autores", incluyendo DOI en los casos que dicho identificador exista. Pueden verse ejemplos en el siguiente link: https://goo.gl/XdCdmS.
8. Incluye como referencias material publicado en revistas de circulación amplia, en libros, información oficial disponible en línea y otros tipos de información citable según el sistema Vancouver. Los resúmenes de trabajos presentados en congresos o simposios solo pueden referenciarse cuando estén publicados en revistas de circulación amplia.
9. Si este estudio comprometió seres humanos o animales de experimentación, en "Materiales y métodos" se ha expresado explícitamente que se cumplieron las normas éticas exigidas a nivel internacional y que el mismo fue aprobado por el comité de ética de la institución o instituciones donde fue realizado, acompañando el envío con la respectiva carta de aprobación por parte del comité de ética.
10. Las tablas y figuras son editables, respetan el máximo permitido de 6 y fueron realizando considerando la cantidad de datos que contienen y los parámetros establecidos en las "Directrices para autores".
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